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Syntéza *N*-(per)fluoralkyl azolů rhodium(II) katalyzovanou transanulací *N*-(per)fluoralkyl-1,2,3-triazolů

Synthesis of *N*-(per)fluoroalkyl azoles by rhodium(II)-catalyzed transannulation of *N*-(per)fluoroalkyl-1,2,3-triazoles

Disertační práce

Školitel: Ing. Petr Beier, Ph.D.

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Charles University

Faculty of Science

Study program: Organic Chemistry

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Doctoral thesis

Supervisor: Ing. Petr Beier, Ph.D.

Prague, 2024

Prohlášení:

Prohlašuji, že jsem závěrečnou práci zpracovala samostatně a že jsem uvedla všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze,

Olga Bakhanovich

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Abstract

This Thesis deals with the synthesis of *N*-fluoroalkyl azoles via rhodium(II)-catalyzed transannulation of *N*-fluoroalkyl-1,2,3-triazoles obtained through copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) of *N*-fluoroalkyl azides and alkynes.

The introductory chapter describes general approaches towards *N*-fluoroalkyl azoles, focusing on the synthesis of *N*-fluoroalkyl pyrroles and azoles.

In the first part of the Thesis, rhodium(II)-catalyzed transannulation of *N*-fluoroalkyl-1,2,3-triazoles with terminal alkynes is described. The reaction provides access to *N*-fluoroalkyl pyrroles. The regioselectivity of the reaction is investigated and modifications of the primary product are suggested.

In the second part of the Thesis, the reactivity of 4-cyclohexyl-*N*-fluoroalkyl-1,2,3-triazoles is investigated. A one-pot two-step reaction is presented, providing access to novel *N*-fluoroalkyl indoles. Several modification routes are suggested.

Abstrakt

Tato práce se zabývá syntézou *N*-fluoralkylazolů prostřednictvím transanulace *N*-fluoralkyl-1,2,3-triazolů katalyzované rhodiem, získaných azido-alkynovou cykloadiční reakcí *N*-fluoralkyl azidů s alkyny, katalyzovanou měďnými solemi.

Úvodní kapitola popisuje obecné přístupy k *N*-fluoralkyl azolům se zaměřením na syntézu *N*-fluoralkyl pyrrolů a azolů.

V první části práce je popsána reakce *N*-fluoralkyl-1,2,3-triazolů katalyzovaná rhodiem s terminálními alkyny. Reakce poskytuje přístup k *N*-fluoralkylpyrrolům. Je zkoumána regioselektivita reakce a jsou navrženy modifikaceí primárních produktů.

V druhé části práce je zkoumána reaktivita 4-cyklohexyl-*N*-fluoralkyl-1,2,3-triazolů. Je prezentována dvoustupňová reakce v jedné nádobě, která poskytuje přístup k novým *N*-fluoralkylindolům. Je navrženo několik modifikačních cest.

List of publications

Part of the work described in this thesis has been published.

Synthesis, Stability and Reactivity of α-Fluorinated Azidoalkanes

O. Bakhanovich, P. Beier, *Chem. – A Eur. J.* **2020**, *26*, 773–782 – *review*.

Synthesis of N-perfluoroalkyl-3,4-disubstituted pyrroles by rhodium-catalyzed transannulation of N-fluoroalkyl-1,2,3-Triazoles with terminal alkynes

O. Bakhanovich, V. Khutorianskyi, V. Motornov, P. Beier, *Beilstein J. Org. Chem*. **2021**, *17*, 504–510 – *full research paper*.

Rhodium(II)-catalyzed transannulation approach to N-fluoroalkylated indoles

O. Bakhanovich, B. Klepetářová, P. Beier, *Org. Biomol. Chem*., **2023**, *21*, 7924-7927 – *full research paper*.

Contributions in the form of a poster or an oral presentation

2022	Advances in Organic, Bioorganic and Pharmaceutical Chemistry – Liblice 2022 (Špindlerův Mlýn, Czech Rep.) – *poster*
2021	XX. Interdisciplinary Meeting of Young Life Scientists – (Online) – *poster*
2019	Advances in Organic, Bioorganic and Pharmaceutical Chemistry – Liblice 2019 (Špindlerův Mlýn, Czech Rep.) – *poster*

Abbreviations

Ac	acetyl
acac	acetylacetone
anh.	anhydrous
APT	attached proton test
aq.	aqueous
Ar	aryl
Boc	*tert*-Butyloxycarbonyl
br.	broad
Bn	benzyl
Bu	butyl
cat.	catalyst/catalytical
COSY	homonuclear correlation spectroscopy
CuAAC	copper-catalyzed azide-alkyne cycloaddition
CuMeSal	copper(I) 3-methylsalicylate
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
EDG	electron-donating group
EI	electron impact ionization
equiv.	equivalent(s)
ESI	electrospray ionization
esp	α,α,α′,α′-tetramethyl-1,3-benzenedipropionate
Et	ethyl
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HFIP	hexafluoroisopropanol
HMBC	heteronuclear multiple bond correlation spectroscopy
HMDS	bis(trimethylsilyl)amine
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation spectroscopy
GCMS	gas chromatography-mass spectrometry
IOCB	Institute of Organic Chemistry and Biochemistry
LG	leaving group
Me	methyl
MW	microwave
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
Oct	octanoate

ORTEP	Oak Ridge thermal ellipsoid plot
pfb	perfluorobutyrate
PMVE	perfluoromethylvinyl ether
Ph	phenyl
Pr	propyl
R_F	(per)fluoroalkyl
ROESY	rotating frame Overhauser effect spectroscopy
rt	room temperature
SSA	silica sulfuric acid
TBAA	tetrabutylammonium acetate
TBAB	tetrabutylammonium bromide
TBACl	tetrabutylammonium chloride
TBAF	tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBTA	tris(benzyltriazolylmethyl)amine
TEBAC	benzyltriethylammonium chloride
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl, tosyl
UV-Vis	ultraviolet-visible spectrophotometry

Contents

1. Introduction

Azoles are a group of compounds containing a five-membered heterocyclic aromatic ring with at least one nitrogen atom. The aromatic ring may contain up to five nitrogen atoms, as well as other heteroatoms such as oxygen or sulfur.

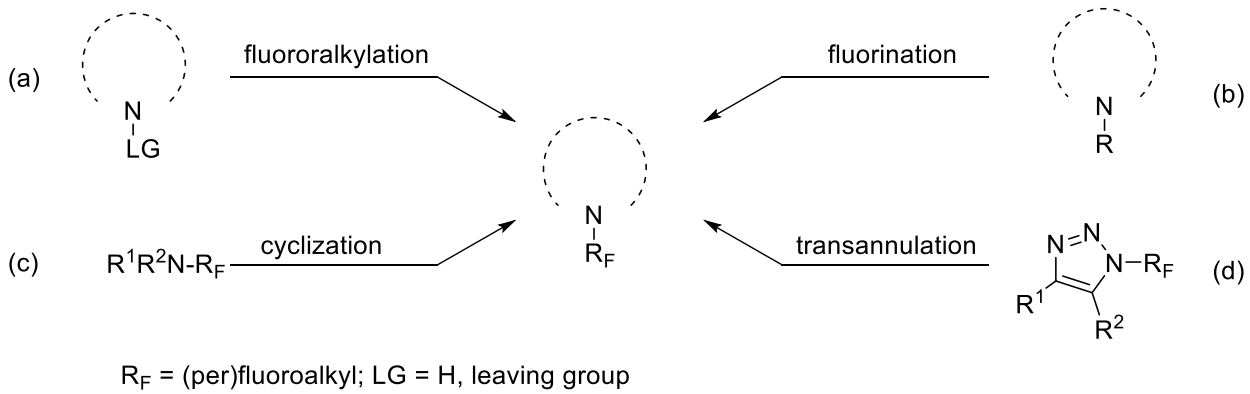
It is difficult to underestimate the importance of azoles in modern-day life. Aside from having various biologically active properties,[1–3] azole-containing compounds are the most used antifungal agents.[4] Azoles show promising properties as chemosensors,[5] corrosion inhibitors,[6] parts of ionic liquids,[7] and polymers.[8,9]

1.1. Synthetic approaches to *N*-(per)fluoroalkyl azoles and their fused analogs

Although the introduction of trifluoromethyl groups is a common strategy to improve the properties of biologically active compounds,[10] *N*-trifluoromethyl moieties on nitrogen-containing compounds (such as azoles) are rarely used. Historically, the synthesis of such moieties was seen as unsafe, as quite often it required the use of toxic HF-containing reagents.[11] The purpose of this chapter is to provide an overview of the existing synthetic methods for the preparation of *N*-fluoroalkyl azoles.

The existing approaches to *N*-(per)fluoroalkyl azoles can be divided into four subsections (Scheme 1):

(a) fluoroalkylation of nitrogen
(b) fluorination of the *N*-R substituent
(c) cyclization of an *N*-R_F containing precursor
(d) transannulation of *N*-R_F-1,2,3-triazoles



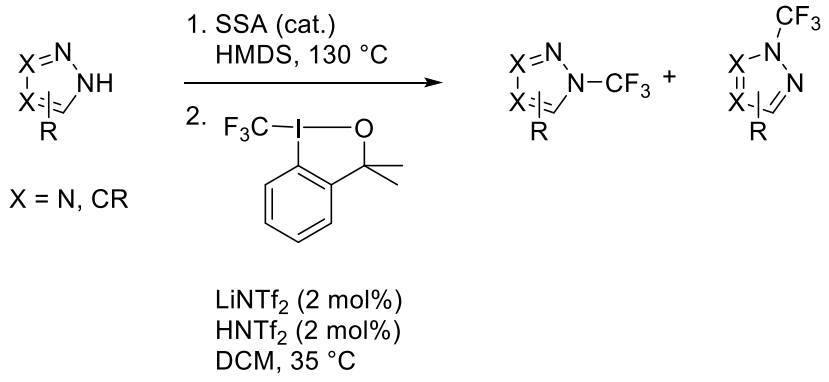
Scheme 1. General approaches towards *N*-(per)fluoroalkyl azoles.

The following chapters demonstrate the existing approaches with a focus on *N*-(per)fluoroalkyl pyrroles and indoles, describing the state of art of synthesis of these azoles.

1.1.1 Fluoroalkylation of azoles

While all approaches have their benefits and limitations, the approach of type (a), for example, has been known since the 1950s and often requires the use of a strong base and elevated temperature for the reaction, as well as utilizing environmentally harmful freons as a fluoroalkyl source.[12]

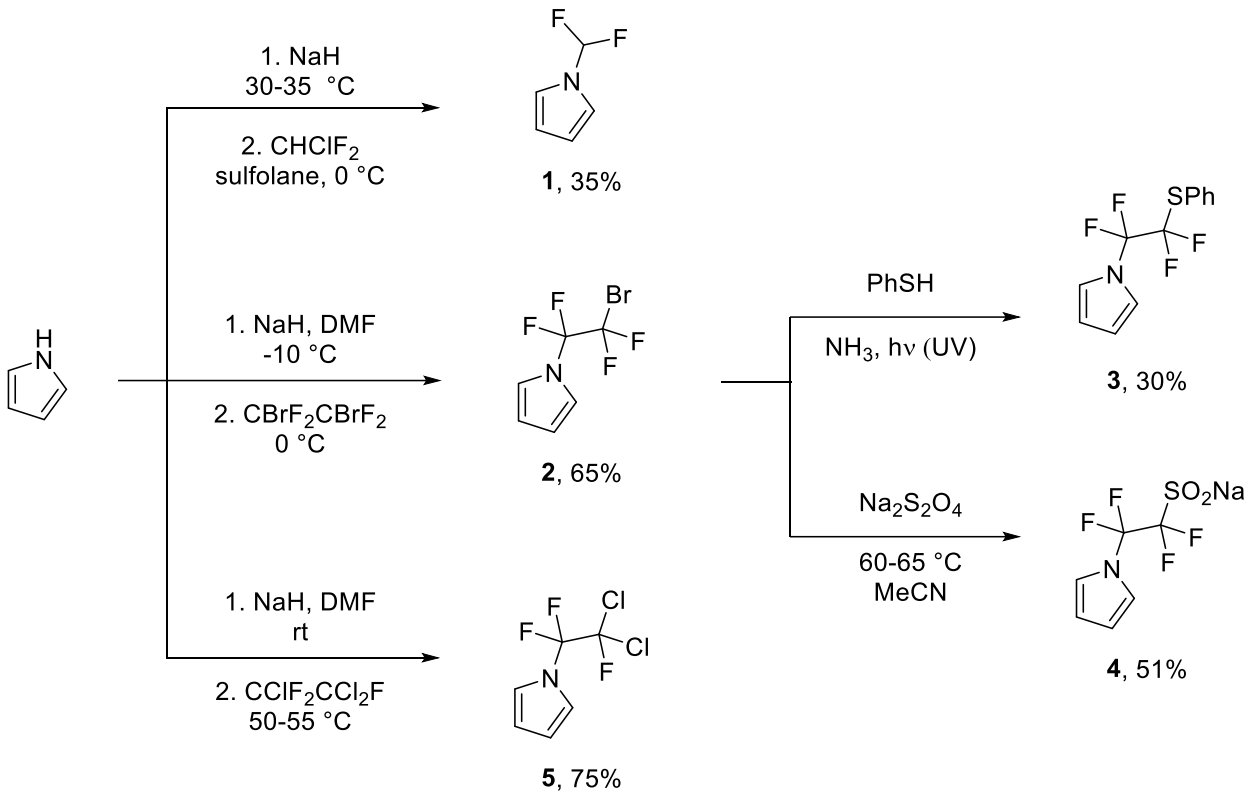
A milder approach of the type (a) strategy uses the Togni reagent.[13] However, the reaction often leads to a mixture of regioisomers (Scheme 2).



Scheme 2. Electrophilic trifluoromethylation of azoles with the Togni reagent.

1.1.1.1 Synthesis of *N*-fluoroalkyl pyrroles

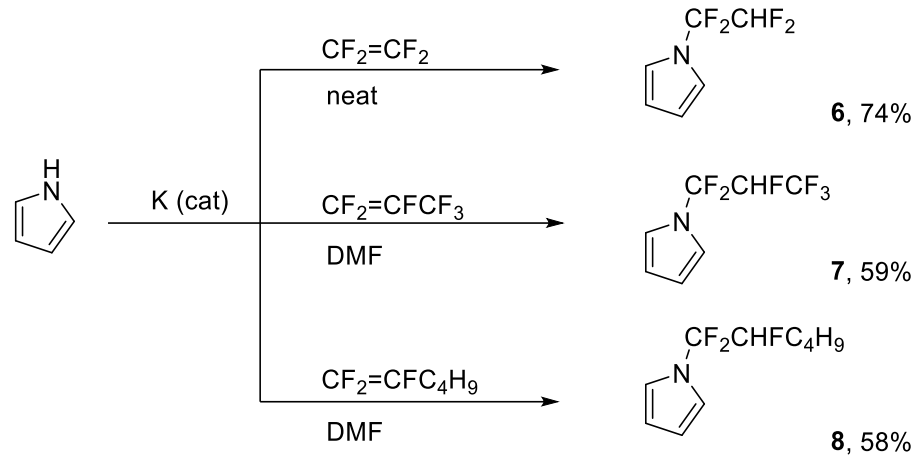
The smallest fluoroalkyl substituent introduced to pyrrole to date is the difluoromethyl group. Due to the low acidity of the pyrrole, the reaction in aqueous media results in a very low yield.[14] When the reaction was performed in anhydrous media, 35% of the target compound **1** was formed[15] (Scheme 3).



Scheme 3. Reactions of sodium pyrrolide with fluorinated alkanes.

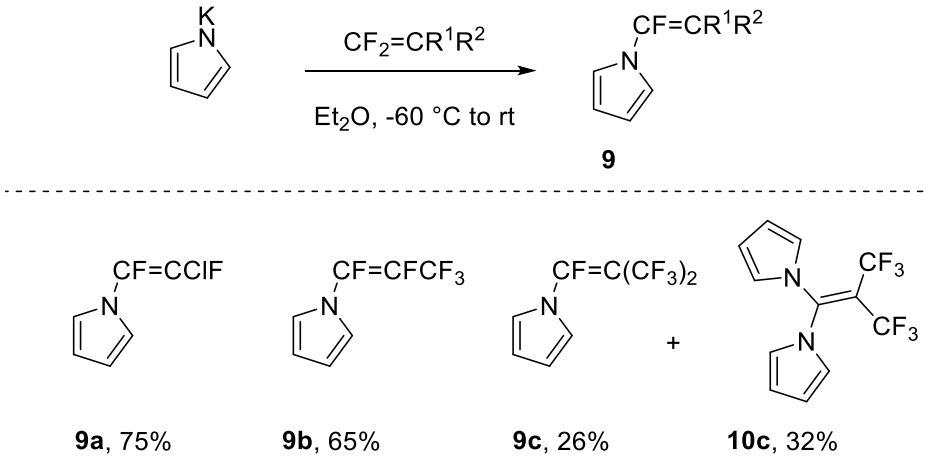
Sodium pyrrolide did not require the presence of a phase-transfer catalyst in reaction with 1,2- dibromotetrafluoroethane and formed pyrrole **3** in good yield[16] (Scheme 3). The authors demonstrated the possibility of modifying the obtained pyrrole **2**, allowing access to fluoroalkyl derivatives **3** and **4**. Similar to the synthesis of pyrrole **2**, no phase-transfer catalyst was required for obtaining 1-(2,2-dichlorotrifluoroethyl)pyrrole **5**[17] (Scheme 3). Unlike the extremely sensitive pyrrole **1**, compound **5** was found to be stable towards diluted acids.

Another studied pathway towards *N*-fluoroalkyl-substituted pyrroles was the reaction of pyrrolides with various fluoroalkenes (Scheme 4).[12]



Scheme 4. Fluoroalkylations of pyrrole with fluorinated alkenes.

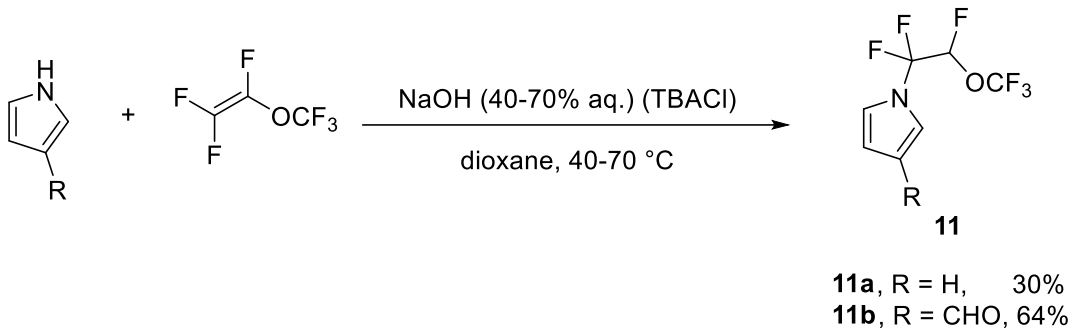
When potassium pyrrolide was prepared and isolated neat, the reaction with fluroolefins resulted in polyfluoroalkenylpyrroles 9**a-c** in moderate to high yields (Scheme 5).



Scheme 5. Reactions of pyrrolide with fluoroolefins.

Products **9a** and **9b** prepared using this procedure were formed as a mixture of *E,Z*-isomers. The most reactive olefin also formed the disubstituted product **10c**.

In contrast to the previously displayed high reactivity of sodium pyrrolide in reactions with freons, the reaction with perfluoromethyl vinyl ether (PMVE) did not proceed under established conditions (melting with NaH) and compounds **11** were obtained by reactions of pyrroles in aqueous suspension of NaOH (in case of pyrrole **11a**, the presence of a phase-transfer catalyst was required).[18]

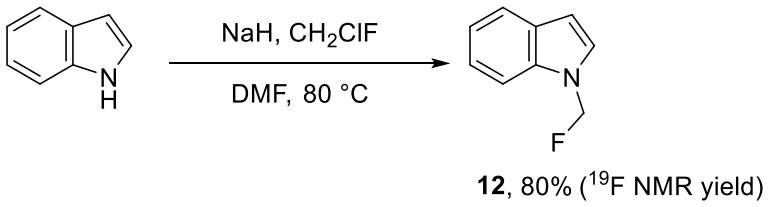


Scheme 6. Synthesis of pyrroles **11**.

1.1.1.2 Synthesis of *N*-fluoroalkyl indoles

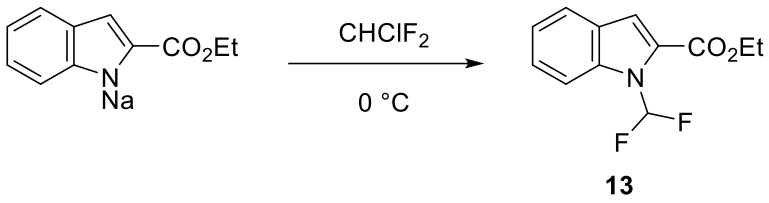
Similar to *N*-fluoroalkyl pyrroles, reactions of indolides with various fluoroalkanes and fluoroalkenes are the most frequently used methods for the synthesis of *N*-fluoroalkyl indoles.

The smallest representative of fluoroalkylated moieties is the monofluoromethyl group. The use of sodium indolide in the reaction with chlorofluoromethane allowed the synthesis of product **12** (Scheme 7).[19] Indole **12** was never isolated due to its high volatility and tendency to decompose.



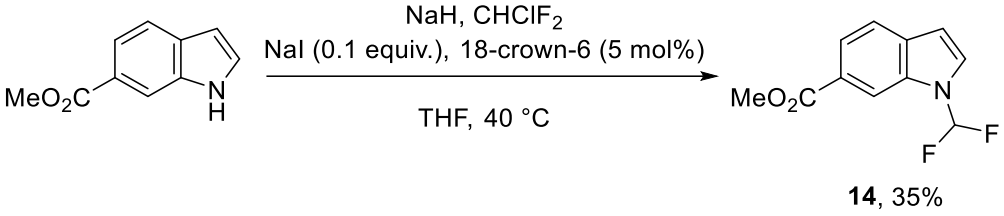
Scheme 7. Synthesis of *N*-fluoromethyl indole **17**.

Chlorodifluoromethane was used as a difluoromethylating agent in the reaction with sodium indolide.[20] The reaction resulted in the formation of *N*-difluoromethylated indole **13** in "very good yield" (no number for this statement was provided).



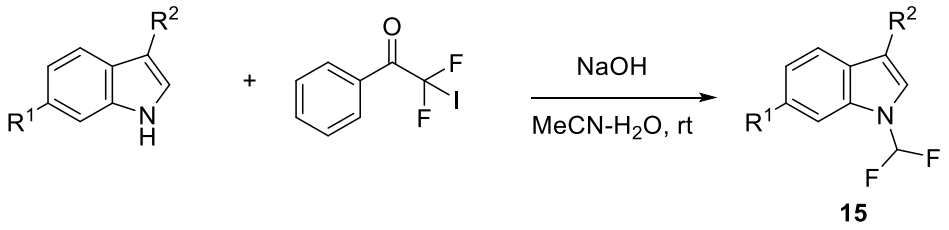
Scheme 8. Synthesis of indole **13**.

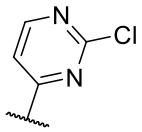
The untypically mild conditions used in the synthesis of indole **13** could be explained by the presence of a strong electron-withdrawing group in the α-position of the starting indolide. When the electron-withdrawing substituent was located on the benzene ring of indole, the synthesis of indole **14** required heating the reaction only to 40 °C (Scheme 9).[21]



Scheme 9. Synthesis of indole derivative **14**.

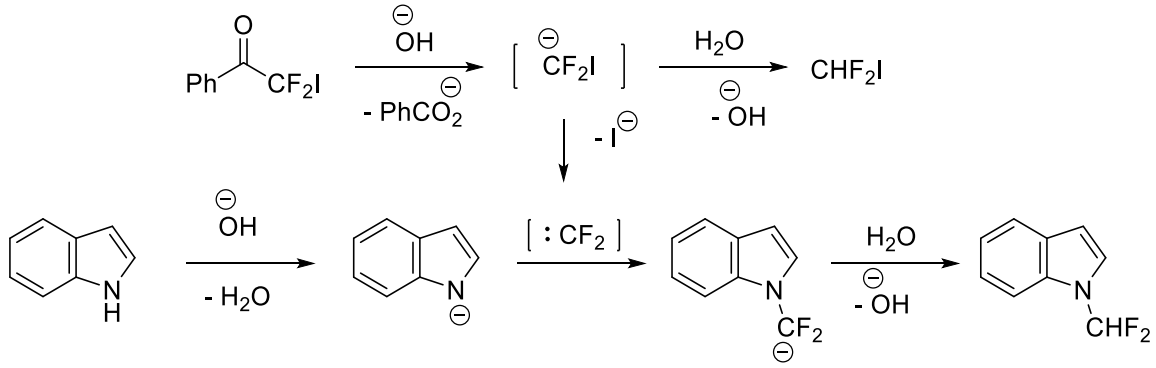
Another study on reactions of difluorocarbene with various secondary amines demonstrated a strong influence of the nature of indole ring substituents on the reactivity of indoles.[22] Although the authors argued that the observed results are explained by the position of the substituent, it is more likely that a substituent with electron-withdrawing properties is essential for the indolides formation under investigated reaction conditions as less acidic indoles were demonstrated to be reactive in hasher conditions.



Product	R^1	R^2	Yield, (%)
15a	H	C(O)Me	81
15b	NO_2	H	86
15c	H	CN	82
15d	H		70
15e	H	Me	0
15f	F	H	0
15g	H	H	0

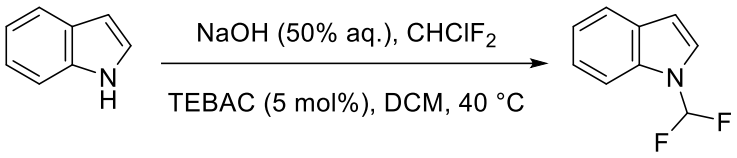
Scheme 10. Synthesis of indoles **15a-d**.

The suggested mechanism includes the generation of an iododifluoromethyl anion that readily underwent α-elimination of iodide ion to release difluorocarbene (Scheme 11). The formed carbene reacted with indolide and the reaction with water resulted in *N*-difluoromethyl indole.



Scheme 11. Possible reaction mechanism of flouoroalkylation.

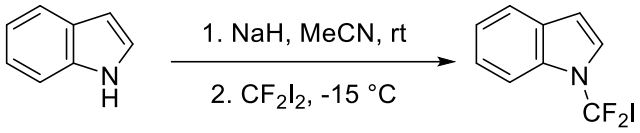
A method to synthesize *N*-difluoromethylated indole **16** was demonstrated in 2005.[14] Performing the reaction under phase-transfer catalysis conditions and elevated temperature, the authors were able to achieve 50% product yield (Scheme 12). Similar to other reports, the low yield of the reaction could be explained by the low acidity of the starting indole.



16, 50%

Scheme 12. Phase-transfer catalysis approach to indole **16**.

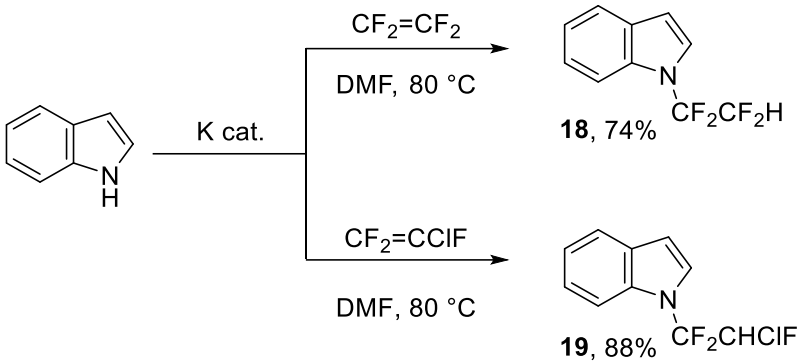
The difluoroiodomethyl substituent on the indole can be introduced by reacting sodium indolide with difluorodiiodomethane.[23] The reaction proceeded at -15 °C and resulted in indole **17** (Scheme 13).



17, 58%

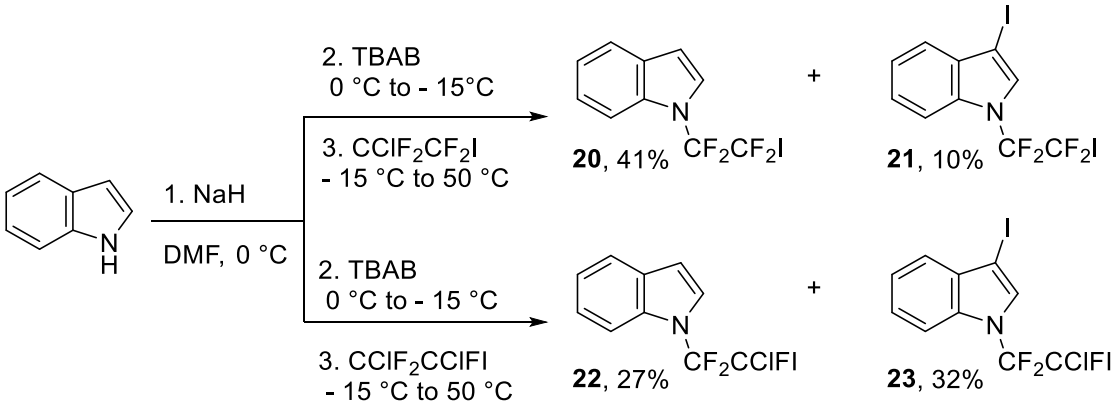
Scheme 13. Synthesis of 1-difluoroiodomethylindole **17**.

To the best of my knowledge, the first synthesis of *N*-tetrafluoroethyl indole was reported in 1960.[12] The use of tetrafluoroethylene is a common synthesis strategy of *N*- tetrafluoroethyl-containing molecules. The reaction was performed in DMF and indole **18** was obtained in a good yield (Scheme 14). The authors also investigated the reaction of indole with chlorotrifluoroethene.



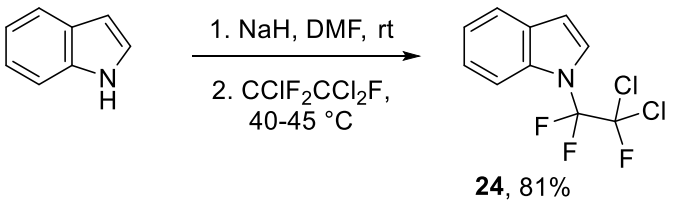
Scheme 14. Synthesis of indoles **18** and **19**.

Analogous syntheses using polyhaloperfluoroethanes as substrates for fluoroalkylation of azoles were published in 2008.[24] Only indoles formed a mixture of products as they were the most prone to electrophilic substitution among the investigated azoles (Scheme 15).



Scheme 15. Reactions of indole with polyhaloperfluoroethanes.

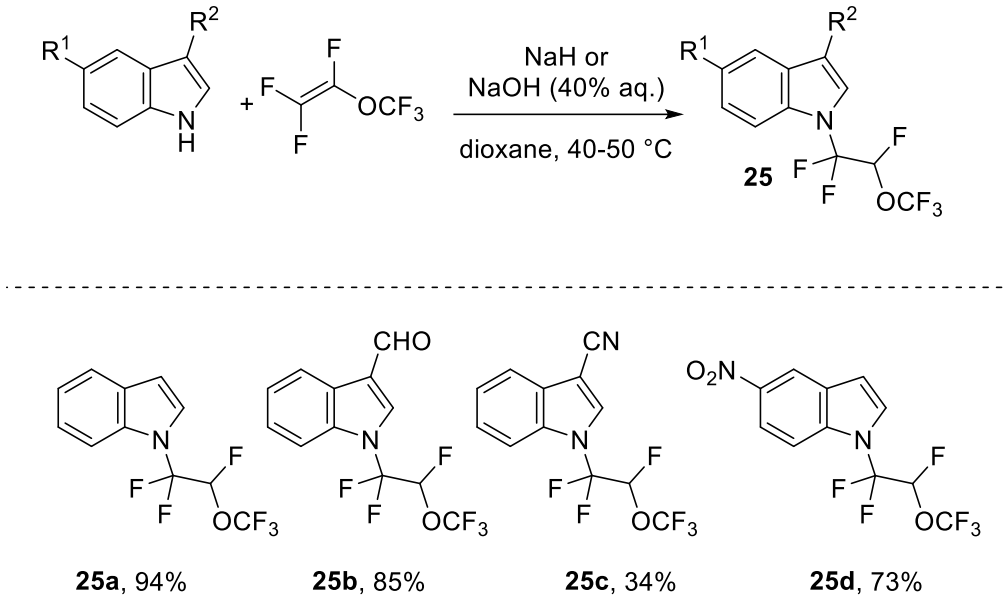
No phase-transfer catalyst was required to obtain indole **24** (Scheme 16).[17] Indole **24** was obtained in high yield and found to be stable to diluted acids or bases.



Scheme 16. Synthesis of indole **24**.

The reaction of sodium indolide with PMVE led to the formation of indole **25a** in a high yield[18] (Scheme 17). An alternative approach was used for indoles bearing an electron-withdrawing group: the target indoles **25b-d** were obtained using a 40% aqueous solution of NaOH. The

low yield of indole **25c** was caused by partial hydrolysis of the cyano group under basic conditions.

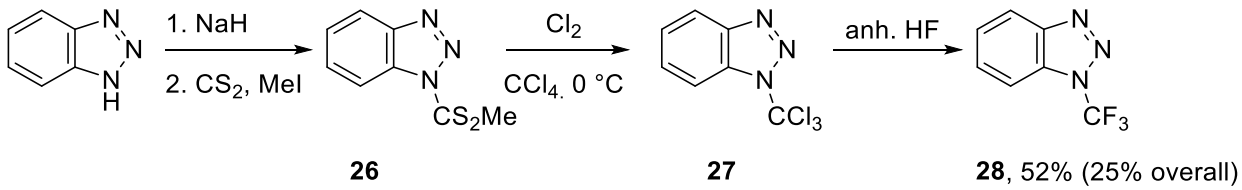


Scheme 17. Reactions of *NH*-indoles with PMVE.

Alkylation of indolides is widely investigated but is limited to highly basic conditions, which could pose some problems in the synthesis of more complex indole-containing structures.

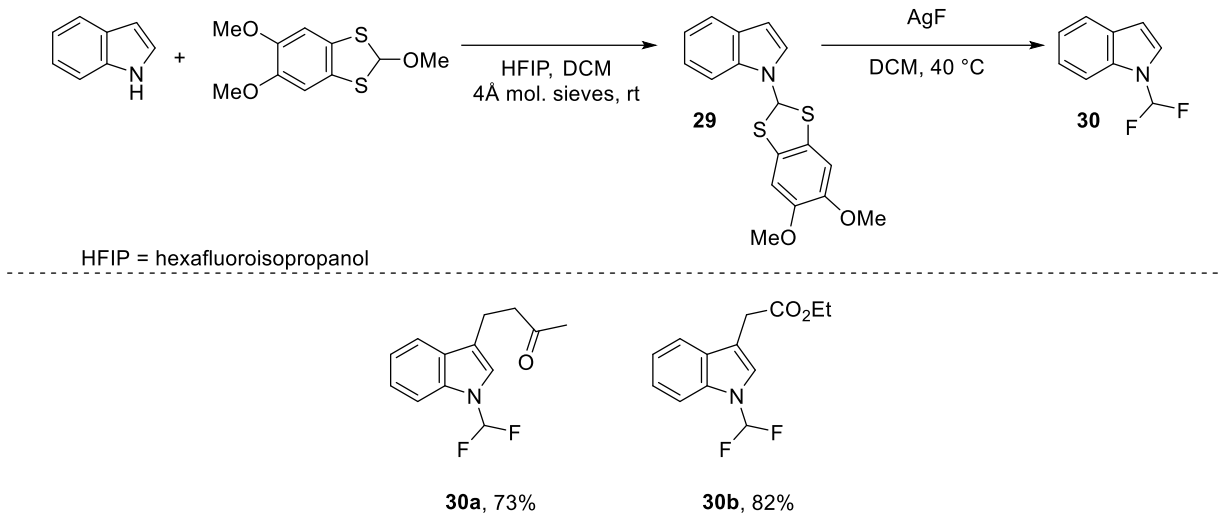
1.1.2 Fluorination of *N*-alkyl azoles and their analogs

These complications can be avoided when using strategy (b). For example, 1-trifluoromethylbenzotriazole can be obtained in three steps from unsubstituted benzotriazole (Scheme 18).[25] A drawback of the method is the necessity of using highly toxic anhydrous hydrofluoric acid in the last step.



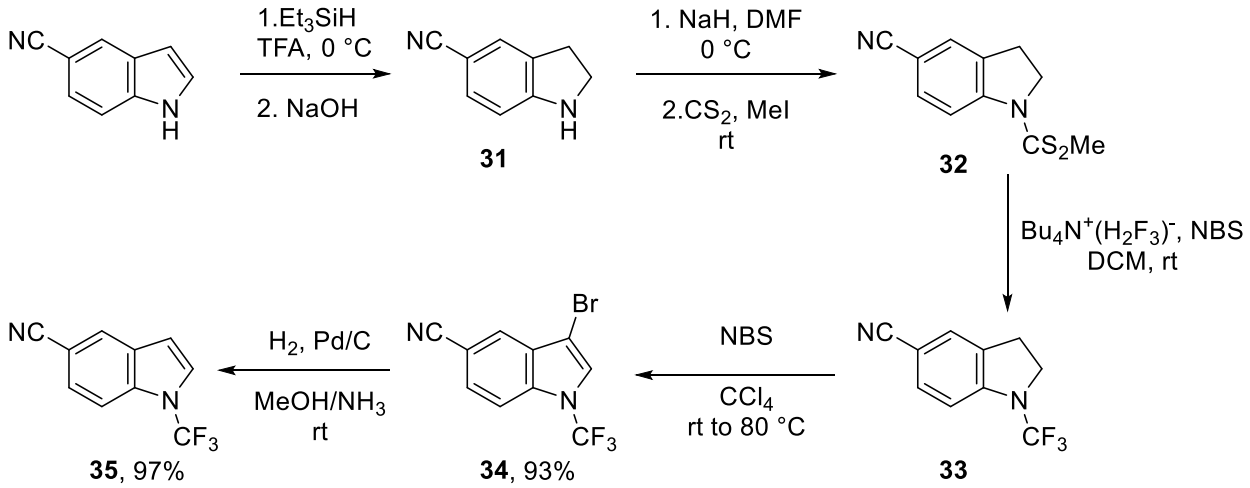
Scheme 18. Synthesis of 1-trifluoromethylbenzotriazole.

A recent study introduced a unique approach based on AgF-promoted desulfurative fluorination of dithioles.[26] Using a two-step synthetic method, indoles **30a-c** were obtained (Scheme 19).



Scheme 19. Synthesis of indoles **30**.

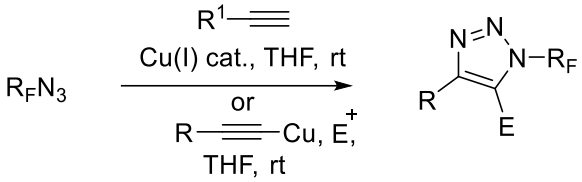
Direct trifluoromethylation of *NH*-indole by the Togni reagent resulted in exclusive C-H substitution and thus, a different method was required for this purpose.[27] A less straightforward approach to access the *N*-fluoroalkyl group on the indole was a prior reduction of the pyrrole ring of the indole, two-step fluoroalkylation, and oxidation back to indole (Scheme 20).[28] Indole **34** can be further modified by reduction, affording non-brominated indole **35**. The demonstrated approach was lengthy but proceeded in mild conditions with excellent yield of the target indoles.



Scheme 20. Synthesis of *N*-trifluoromethylated indoles **34** and **35**.

1.1.3 Cyclization approaches.

Strategy (c) includes a vast amount of reaction types, all leading to the formation of *N*-fluoroalkyl heterocycles[29]. The one that is particularly important for this Thesis is the copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC), a representative of click chemistry. Utilizing a wide scope of newly presented fluoroalkyl azides[30–33] our group demonstrated their use in 1,2,3-triazole synthesis (Scheme 21).

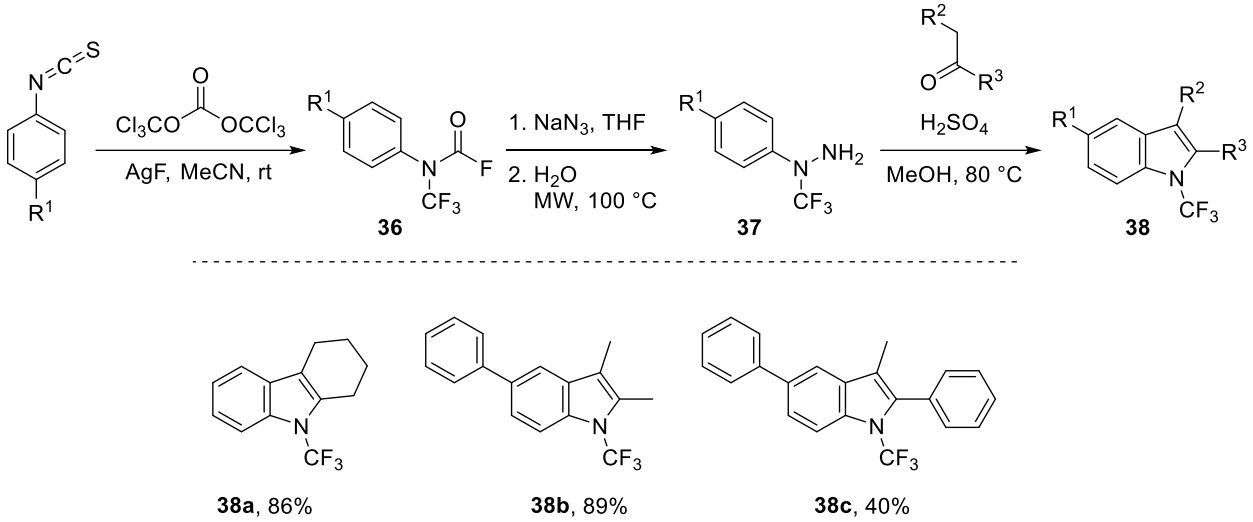


R_F = CF_3, C_2F_5, HCF_2, FCH_2, $PhSO_2CF_2$, $PhOCF_2CF_2$, $PhSCF_2CF_2$, HCF_2CF_2, $BrCF_2CF_2$

E = H, I, Br, allyl

Scheme 21. Use of fluoroalkyl azides in 1,2,3-triazole synthesis.

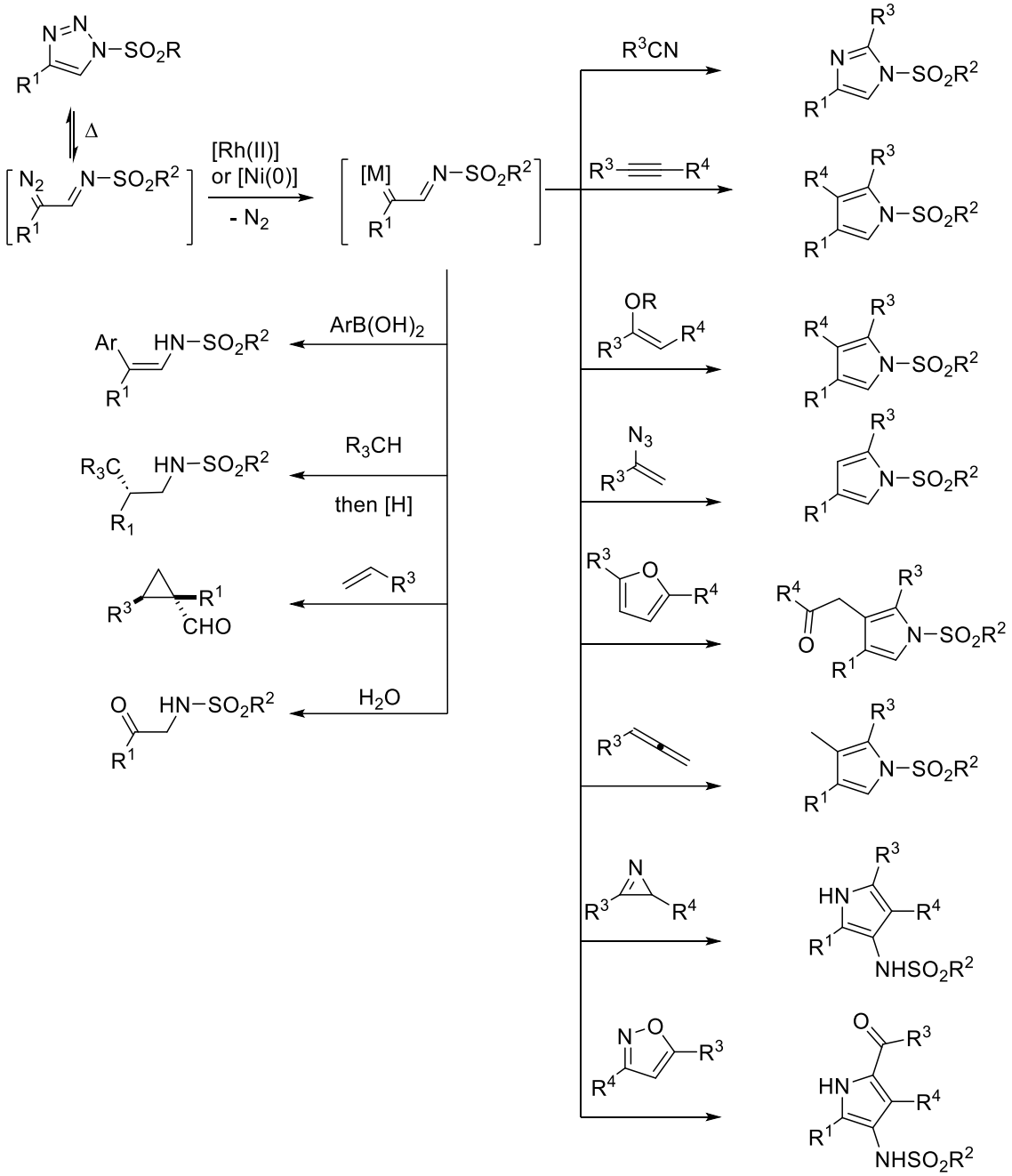
N-CF_3 hydrazines can form *N*-trifluoromethyl indoles under typical Fischer indole synthesis conditions (Scheme 22). *N*-CF_3 hydrazines **37** were prepared in three steps from isothiocyanates. Indoles **38** were formed in moderate to high yields. Unfortunately, the reaction is limited to *N*-trifluoromethyl substrates and 2,3-substituted indoles.



Scheme 22. Fischer indole synthesis of indoles **38**.

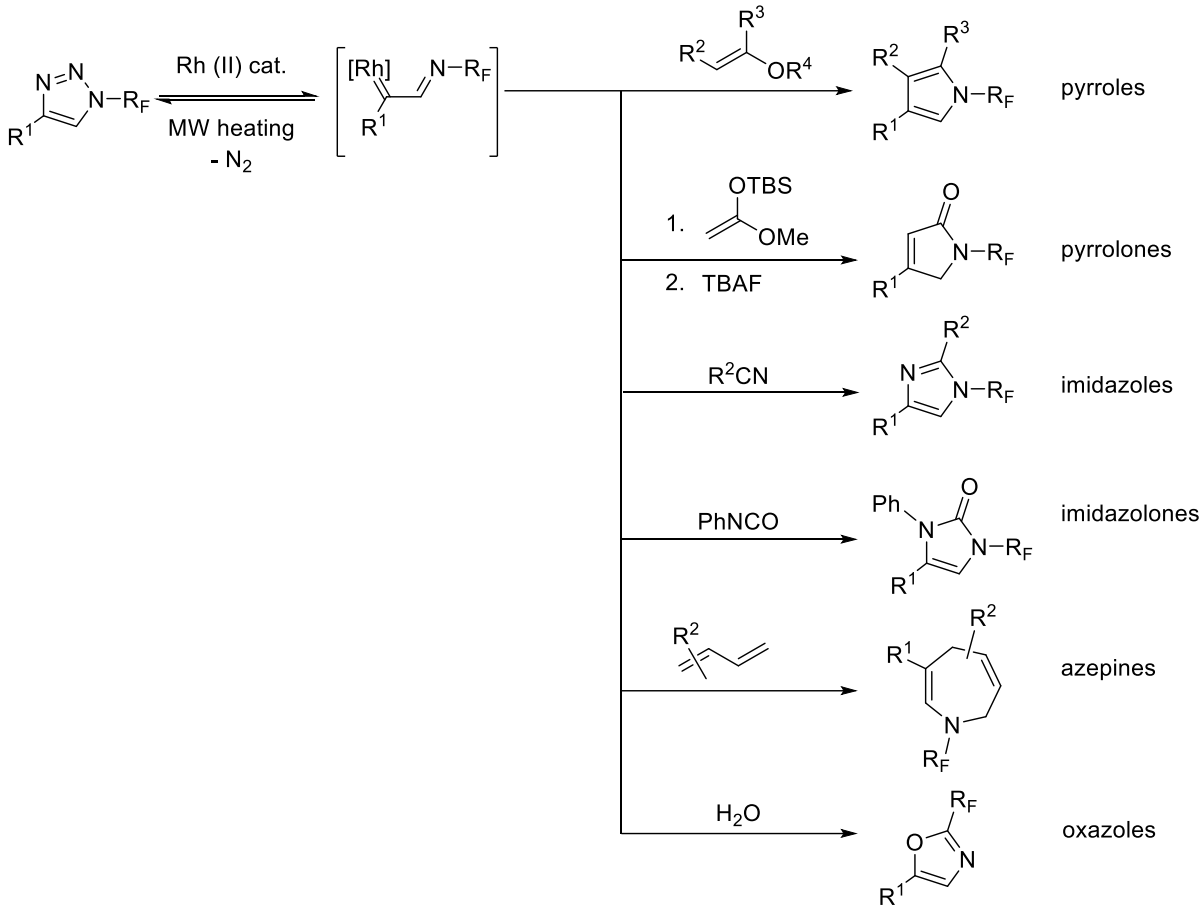
1.1.4 Transannulation approach

Another synthetic strategy is the transannulation of *N*-fluoroalkyl-1,2,3-triazoles (strategy d). It is known that *N*-sulfonyl triazoles exist in equilibrium with the diazoimine tautomer. Rhodium(II) catalyst facilitated the ring-chain isomerization of the triazole and the subsequent nitrogen expulsion. This way, *N*-sulfonyl triazoles offered an entry to rhodium(II)-stabilized imino metallocarbenes. Rhodium(II)-stabilized carbenes underwent a variety of reactions, including hydrolysis, cycloaddition, C–C bond formation, C–H bond functionalization, as well as ylide formation (Scheme 23).[34] Transannulation reactions have an important place among these modifications. Providing easy access to various heterocycles, the reaction was widely studied on various *N*-sulfonyl-1,2,3-triazoles.[35–37]



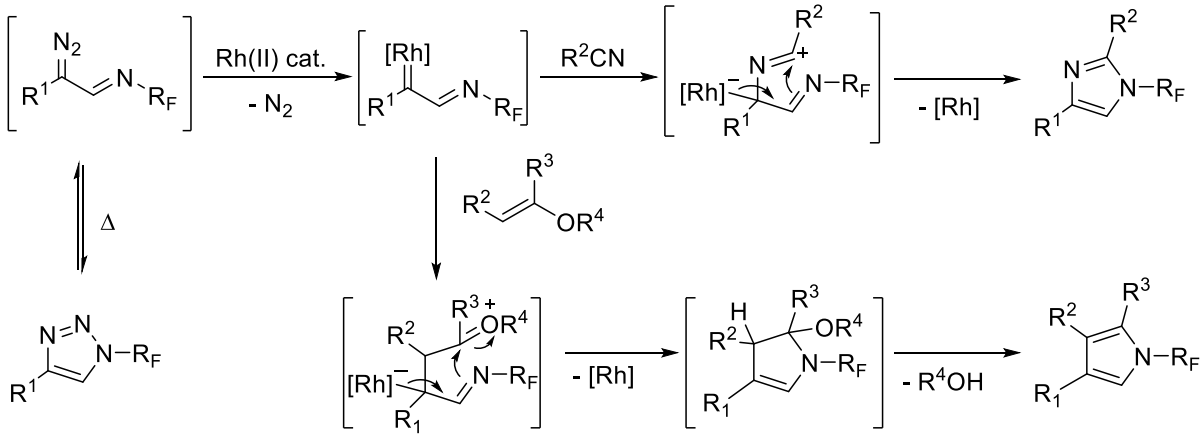
Scheme 23. Reactivity of *N*-sulfonyl-1,2,3-triazloes in transannulation reactions.

In our group, it was shown that *N*-fluoroalkyl-1,2,3-triazoles can undergo similar Rh(II)-catalyzed transformations, leading to new heterocycles[38–41] (Scheme 24), thermal rearrangement to ketenimines,[42] and acid-mediated reactions to vinyl triflates[43] and imidoyl halides[43]. Using the developed methods, previously unknown *N*-(per)fluoroalkyl pyrroles, pyrrolones, imidazoles, imidazolones,[38] azepines[39] and oxazoles[40,41] can be efficiently prepared.



Scheme 24. *N*-fluoroalkyl-1,2,3-triazoles in transannulation reactions.

Similar to *N*-tosyl-1,2,3-triazoles, the initial step in the transannulation reaction was heat-induced ring opening and the formation of rhodium carbenoid species (Scheme 25). The formed carbenoid then reacted with (in the demonstrated example) the nitrile molecule. Cyclization and [Rh] elimination produced the product.



Scheme 25. Mechanism of *N*-fluoroalkyl-1,2,3-triazoles transannulation reactions.

The reaction between *N*-fluoroalkyl-1,2,3-triazoles and various vinyl ethers resulted in the formation of substituted pyrroles (Scheme 24). This approach allowed access to previously unreported *N*-trifluoromethyl-substituted pyrroles. Unlike the methods described in chapter 1.1.1.1 of this Thesis, no work with dangerous gases was required. The approach gave access to mono- and disubstituted pyrroles.

The presented approach to *N*-(per)fluoroalkyl azoles is atom-economic, and the only by-product of the reaction is non-toxic nitrogen gas. Easily available starting materials opened access to various azoles, and a wide variety of fluoroalkyl moieties allowed tuning the properties of the target products.

2. Aims of the thesis

The objectives of this Thesis are to investigate the reactivity of *N*-fluoroalkyl-1,2,3-triazoles and to present novel synthetic approaches to diverse azoles with *N*-fluoroalkyl groups. To achieve these objectives, the Work will tackle the following synthetic tasks:

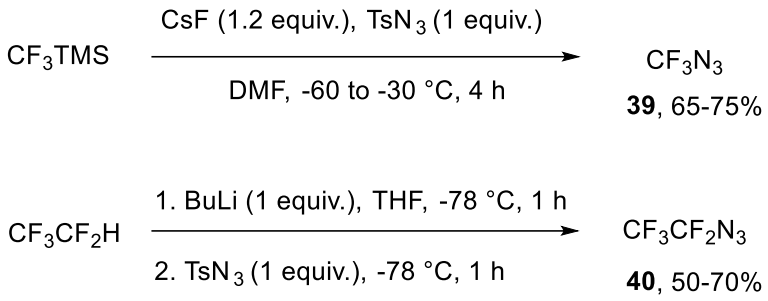
1. Exploration of reactivity of *N*-fluoroalkyl-1,2,3-triazoles in rhodium(II)-catalyzed reactions with alkynes to access *N*-fluoroalkyl-substituted pyrroles and investigation of their reactivity.
2. Preparation of 4-cyclohexenyl substituted *N*-fluoroalkyl-1,2,3-triazoles and exploration of reactivity of *N*-fluoroalkyl-1,2,3-triazoles in rhodium(II)-catalyzed reactions.
3. Exploration of a one-pot synthetic process to *N*-fluoroalkyl indoles from 4-cyclohexenyl substituted *N*-fluoroalkyl-1,2,3-triazoles and investigation of their reactivity.

3. Results and discussion

3.1 Reactivity of *N*-fluoroalkyl-1,2,3-triazoles with alkynes in rhodium-catalyzed reactions

3.1.1 Preparation of starting materials

The work started with the preparation of starting materials required for the synthesis of the scope of triazoles. While all used acetylenes were commercially available, azides were prepared according to procedures developed in our group (Scheme 26).[30]



Scheme 26. Synthesis of the starting azides.

The obtained fluoroalkyl azides were used in CuAAC reaction to obtain triazoles. All the obtained triazoles were shelf-stable solids and were prepared on a 5-10 mmol scale. The triazoles were previously reported[30] by our group and did not require additional characterization.

3.1.2 Rhodium(II)-catalyzed reactions with alkynes

Inspired by the work of Gevorgyan and colleagues on the transannulation of *N*-tosyl-1,2,3-triazoles with terminal alkynes[44], we subjected *N*-fluoroalkyl-1,2,3-triazoles to reactions with alkynes.

Triazole **41a** reacted with phenylacetylene in cyclohexane at 70 °C. The reaction resulted in full conversion of the starting triazole **41a**. Against expectations, GCMS (Figure 1) and ^{19}F NMR (Figure 2) analyses of the crude reaction mixture showed the formation of two products with the same molecular weight and ^{19}F NMR shifts (singlets) approximately 5 ppm apart.

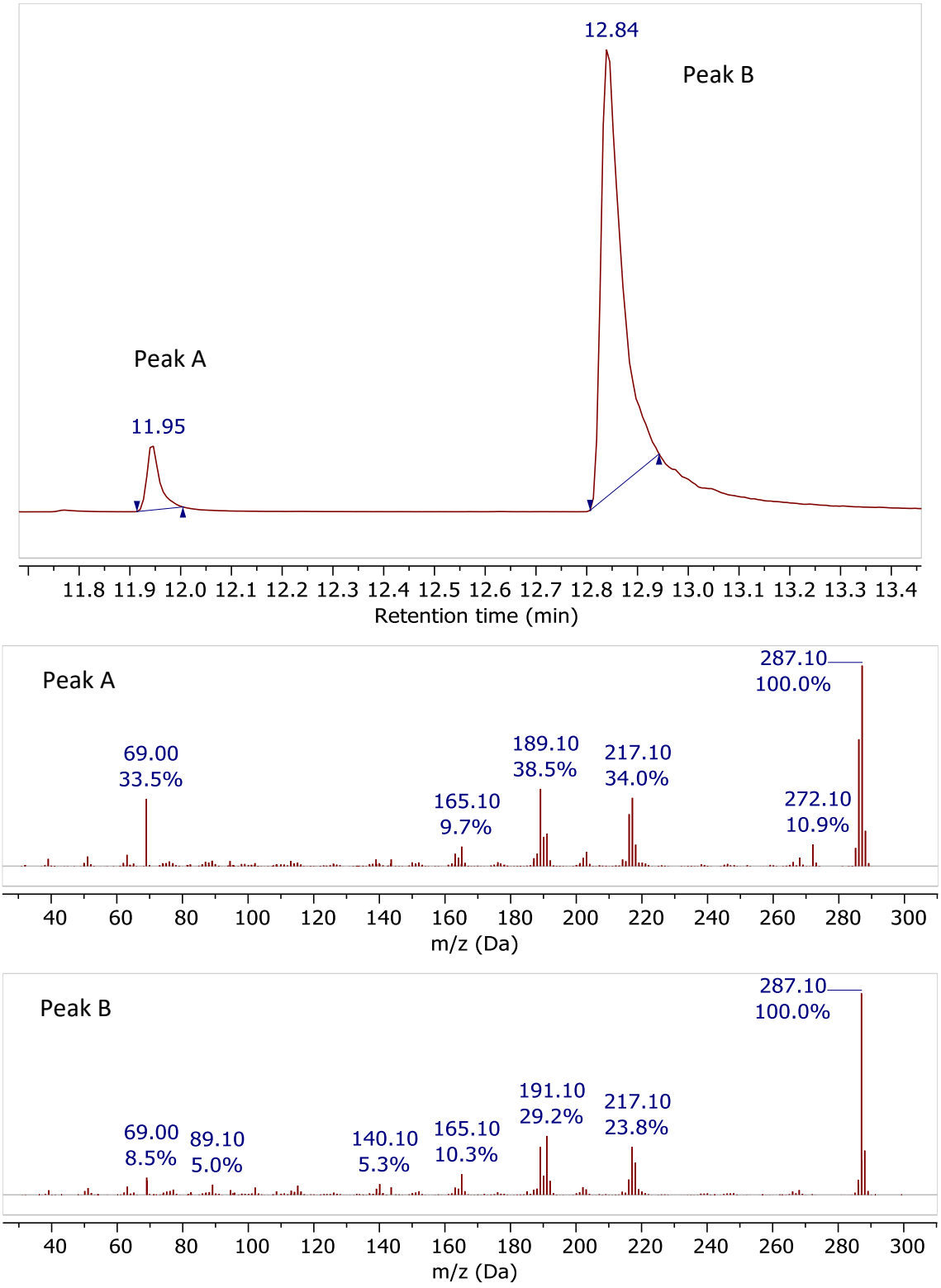


Figure 1. GCMS analysis of the crude reaction mixture.

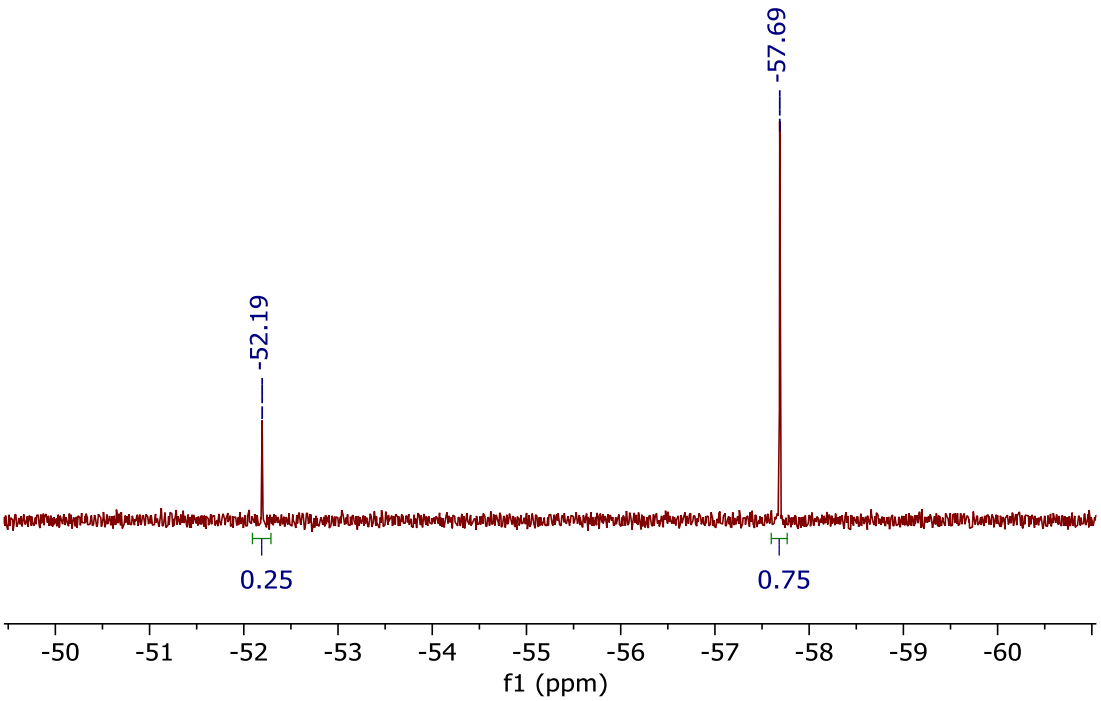
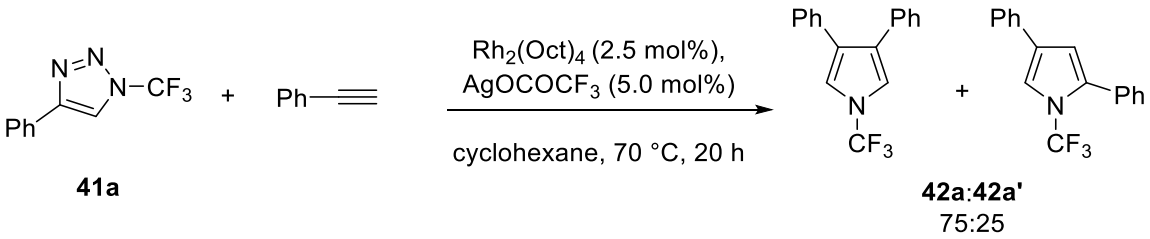


Figure 2. ^{19}F NMR (377 MHz, $CDCl_3$) analysis of the crude reaction mixture.

With the help of HMBC NMR analysis, it was discovered that both 2,4-diphenyl-1-(trifluoromethyl)-1*H*-pyrrole (**42a**) and 3,4-diphenyl-1-(trifluoromethyl)-1*H*-pyrrole (**42a'**) were formed in the reaction (Scheme 27).

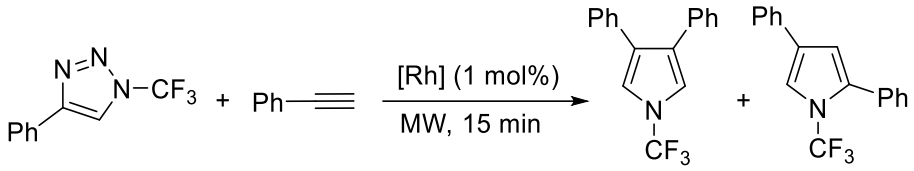


Scheme 27. Reaction of triazole **41a** with phenylacetylene.

During optimization, it was found that the reaction proceeded well in the absence of a silver catalyst (which was required in the case of *N*-tosyl-1,2,3-triazoles). Other transition metal catalysts known to form carbenoids with triazoles were not efficient in the transannulation (tested catalysts: $NiCl_2$, $Pd_2(OAc)_6$, $Pd(acac)_2$, CuMeSal, CuCl, CuI, $Cu(OTf)_2$, CuOAc, dppe$NiCl_2$). Furthermore, repeating the reaction under microwave-assisted conditions which were effective for the transannulation of researched triazoles,[38] also led to the formation of both pyrrole products with the same ratio (Table 1). The reaction was optimized with respect

to the catalyst, solvent and temperature. Chloroform was found to be the most suitable solvent (Entry 2). $Rh_2(esp)_2$ was chosen as the catalyst of choice because it gave the best **42a:42a'** ratio. The reaction could be carried out even at 80 °C (Entry 8), but heating to 100 °C for 20 min was used in later experiments.

Table 1. Reaction conditions screening for the transannulation of triazole **41a** with phenylacetylene.

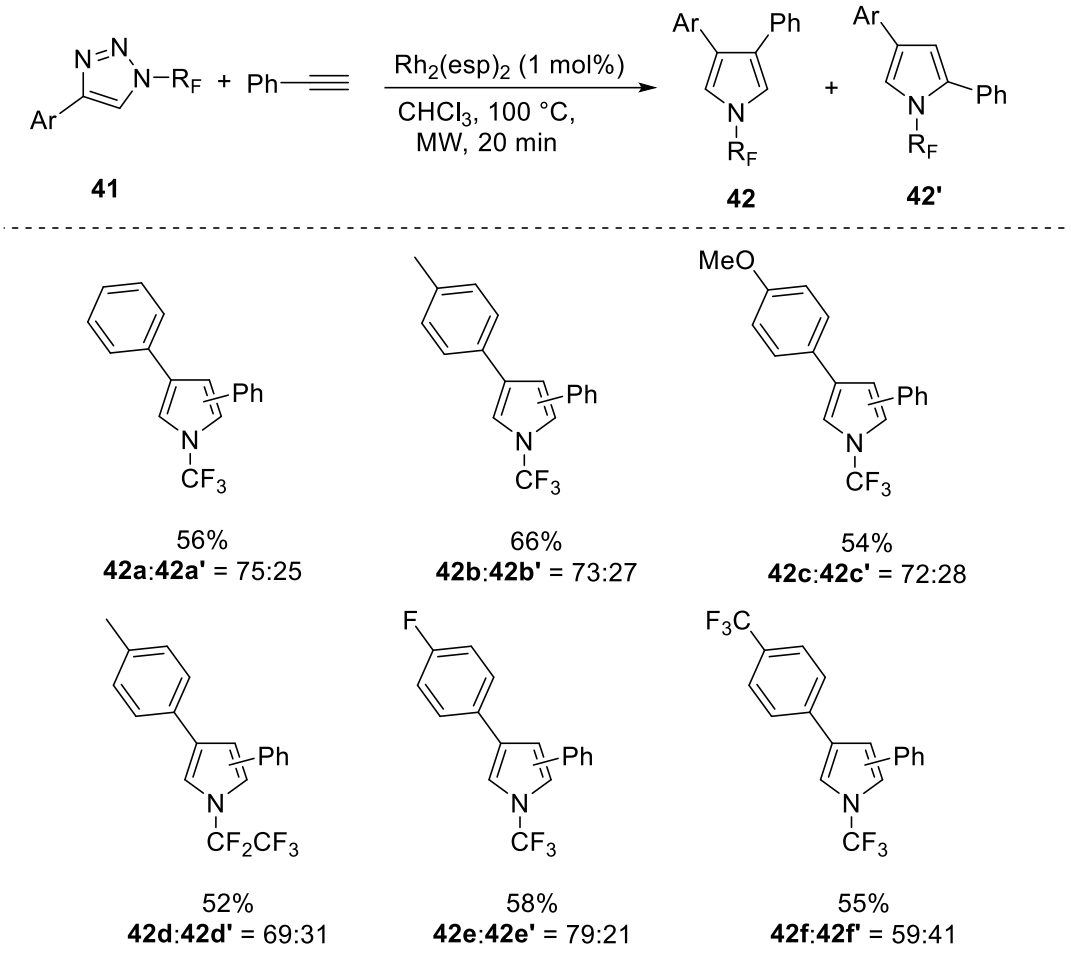


41a (3 equiv.) **42a** **42a'**

Entry	[Rh]	Solvent	Temp. (°C)	Conv. (%)[a]	**42a:42a´**
1[b]	$Rh_2(Oct)_4$	Cyclohexane	120	90	75:25
2	$Rh_2(Oct)_4$	$CHCl_3$	120	100	60:40
3	$Rh_2(OAc)_4$	$CHCl_3$	120	100	34:66
4	$Rh_2(esp)_2$	$CHCl_3$	120	100	75:25
5	$Rh_2(pfb)_4$	$CHCl_3$	120	54	14:86
6	$Rh_2(esp)_2$	$CHCl_3$	100	100	75:25
7	$Rh_2(esp)_2$	DCE	100	100	40:60
8	$Rh_2(esp)_2$	$CHCl_3$	80	100	75:25
9	$Rh_2(esp)_2$	$CHCl_3$	60	0	-

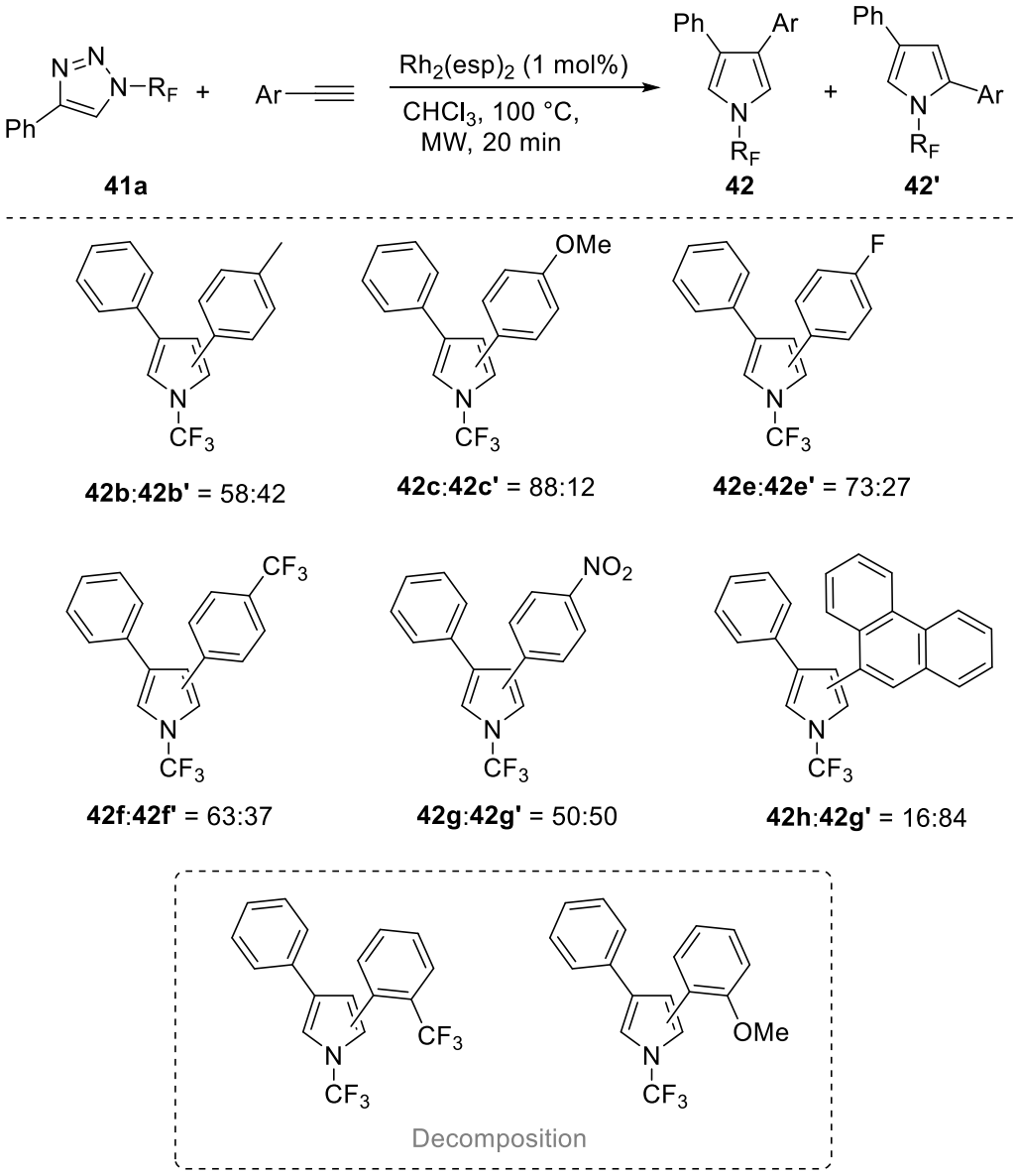
[a] Conversion of **41a** determined by ^{19}F NMR. [b] The same result was observed in the presence of CF_3COOAg (5 mol%) in addition to $Rh_2(Oct)_4$ (1 mol%).

Under optimized conditions (Entry 6, Table 1), a range of different substituted triazoles (Scheme 25) were tested in the reaction with phenylacetylene. No direct correlation between the ratio of the pyrrole products **42** and **42'** was observed, but it is likely that the presence of an electron-withdrawing group on the phenyl substituent of triazole **41** favoured the 2,4-substituted pyrrole **42'**.



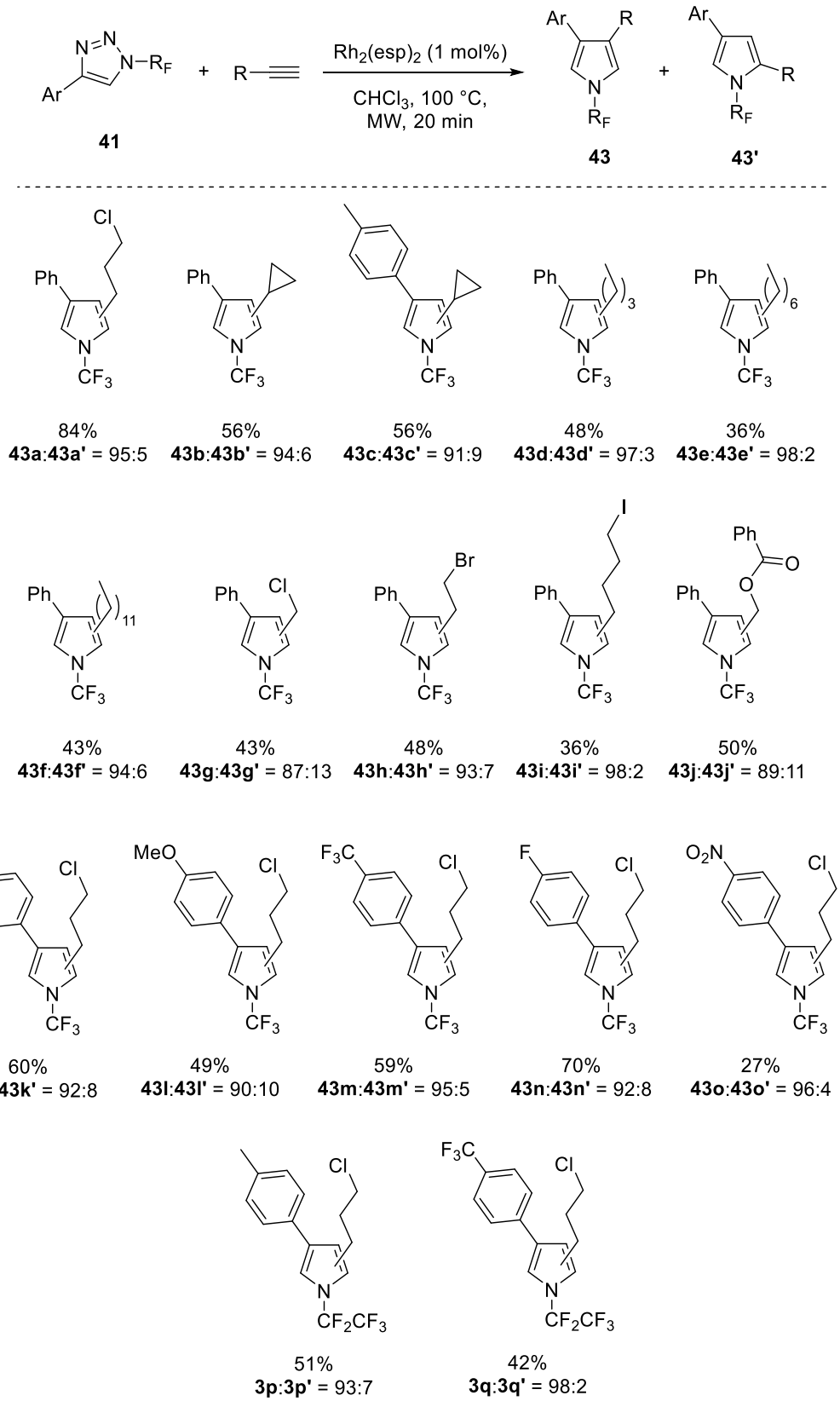
Scheme 28. Reactivity of triazoles **41** with phenylacetylene.

Even though the starting terminal arylalkynes were not separable from the reaction mixture due to the high boiling point of the alkynes and similar retention factor (R_f) values, a small scope of transannulations was performed to further investigate the influence of substituents on the product regioselectivity (Scheme 29). While using a bulky acetylene shifted the ratio of the products **42l** to **42l'** towards the less strained pyrrole **42l'**, no clear pattern of the influence of electron-withdrawing properties of substituents was found. Reactions of triazole **41a** with phenylacetylenes with substituents in the *ortho*-position resulted in total product decomposition.



Scheme 29. Ratios of pyrroles **42** to **42'** determined by ^{19}F NMR analysis.

While aliphatic alkynes were found inefficient in transformations with *N*-tosyl-1,2,3-triazoles,[44] surprisingly, the reaction with *N*-perfluoroalkyl-1,2,3-triazoles showed not only good reactivity but also unexpected selectivity for the formation of 3,4-substituted-1-(perfluoroalkyl)-1*H*-pyrroles **43** (Scheme 30). The **43**:**43'** ratio varied between 87:13 and 98:2 and most compounds were characterized as mixtures.

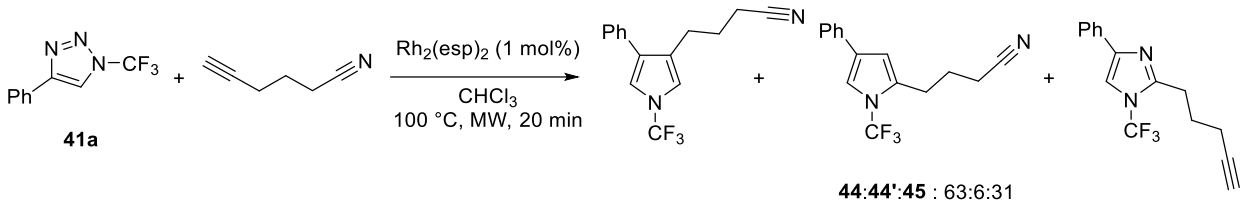


Scheme 30. Transannulation reactions of triazoles **41** with aliphatic alkynes.

A wide range of acetylenes was tested in the reaction. The least selective reactions (products **43g**/**43g'** and **43j**/**43j'**) had only one CH_2 group between the pyrrole ring and the bulky substituent, leading to a slight shift towards the formation of the less sterically hindered 2,4-substitution product.

3.1.3 Competitive reaction of **41a** with 5-hexynenitrile

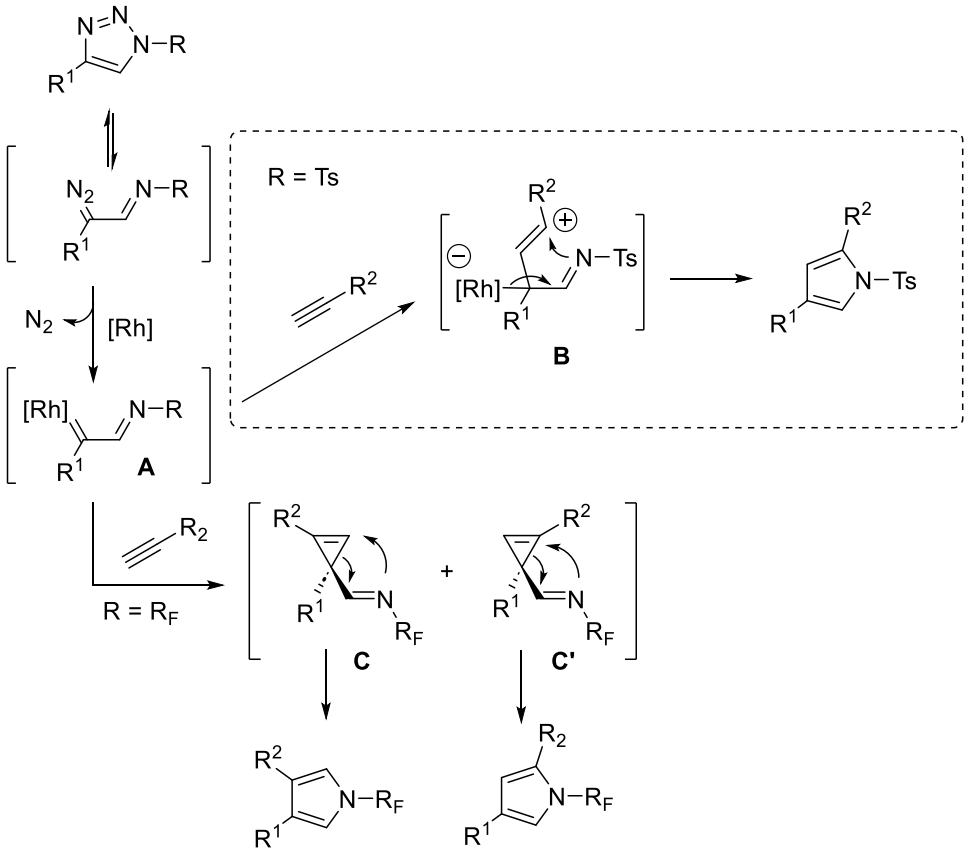
N-(per)fluoroalkyl-1,2,3-triazoles are known to react with nitriles in a transannulation reaction to form imidazoles.[38] If both nitrile and alkyne moieties are present in the reaction, a competitive reaction occurs. The reaction with 5-hexynenitrile resulted in the formation of one imidazole and two pyrrole products (Scheme 31). While 3,4-substituted pyrrole remained the major regioisomer, imidazole **45** also readily formed in this reaction. No product of "double transannulation" on both reactive ends of the alkyne-nitrile reactant was observed.



Scheme 31. Reaction of triazole **41a** with 5-hexynenitrile.

3.1.3 Plausible reaction mechanism

In the work performed on *N*-tosyl-1,2,3-triazoles,[44] the proposed mechanism involved a direct nucleophilic attack of the terminal alkyne on the Rh iminocarbene **A**, resulting in zwitterion **B** (Scheme 32). Elimination of the Rh(II) catalyst resulted in the formation of 1,2,4-substituted pyrrole. Although the reaction did not proceed without the silver co-catalyst, its exact interaction with the reaction intermediates is unclear. In the reaction of *N*-perfluoroalkyl-1,2,3-triazoles, the formation of the 1,3,4-substituted pyrrole product was the major process, and therefore the reported mechanism cannot apply. Instead, I propose that the reaction of Rh(II) iminocarbene **A** with an alkyne results in the formation of cyclopropene intermediates **C** and **C'** which later rearrange into the observed pyrroles (Scheme 32).



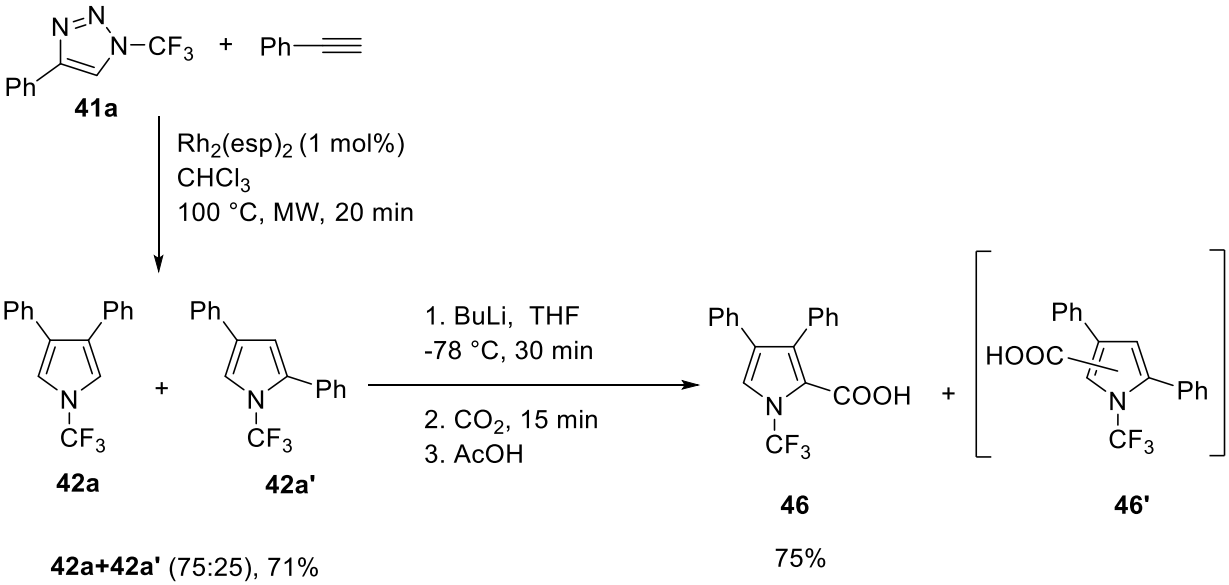
Scheme 32. Comparison of the proposed reaction mechanisms.

3.1.4 Modification of the pyrrole ring

Since the formed pyrroles were found to be unstable on air and oxidized over time, immediate modification of the product was attempted in order to stabilize the material.

My initial attempt was Friedel-Crafts acylation with acyl chloride using $AlCl_3$ as the catalyst. Unfortunately, the reaction was unsuccessful.

On the other hand, the lithiation-carboxylation sequence afforded the desired product **46** which was purified via recrystallization and fully characterized (Scheme 33).



Scheme 33: Carboxylation of pyrrole **42a**.

3.1.5 Conclusions and Outlook

The transannulation reaction of *N*-perfluoroalkyl-1,2,3-triazoles with terminal alkynes was investigated. This procedure was found to be efficient for the synthesis of 1,3,4-trisubstituted pyrroles from various 4-substituted *N*-perfluoroalkyl-1,2,3-triazoles and aliphatic terminal alkynes. It was also shown that a competitive reaction between nitrile and alkyne reactive moieties can take place. A mechanistic rationale for the observed reactivity was proposed. From the reaction mechanism point of view, the reaction of *N*-perfluoroalkyl-1,2,3-triazoles with terminal alkynes is different from the one of *N*-tosyl-1,2,3-triazoles. The transannulation proceeded not only in the absence of silver co-catalyst, leading to two regioisomer products, but it was also found that electron-deficient arylalkynes and all tested aliphatic alkynes were effective in this transformation.

3.2 Conversion of *N*-fluoroalkyl-1,2,3-triazoles to *N*-fluoroalkyl indoles

Indole rings are found in many natural and biologically active compounds. While in many cases the presence of the *N*-H bond of indoles is necessary to preserve the biological activity,[45] several *N*-R substituted indole-containing drugs are present on the market (Figure 3).

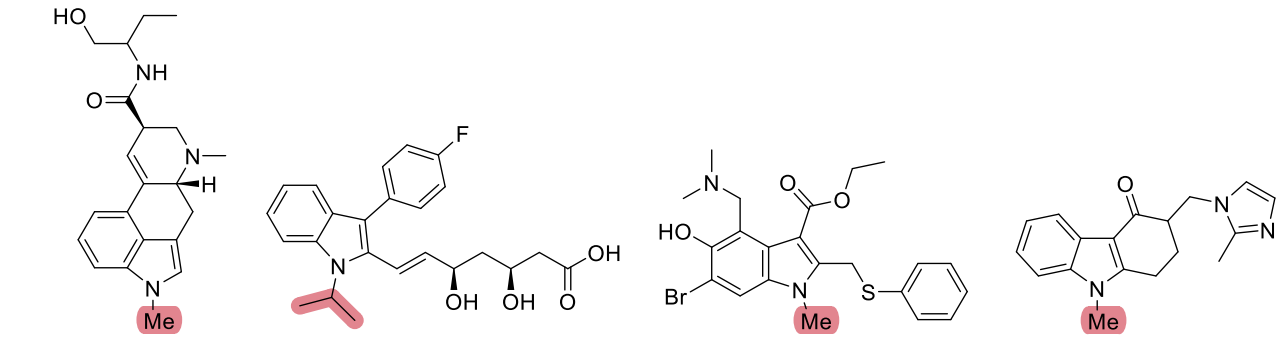
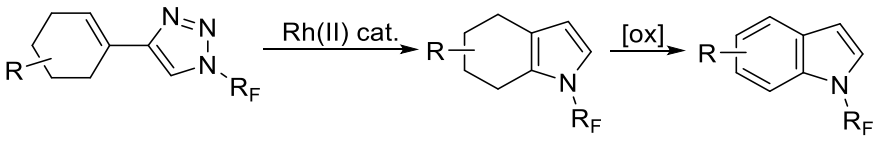


Figure 3. Selected *N*-substituted indole-containing drugs.

Introducing the fluoroalkyl moiety in a molecule is a way to enhance the properties of biologically active compounds.[46] Our research group has already shown many ways to obtain and apply fluoroalkyl azides in the synthesis of *N*-fluoroalkyl heterocycles, however, the synthesis of *N*-fluoroalkylated indoles was not attempted.

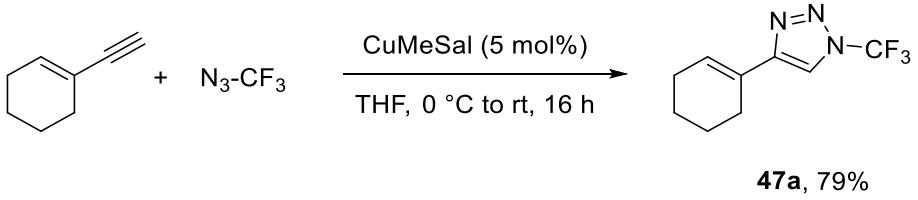
Based on the widely investigated reactivity of *N*-sulfonyl triazoles,[47] we devised a new strategy for the synthesis of *N*-fluoroalkyl indoles involving the CuAAC reaction, rhodium(II)-catalyzed transannulation and oxidation, resulting in previously unreported *N*-fluoroalkyl indoles (Scheme 34).



Scheme 34: General scheme of the planned transformations.

3.2.1 Conditions optimization

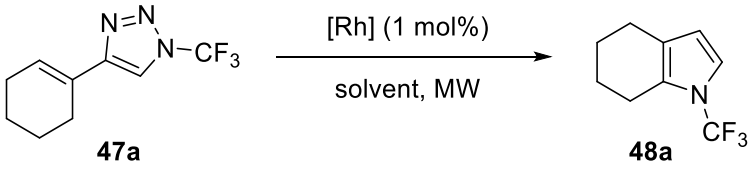
The synthetic approach was initially tested on the reaction of azidotrifluoromethane and ethynyl cyclohexene. Triazole **47a** was prepared according to the standard procedure[30] resulting in good yield (Scheme 35). Triazole **47a** is a colorless oil, sensitive to moisture or air exposure, and should be stored under inert atmosphere.



47a, 79%

Scheme 35. Preparation of triazole **47a**

Optimization of the transannulation step included testing various rhodium catalysts, solvents, and temperatures (Table 2). Conventional heating at 80 °C in chloroform was found to be inefficient and led to the formation of multiple products of decomposition. Therefore, all optimizations were performed using microwave-assisted heating. Similar to the reaction of pyrrole formation in the previous chapter, $Rh_2(esp)_2$ was found to be the most efficient catalyst for the tetrahydroindole formation (Entry 3). Chlorinated solvents (Entries 5, 8, 11) performed in the reactions better than non-chlorinated ones (Entries 7, 9, 10, 12).



47a **48a**

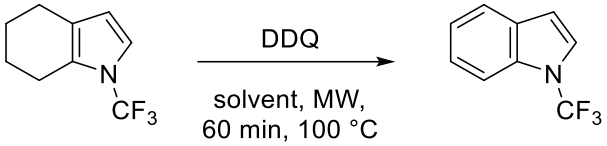
Entry[a]	Rh(II)	Solvent	Temp. (°C)	Time (min)	**48a** Yield (%)[b]
1	$Rh_2(Oct)_4$	$CHCl_3$	100	10	4[c]
2	$Rh_2(OAc)_4$	$CHCl_3$	100	10	22[c]
3	$Rh_2(esp)_2$	$CHCl_3$	100	10	50
4	$Rh_2(esp)_2$	$CHCl_3$	100	5	47[c]
5	$Rh_2(esp)_2$	$CHCl_3$	80	10	38[c]
6	$Rh_2(esp)_2$	DCE	100	10	50
7	$Rh_2(esp)_2$	Toluene	100	30	51
8	$Rh_2(esp)_2$	DCM	100	30	55
9	$Rh_2(esp)_2$	THF	100	30	0
10	$Rh_2(esp)_2$	DMF	100	30	0
11	$Rh_2(esp)_2$	DCE	100	30	64
12	$Rh_2(esp)_2$	Hexane	100	30	30

[a] Reaction conditions: **47a** (0.2 mmol), solvent (2 mL). [b] ^{19}F NMR yield, isolation was not attempted, [c] Full conversion of triazole was not achieved.

Table 2. Optimization of the transannulation of compound **47a**

The best NMR yield was found to be 64%. This might be related to the high reactivity of the *N*-CF_3 substituted pyrroles or intermediate rhodium carbenoid. As no substantial amount of side-products were formed in the reaction (according to ^{19}F NMR), polymerization or decomposition might have taken place during the reaction in the microwave reactor.

As the oxidation step was reported to proceed in a one-pot reaction starting from triazole, the oxidation step optimization was performed on the crude reaction mixture from the transannulation step.



48a **49a**

Entry[a]	Solvent	Time (min)	**49a** Yield (%)[b]
1	$CHCl_3$	60	38
2	DCE	60	89
3	Toluene	60	20[c]
4	DCM	60	93
5	$CHCl_3$	30	80[c]

[a] Reaction conditions: **47a** (0.2 mmol), solvent (2 mL). [b] ^{19}F NMR yield, isolation was not attempted, [c] Full conversion of pyrrole was not achieved.

Table 3. Oxidation of pyrrole **48a**.

Although toluene could be used in the transannulation step of the synthesis (Table 2, Entry 7), toluene could not compete with the performance of chlorinated solvents in the oxidation step (Table 3, Entry 3). While chloroform and DCM both showed good results, DCE was found to be the most suitable when taking into consideration the workup procedure and further modification of the obtained indole.

Indole **49a** is a volatile compound. An attempt to evaporate the solvent from the reaction mixture resulted in a substantial decrease of product yield. In order to characterize the compounds **48a** and **49a**, the synthesis was carried out in $CDCl_3$ and the crude mixtures were filtered through a short pad of alumina to remove impurities.

3.2.2 Reaction scope

To show the versatility of the proposed approach and to improve the handling of indoles, a line of optimizations was proposed. This allowed the modification of target indoles at different stages of the synthesis (Figure 4).

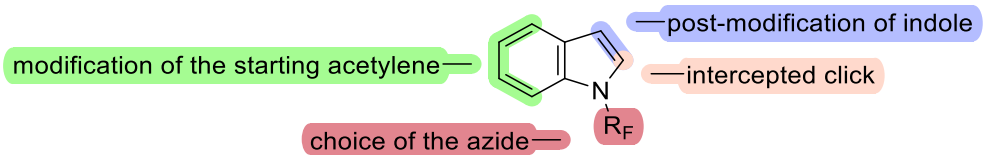
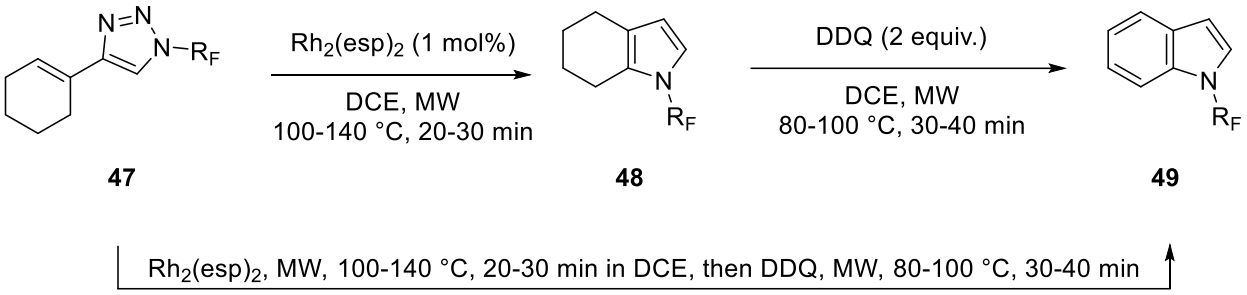


Figure 4. Suggested modification routes.

The suggested modifications included the variation of acetylenes used for the triazole synthesis, which aimed to improve the physical properties of the products. Using the variety of fluoroalkyl azides developed in our group, previously unreported *N*-fluoroalkyl indoles can be accessed. Finally, since indoles bearing electron-withdrawing groups on nitrogen are known to be deactivated towards electrophilic substitution, it is important to show the possibility of substituting the indoles directly.

3.2.2.1 Variation of the azide

Similar to *N*-trifluoromethyl indole which was reported to be volatile and thus was not even isolated,[19] both, fused pyrrole **48a** and indole **49a** have low boiling points, making the further manipulation of the compounds challenging. In an attempt to avoid these challenges, we synthesized triazoles **47b**-**d** using optimized conditions[30] and used them for the modification sequence affording indoles **49b**-**d** (Scheme 36). The optimized conditions for each of the substrates varied. For example, substrate **47b** was the fastest to undergo the transannulation and the subsequent oxidation, and substrate **47d** required higher temperatures to achieve the full conversion to pyrrole **48d** in 30 minutes. Indoles **49b** and **49d** did not show a significant increase in boiling point compared to indole **49a**: an attempt to distill indole **49b** from the crude reaction mixture resulted in a mixture of DCE and the target indole **49b**.



R_F = **b**, C_2F_5; **c**, CF_2SO_2Ph; **d**, CF_2CF_2H

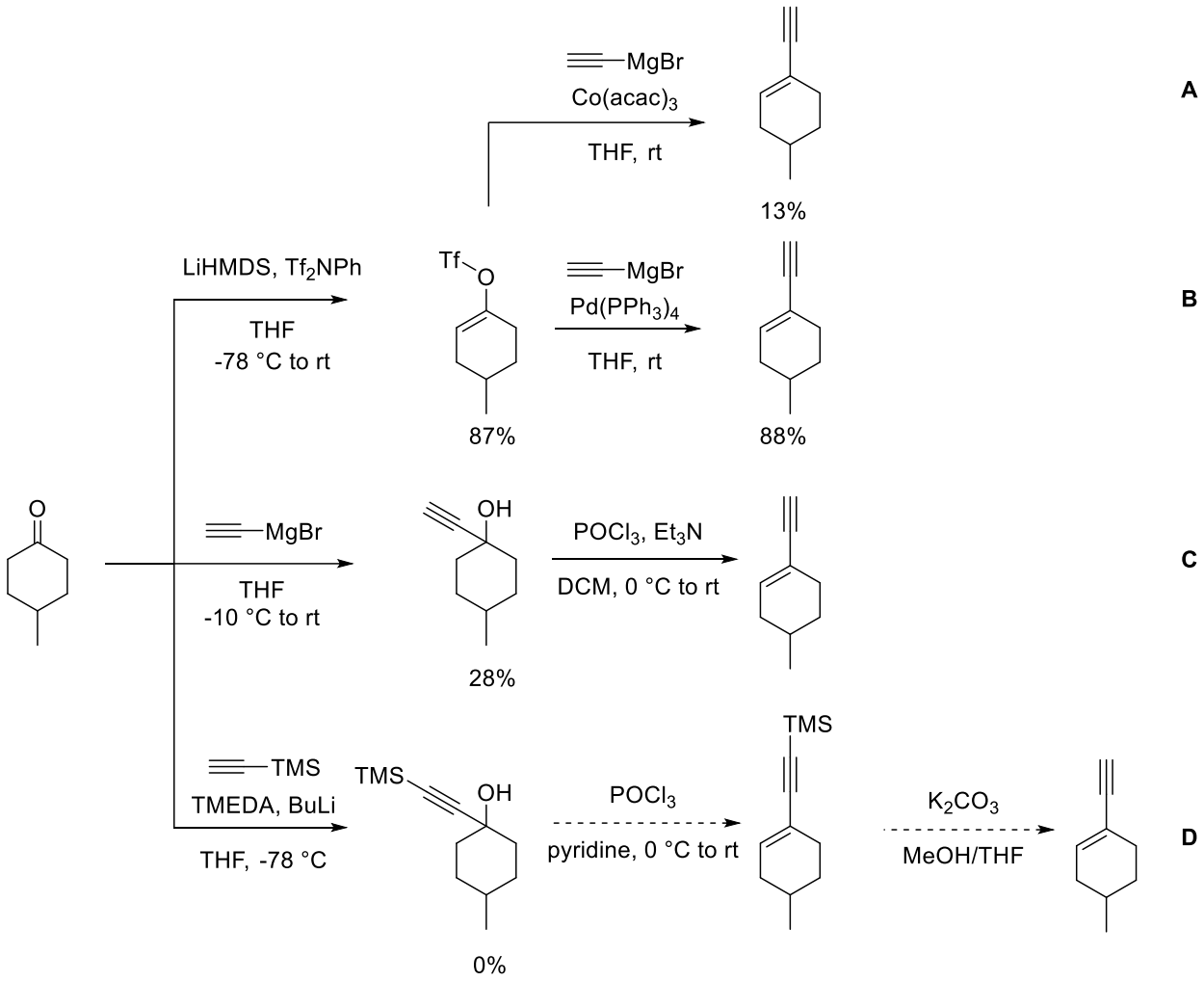
Compound and yield (%)	**47**	**48**	**49**[b]
b	60	10 (85)[a]	50 (87)[a]
c	80	42	50 (90)[a]
d	91	54	46

[a] ^{19}F NMR yield, [b] yield over two steps

Scheme 36. Reaction sequence for triazoles **47**.

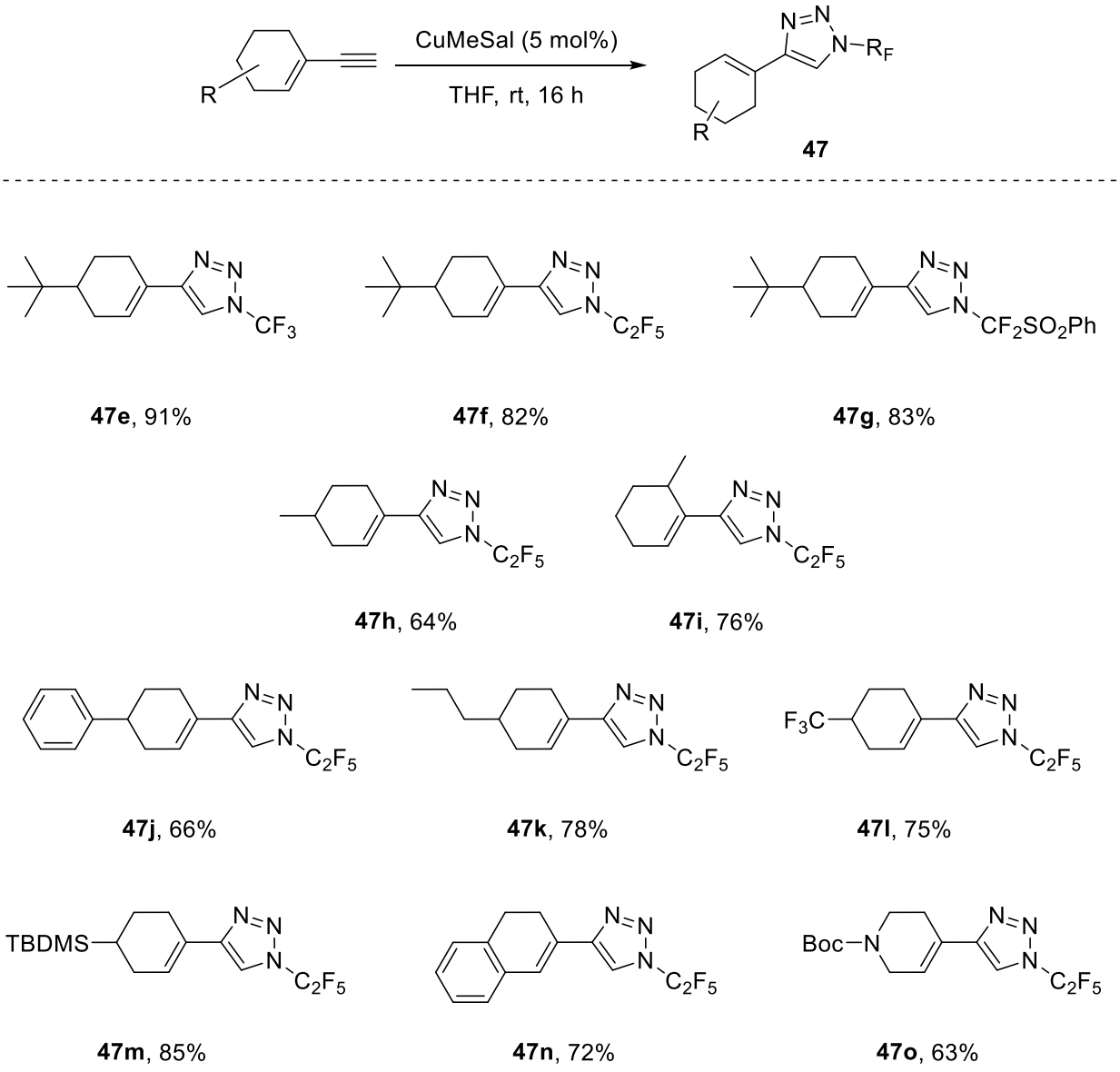
3.2.2.2 Variation of the alkyne substrate

To increase the scope of the indoles, several substituted cyclohexene acetylenes were prepared. The initial reproduction of the published approach used a two-step process: first, the preparation of a triflate from a cyclic ketone, then Kumada-type coupling using $Co(acac)_3$ (Scheme 37A). This approach did not result in satisfactory yields. Several other tactics were attempted and were found to be unsuitable (Scheme 37C, 37D). When the catalyst for the Kumada-type coupling was replaced with $Pd(PPh_3)_4$, high product yields were achieved (Scheme 37B). The optimized method was used for the synthesis of the scope of acetylenes.



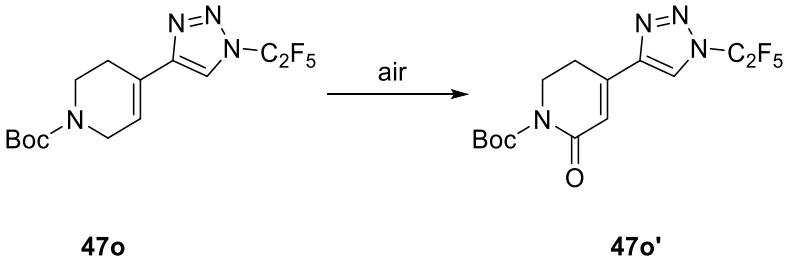
Scheme 37. Preparation of 1-ethynyl-4-methylcyclohex-1-ene.

The chosen approach limits the scope of acetylenes to the ones bearing substituents and functional groups unreactive to the Gringard reagent used in the first step of the synthesis. Using the prepared acetylenes, previously unreported triazoles with low to excellent overall yields were obtained (Scheme 38).



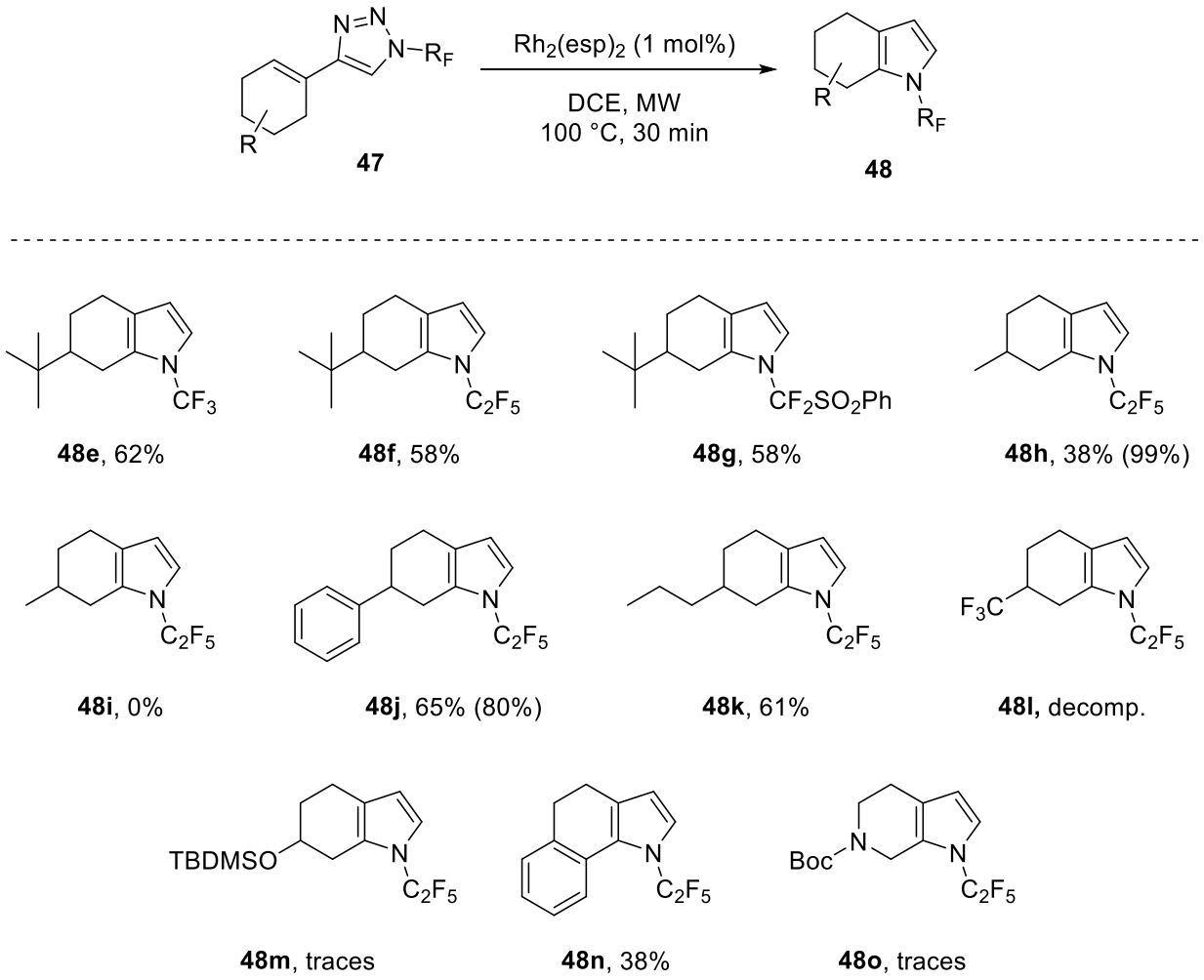
Scheme 38. Preparation of triazoles **47**.

Triazole **47o**, although formed, was not stable and oxidized to triazole **47o'** upon contact with air over time (Scheme 39).



Scheme 39. Oxidation of triazole **47o**.

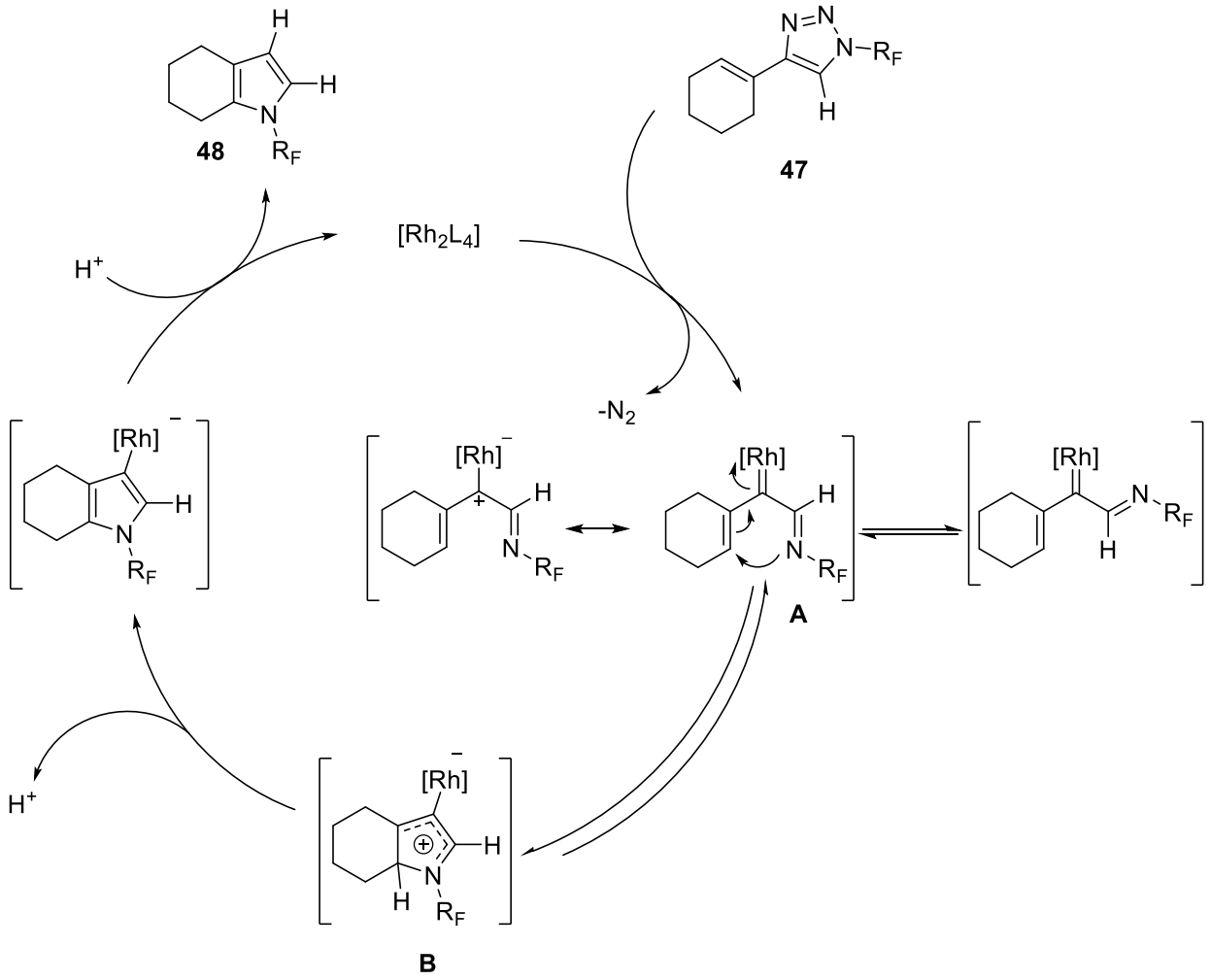
Having prepared the triazoles, transannulation reactions resulting in a scope of previously unreported *N*-fluoroalkylated fused pyrroles (Scheme 40) were performed. Bulky substituents on the cyclohexyl moiety decreased the volatility of the pyrrole products, making them easier to handle. However, there several limitations were observed. Products **48m** and **48o** formed in trace amounts, while an attempt to obtain product **48l** resulted in the full decomposition of the starting triazole **47l**. Having an electron-withdrawing group attached to the cyclohexyl moiety led to destabilization of the forming rhodium carbenoids and partial or full decomposition. Triazole **47i** was not reactive under the investigated reaction conditions and was excluded from the investigation scope.



Scheme 40. Transannulation of triazoles **47**.

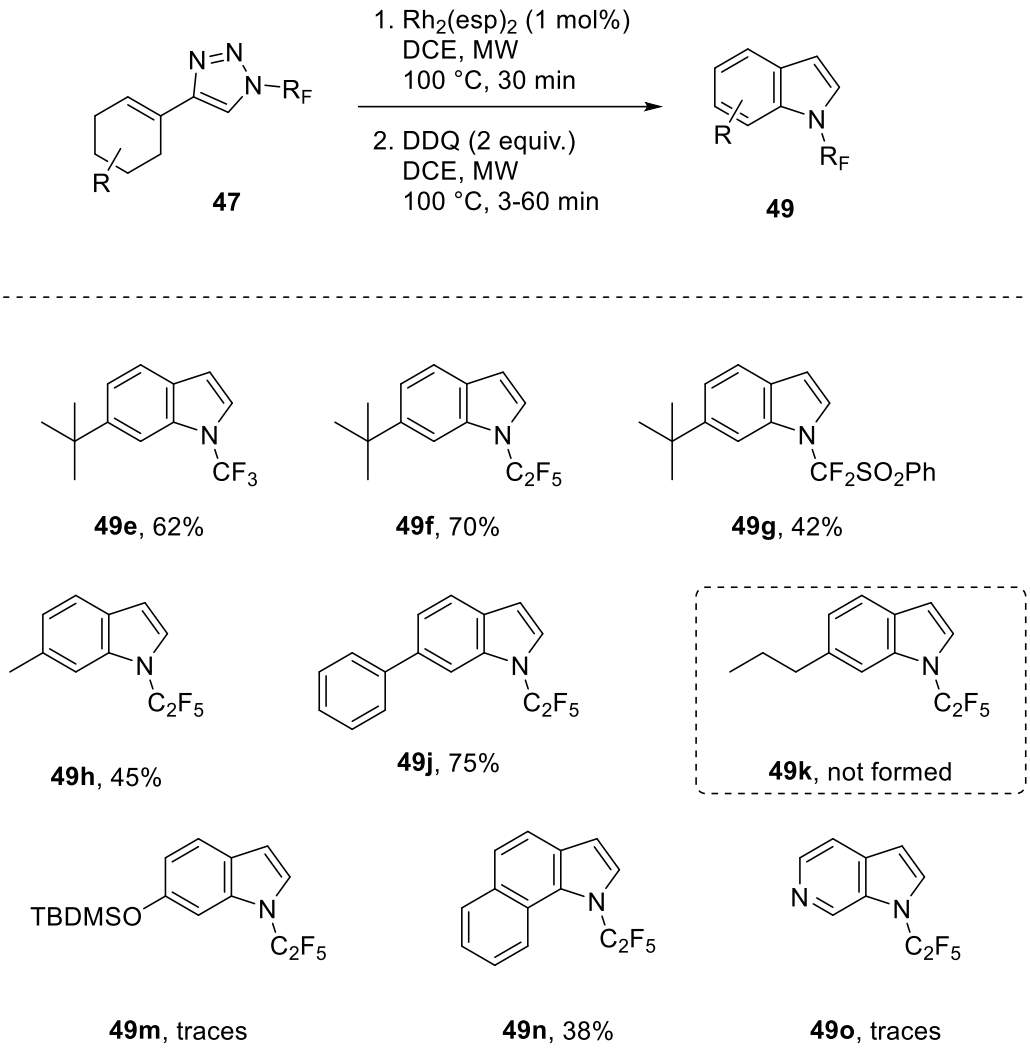
According to the proposed mechanism (Scheme 41), heating of triazole **47** in the presence of the rhodium catalyst generates rhodium-stabilized iminocarbene intermediate **A**. When the iminocarbene intermediate adopts the s-*trans* geometry it undergoes a 4π electrocyclization,

resulting in the formation of cation **B**. Subsequent aromatization and rhodium elimination produces pyrrole **48**.



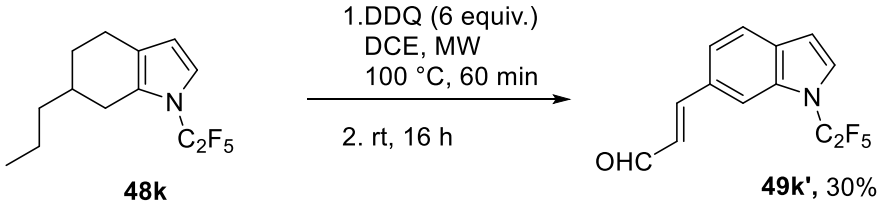
Scheme 41. Proposed mechanism of pyrrole **48** formation.

The synthesis of indoles **49** was performed in a one-pot reaction starting from triazoles **47** (Scheme 42). Due to the strong influence of the electron-withdrawing substituents, indoles **49m** and **49o** were formed only in trace amounts. While most of the reactions resulted in the desired indoles, the reaction of propyl-substituted triazole **47k** did not provide indole **49k** upon oxidation.



Scheme 42. Synthesis of indoles **49**.

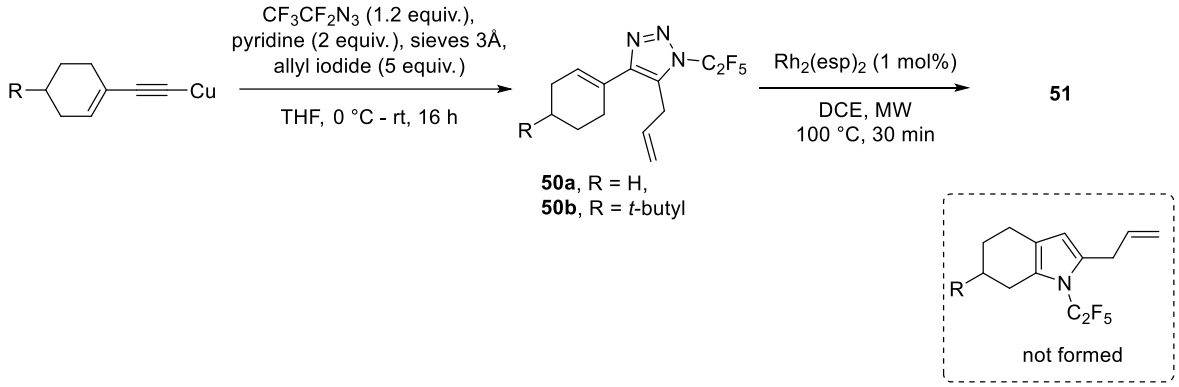
Tetrahydroindole **48k** was isolated and oxidized with an excess of DDQ. After 60 min of microwave irradiation at 100 °C several products of partial oxidation were observed. Overnight oxidation resulted in the formation of α,β-unsaturated aldehyde **49k'** (Scheme 43).



Scheme 43. Formation of aldehyde **49k'**.

3.2.2.3 Intercepted click

Using a method developed in our group,[48] 1,4,5-substituted triazoles **50a** and **50b** were obtained. The transannulation reaction resulted in a single pure product **51** of unknown structure. The expected tetrahydroindoles were not formed (Scheme 44).

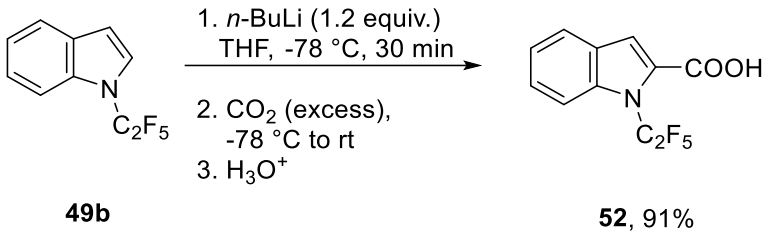


Scheme 44. Transannulation of triazoles **50**.

The molecular weight of **51a** and **51b** corresponded to that of the expected pyrroles. Detailed NMR analysis revealed the presence of the allyl group and the absence of the cyclohexene double bond proton, but also the absence of the signal from the potential pyrrole ring proton. Due to the complexity of the ^{1}H NMR spectra in the aliphatic region, identification of the exact structure of compounds **51** was not possible. Since a single product was formed and no by-products were observed, the reaction deserves to be investigated in the future.

3.2.2.4 Direct modification of the *N*-fluoroalkyl indoles

The direct modification of indole rings is possible through several approaches. First, similar to what was described in part 3.1.4, lithiation of indole with subsequent carboxylation was performed (Scheme 45). The reaction proceeded efficiently, resulting in indole-2-carboxylic acid. The structure was additionally proven by an X-Ray measurement (Figure 6).



Scheme 45. Carboxylation of indole **49b**.

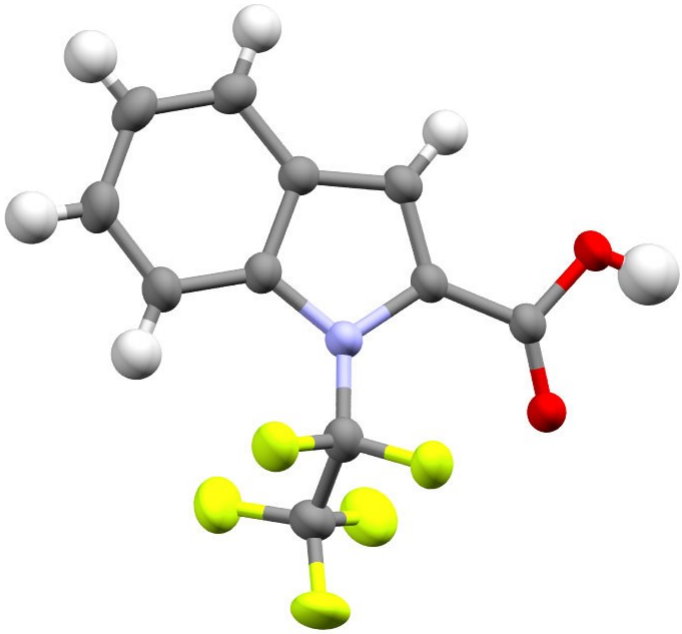
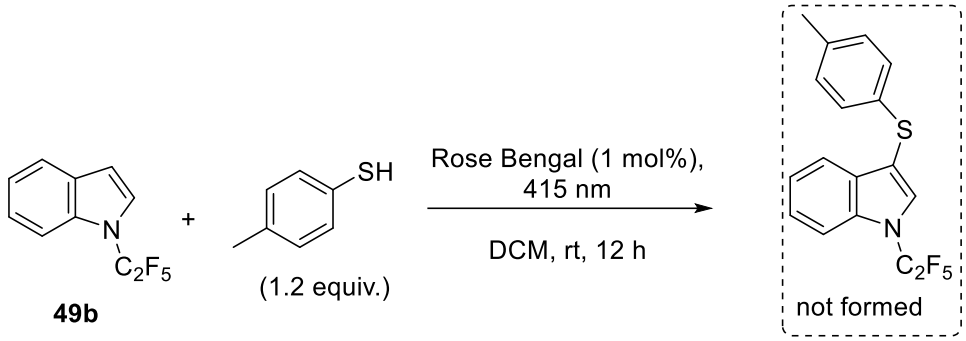


Figure 6. ORTEP diagram of **52**, displacement ellipsoids shown with 50 % probability.

An attempt to perform a photocatalytic radical reaction known for *N*-tosyl indole[49] was not successful (Scheme 46). Continuous irradiation in the presence of Rose Bengal did not result in the conversion of starting indole **49b**. A molybdenum(V)-mediated oxidative sulfenylation

reaction known to work on *N*-tosyl and mesyl indoles[50] led to full decomposition of starting indole **49b**.

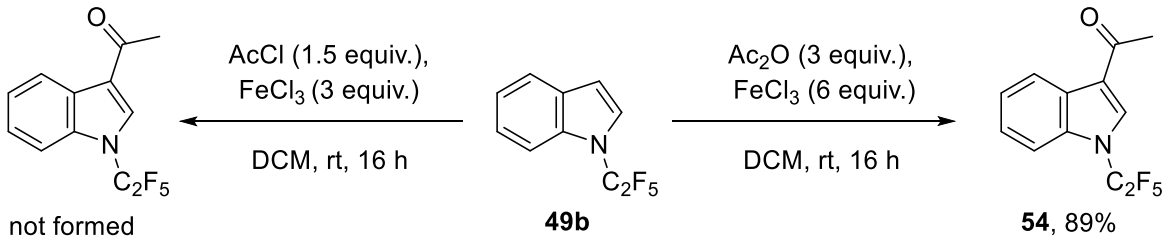


Scheme 46. An attempt of sulfenylation of **49b**.

Friedel-Crafts acylation was first performed on the substrate **49f**. The reaction resulted in a single product (Scheme 47). The spectral data analysis revealed the product to be the result of S_N1 substitution of the *tert*-butyl group and partial halogen exchange on the pentafluoroethyl group.

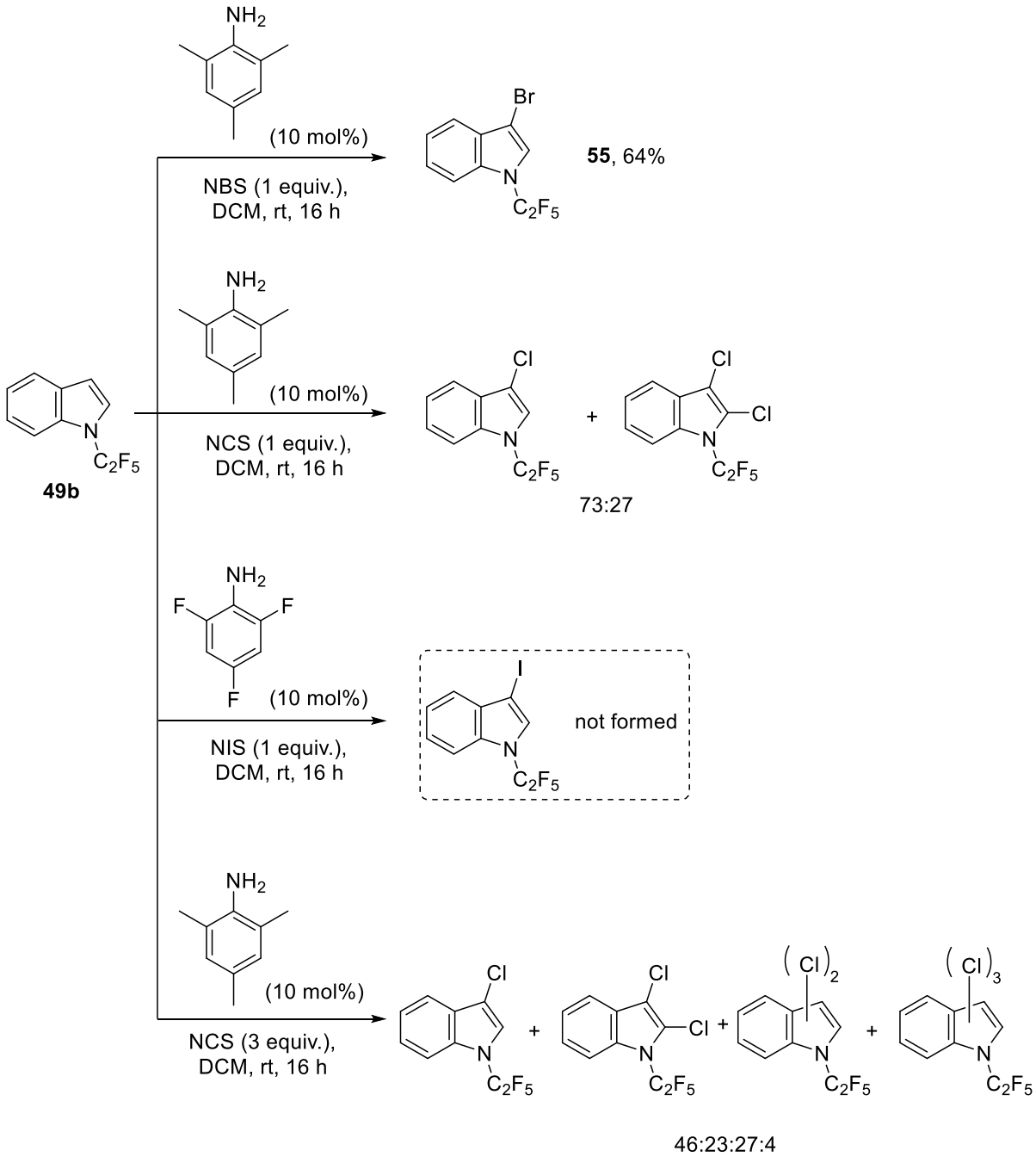
Scheme 47. Acylation of indole **49f**.

To avoid these side-reactions, the Lewis acid was switched to less reactive $FeCl_3$ and the researched substrate was chosen to be the indole **49b**. Two separate attempts were performed: the use of acyl chloride did not lead to any conversion of the starting indole (Scheme 48). The reaction with acetic anhydride afforded the target product in high yield.



Scheme 48. Acylation of indole **49b**.

To study the halogenation of our indoles, the conditions used on various 'deactivated' indole rings were applied.[51] Catalytic halogenations using arylamine as a catalyst and *N*-halo succinimides as halogenating reagents were performed (Scheme 49).



Scheme 49. Halogenation of indole **49b**.

Bromination was effective and gave the brominated indole product **55** in good yield. Chlorination of indole **49b** with two equivalents of NCS afforded a mixture of mono- and dichlorinated indole. Iodination using NIC was not successful: no conversion of the starting

indole was observed; elevating the temperature and prolonging the reaction time did not result in any product formation either. Attempting double chlorination on purpose, by addition of three equivalents of NCS to the reaction led to the formation of an even more complex mixture of multi-substituted indoles than in the reaction with two equivalents of NCS.

3.2.3 Conclusions and Outlook

In conclusion, this part of the work presented a useful synthetic method for *N*-fluoroalkyl indole synthesis and modification. The obtained indoles were shown to be reactive in reactions typical for their non-*N*-fluoroalkylated analogs (e.g. Friedel-Crafts acylation, bromination, lithiation). Access to halo-substituted indoles also presents them as potential substrates for transition metal-catalyzed cross-coupling reactions. This work showed the possibilities for the use of *N*-fluoroalkyl azides and 1,2,3-triazoles and opened access to new *N*-(per)fluoroalkyl indoles.

4. General conclusions and outlook

The main aims of this Thesis, the development of novel synthetic methodologies to *N*-(per)fluoroalkyl-substituted azoles using the reactivity of *N*-fluoroalkyl-1,2,3-triazoles, were achieved.

First, rhodium-catalyzed reactions of *N*-fluoroalkyl-1,2,3-triazoles with terminal alkynes were investigated. A new methodology for rhodium(II)-catalyzed denitrogenation of *N*-(per)fluoroalkyl triazoles and transannulation with alkynes to provide *N*-fluoroalkylated pyrroles was developed. New *N*-(per)fluoroalkyl pyrroles were formed in this reaction. The unique properties of *N*-fluoroalkyl-1,2,3-triazoles allowed the reaction to proceed without the aid of a silver co-catalyst. The triazoles also readily reacted with aliphatic alkynes – a reactivity not characteristic of analogous *N*-tosyl triazoles. Not only did the transannulation reaction with aliphatic alkynes proceed, but rare 3,4-substituted pyrroles were the main products of the transformation. The observed selectivity was discussed and a mechanistic solution was proposed. Since *N*-trifluoromethyl azoles are valuable substructures in medicinal chemistry, further modification of the obtained pyrroles was demonstrated.

The second part of the Thesis focused on the synthesis of *N*-(per)fluoroalkyl indoles. After a scope of new 4-cyclohexyl substituted *N*-fluoroalkyl-1,2,3-triazoles was obtained, a new methodology for the synthesis of *N*-(per)fluoroalkyl indoles was developed. The synthesis consisted of two steps. The first step was the transannulation of the triazoles which led to the formation of novel tetrahydroindoles. The transformation was limited to the presence of electron-withdrawing groups on the cyclohexyl moieties. The indoles were obtained using a one-pot reaction from triazoles. Rhodium(II)-catalyzed transannulation was followed by oxidation with DDQ, resulting in novel *N*-(per)fluoroalkyl indoles. The methodology allowed the preparation of indoles with not only *N*-CF_3 substitution but other *N*-(per)fluoroalkyl groups. Further modification of the obtained indoles was shown to be possible, demonstrating that, despite strong electron-withdrawing properties of the (per)fluoroalkyl groups on the nitrogen atom, the indole ring remained capable of the characteristic transformations – acylation, halogenation, and lithiation with subsequent carboxylation. As demonstrated in the Introduction, *N*-fluoroalkyl indoles are rare and a new synthetic access

to them is sought after. Indoles in general are widely used as bioactive compounds and thus the development of new methodologies towards these structures is important.

In summary, the results of this Thesis contributed to the expansion of synthetic methods of specific azoles. The Thesis demonstrated that *N*-(per)fluoroalkyl 1,2,3-triazoels are highly important for the development of new *N*-fluoroalkyl heterocycles.

5. Experimental part

5.1 General remarks

All commercially available chemicals were used as received unless stated otherwise. Starting acetylenes, azides and triazoles were prepared according to procedures published in the literature.[30,31,47]

Automated flash column chromatography was performed on Teledyne ISCO CombiFlash Rf+ Lumen Automated Flash Chromatography System with UV/Vis detection using silica gel 60 (0.040– 0.063 mm) or C_{18} silica gel.

^{1}H, ^{13}C, and ^{19}F NMR spectra were measured at ambient temperature using 5 mm diameter NMR tubes. ^{13}C spectra were proton decoupled. The chemical shift values (δ) are reported in ppm relative to internal Me_4Si (0 ppm for ^{1}H and ^{13}C NMR) or residual solvents and internal $CFCl_3$ (0 ppm for ^{19}F NMR). Coupling constants (*J*) are reported in hertz. Structural elucidation was aided by the additional acquisition of ^{13}C APT and/or various 2D spectra (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{13}C-^{19}F HMBC).

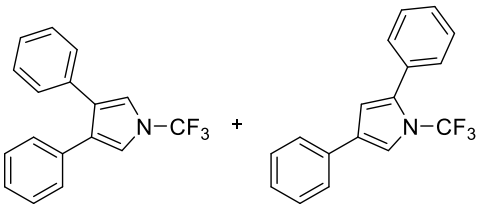
GCMS spectra were recorded on Agilent 7890A GC (column HP-5MS, 30 m × 0.25 mm × 0.25 µm, 5% phenyl methylpolysiloxane) coupled with 5975C quadrupole mass selective electron impact (EI) detector (70 eV). High-resolution MS spectra (HRMS) were recorded on a Waters Micromass AutoSpec Ultima or Agilent 7890A GC coupled with Waters GCT Premier orthogonal acceleration time-of-flight detector using electron impact (EI) ionization or chemical ionization (CI), Q-Tof micro (Waters) is a quadrupole orthogonal acceleration time-of-flight tandem mass spectrometer using atmospheric-pressure chemical ionization (APCI). CEM Discover System (300 W power) was used for reactions carried out in a microwave reactor.

5.2 Synthesis and characterization of *N*-perfluoroalkylpyrroles

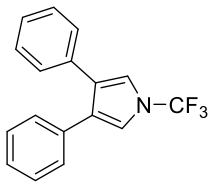
General procedures A and B for reactions of triazoles and alkynes

N-perfluoroalkyl-triazole **41a-41i** (0.20 mmol) was dissolved in dry $CHCl_3$ (2 mL) in a 10 mL microwave tube. Alkyne (0.60 mmol, 3 equiv.) and bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] (0.002 mmol, 1.52 mg, 1 mol%) were added. The vial was capped and heated at 100 °C for 20 min in a microwave reactor. The solvent and unreacted alkyne were removed under reduced pressure and the product was purified by CombiFlash automatic column chromatography (silica gel, using pentane as the mobile phase – **General procedure A** or reverse phase chromatography using water/MeCN as the mobile phase – **General procedure B**).

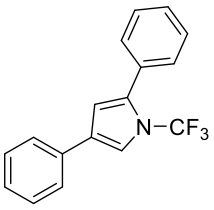
3,4-diphenyl-1-(trifluoromethyl)-1H-pyrrole and *2,4-diphenyl-1-(trifluoromethyl)-1H-pyrrole (***42a** + **42a'***)*: Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 56%; colorless oil; crude ^{19}F NMR ratio: 75:25; ^{19}F NMR (377 MHz, $CDCl_3$) δ -52.18 (s, **42a'**), -57.67 (s, **42a**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.60 – 7.53 (m, 2H, **42a'**), 7.53 – 7.48 (m, 2H, **42a'**), 7.47 – 7.43 (m, 4H, **42a'**), 7.43 – 7.41 (m, 1H, **42a'**), 7.41 – 7.39 (m, 1H, **42a'**), 7.36 (dq, *J* = 1.7, 0.9 Hz, 1H, **42a'**), 7.35 – 7.23 (m, 10H, **42a**), 7.11 (s, 2H, **42a'**), 6.61 (dq, *J* = 1.7, 0.8 Hz, 1H, **42a'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 133.9, 133.8, 132.6, 131.7, 129.7, 129.0, 128.7, 128.6, 128.5, 128.3, 127.3, 127.0, 127.0, 125.7, 119.1 (q, $^{1}J_{C-F}$ = 260.5 Hz), 116.4, 115.4, 112.4; HRMS (EI^+) *m/z* calcd. for $C_{17}H_{12}F_3N$ $[M]^+$: 287.0922, found 287.0920.



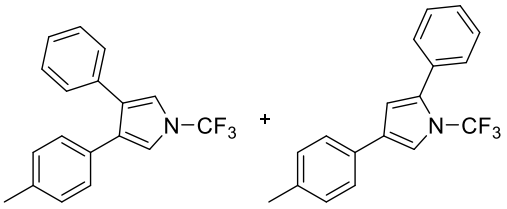
*3,4-diphenyl-1-(trifluoromethyl)-1H-pyrrole (***42a***)*: white crystalline solid; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.68 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 10H), 7.01 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 128.7, 128.5, 127.3, 127.0, 119.1 (q, $^{1}J_{C-F}$ = 260.7 Hz), 116.4.



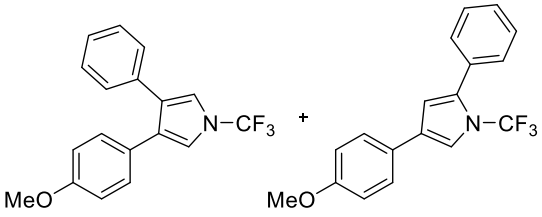
*2,4-diphenyl-1-(trifluoromethyl)-1H-pyrrole (**42a'**)*: colorless oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -52.18 (s) ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.57 – 7.52 (m, 2H), 7.51 – 7.46 (m, 2H), 7.45 – 7.36 (m, 4H), 7.34 (dd, *J* = 2.0, 0.9 Hz, 1H), 7.30 – 7.27 (m, 1H), 6.59 (dd, *J* = 2.0, 1.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 133.8, 131.7, 129.7, 129.7, 129.0, 128.6, 128.3, 127.0, 126.8, 126.8, 125.7, 119.6 (q, $^{1}J_{C\text{-}F}$ = 262.6 Hz), 115.41, 115.39, 115.37, 115.35, 112.39, 112.38.



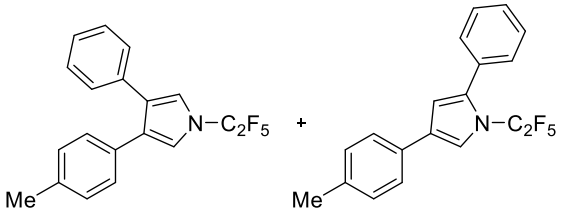
3-phenyl-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole in mixture with *2-phenyl-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole (**42b** + **42b'**)*: Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 66%; colorless oil; crude ^{19}F NMR ratio: 73:27; ^{19}F NMR (377 MHz, $CDCl_3$) δ -51.61 (s, **42b'**), -57.14 (s, **42b**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.55 – 7.05 (m, 11H + 10H**'**, **42b** + **42b'**), 6.58 (dd, *J* = 1.9, 0.9 Hz, 1H, **42b'**), 2.39 (s, 3H, **42b'**), 2.36 (s, 3H, **42b**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 136.7, 134.6, 134.0, 131.8, 130.9, 129.6, 129.2, 128.7, 128.6, 128.5, 128.4, 128.3, 127.2, 126.9, 126.8, 125.6, 119.4 (q, $^{1}J_{C\text{-}F}$ = 262.3 Hz), 119.1 (q, $^{1}J_{C\text{-}F}$ = 260.4 Hz), 116.4, 116.2, 115.1, 115.0, 112.4, 112.4, 21.3; HRMS (EI^{+}) *m/z* calcd. for $C_{18}H_{14}F_3N$ [M]$^{+}$: 301.1078, found 301.1076.



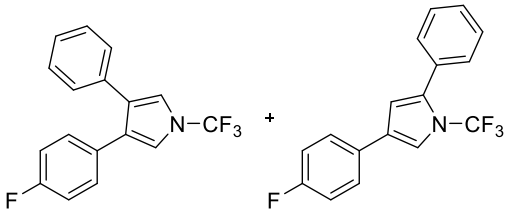
3-(4-methoxyphenyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and *4-(4-methoxyphenyl)-2-phenyl-1-(trifluoromethyl)-1H-pyrrole (**42c** + **42c'**)*: Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 54%; colorless oil; crude ^{19}F NMR ratio: 72:28; ^{19}F NMR (377 MHz, $CDCl_3$) δ -52.11 (s, **42c'**), -57.65 (s, **42c**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.55 – 7.24 (m, 5H + 9H**'**, **42c** + **42c'**), 7.23 – 7.14 (m, 2H, **42c**), 7.09 (dd, J = 15.5, 2.5 Hz, 2H, **42c**), 7.01 – 6.92 (m, 2H, **42c'**), 6.91 – 6.80 (m, 2H, **42c**), 6.56 (dq, *J* = 1.7, 0.8 Hz, 1H, **42c'**), 3.87 (s, 3H, **42c'**), 3.84 (s, 3H, **42c**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 134.0, 129.9, 129.6, 128.7, 128.5, 128.5, 128.3, 127.2, 126.9, 126.8, 126.3, 119.4 (q, $^{1}J_{C\text{-}F}$ = 262.1 Hz), 119.1 (q, $^{1}J_{C\text{-}F}$ = 260.6 Hz), 117.8, 116.3, 119.0, 114.4, 113.9, 112.4, 55.4, 55.4; HRMS (EI^{+}) *m/z* calcd. for $C_{18}H_{14}F_3NO$ [M]$^{+}$: 317.1027, found 317.1026.



1-(perfluoroethyl)-3-phenyl-4-(p-tolyl)-1H-pyrrole *F*with *1-(perfluoroethyl)-2-phenyl-4-(p-tolyl)-1H-pyrrole (***42d** + **42d'***)*: Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 52%; colorless oil; crude ^{19}F NMR ratio: 69:31; ^{19}F NMR (377 MHz, $CDCl_3$) δ -84.75 (s, -CF_3, **42d'**), -85.70 (s, -CF_3, **42d**), -93.82 (s, *N*-CF_2, **42d'**), -99.11 (s, *N*-CF_2, **42d**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.56 – 7.22 (m, 5H + 8H', **42d'** + **42d'**), 7.21 – 7.12 (m, 4H + 1H', **42d'** + **42d'**), 7.10 – 7.02 (m, 2H + 1H', **42d'** + **42d'**), 6.60 (dt, *J* = 2.0, 1.0 Hz, 1H, **42d'**), 2.42 (s, 3H, **42d'**), 2.39 (s, 3H, **42d'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.11, 139.56, 139.35, 139.16, 136.83, 136.70, 135.91, 135.11, 135.05, 133.98, 132.48, 132.30, 132.09, 131.22, 130.88, 130.78, 130.39, 130.31, 129.79, 129.65, 129.36, 129.22, 128.88, 128.84, 128.74, 128.61, 128.49, 128.46, 128.27, 128.19, 128.15, 128.09, 128.03, 127.92, 127.88, 127.81, 127.75, 127.69, 127.51, 127.49, 127.48, 127.24, 126.96, 125.58, 124.14, 124.02, 123.98, 123.19, 123.01, 122.41, 122.32, 122.13, 121.83, 120.71, 119.74, 119.28, 118.81, 116.89, 116.75, 115.80, 113.58, 113.29, 112.02, 111.60, 111.08, 110.67, 109.01, 108.68, 108.46, 108.29, 107.96, 21.30; HRMS (EI$^+$) *m/z* calcd. for $C_{19}H_{14}F_5N$ [M]$^+$: 351.1046, found 351.1045.



3-(4-fluorophenyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 4-(4-fluorophenyl)-2-phenyl-1-(trifluoromethyl)-1H-pyrrole (**42e** + **42e'**): Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 58%; colorless oil; crude ^{19}F NMR ratio: 79:21; ^{19}F NMR (377 MHz, $CDCl_3$) δ -51.69 (s, *N*-CF_3, **42e'**), -57.18 (s, *N*-CF_3, **42e**), -115.61 to -115.73 (m, **42e**, **42e'**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.57 – 7.39 (m, 7H, **42e'**), 7.38 – 7.27 (m, 3H + 1H', **42e** + **42e'**), 7.25 – 7.16 (m, 4H, **42e**), 7.14 – 7.06 (m, 2H + 2H', **42e** + **42e'**), 7.04 – 6.95 (m, 2H, **42e**), 6.55 (dq, *J* = 1.6, 0.8 Hz, 1H, **42e'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1 (d, *J* = 245.8 Hz), 162.1 (d, *J* = 245.6 Hz), 134.7, 133.6, 131.5, 131.1, 130.3, 130.2, 130.0, 129.9, 129.9, 129.9, 129.8, 129.8, 129.6, 129.6, 129.5, 129.5, 129.2, 129.1, 128.9, 128.6, 128.5, 128.5, 128.5, 128.2, 128.0, 127.9, 127.5, 127.2, 127.1, 127.0, 127.0, 126.6, 126.6, 126.2, 125.8, 125.4, 122.8, 119.4 (q, *J* = 262.7 Hz), 119.1 (q, *J* = 260.8 Hz), 116.3, 116.2, 115.8, 115.8, 115.6, 115.4, 115.2, 115.0, 112.2, 112.2.; HRMS (APCI$^+$) *m/z* calcd. for $C_{17}H_{11}F_4N$ [M + H]$^+$: 306.09004, found 306.08998.

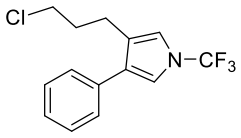


3-phenyl-1-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole with *2-phenyl-1-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (***42f** + **42f'***)*: Prepared according to **general procedure A** with phenylacetylene as the starting alkyne. Yield: 55%; colorless oil; crude ^{19}F NMR ratio: 59:41; ^{19}F NMR (377 MHz, $CDCl_3$) δ -52.33 (s, *N*-CF_3, **42f'**), -57.76 (s, *N*-CF_3, **42f**), -62.93 (s, **42f'**), -62.94 (s, **42f**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.64 (s, 4H, **42f'**), 7.55 – 7.51 (m, 2H, **42f**), 7.50 – 7.46 (m, 2H, **42f'**), 7.46 – 7.42 (m, 1H, **42f**), 7.42 – 7.39 (m, 1H, **42f'**), 7.36 – 7.28 (m, 4H + 3H', **42f** + **42f'**), 7.24 – 7.20 (m, 2H, **42f**), 7.13 (dd, *J* = 16.3, 2.5 Hz, 2H, **42f**), 6.60 (dd, *J* = 2.0, 0.9 Hz, 1H, **42f'**); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4, 136.2, 134.0, 132.2, 130.1, 128.7, 128.6, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.9, 127.9, 127.9, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 127.6, 127.6, 127.6, 127.5, 127.5, 127.4, 127.3, 127.2, 126.9, 126.9, 126.9, 126.9, 126.8, 126.5, 126.1, 126.1, 124.9, 124.8, 124.8, 124.8, 124.7, 124.7, 124.6, 124.6, 124.5, 124.4, 124.3, 124.3, 124.3, 124.2, 124.2, 124.1, 124.0, 123.7, 123.5, 123.2 (q, *J* = 271.7 Hz, **42f'**), 123.2 (q, *J* = 272.1 Hz, **42f**), 123.0, 118.1, 118.1, 118.0 (q, *J* = 263.0 Hz, **42f'**), 117.8 (q, *J* = 261.0 Hz, **42f**), 115.8, 115.7, 115.0, 115.0, 115.0, 115.0, 114.9, 114.4, 110.9; HRMS (APCI$^+$) *m/z* calcd. for C18H1F6N [M + H]$^+$: 356.08685, found 356.08675.

3-cyclopropyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 2-cyclopropyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43a** + **43a'**): Prepared according to **general procedure A** with 1-chloro-pent-4-yne the as starting alkyne. Yield: 84%; colorless oil; crude ^{19}F NMR ratio: 95:5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.00 (s, **43a'**), -57.55 (s, **43a**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H, **43a'**), 7.44 – 7.36 (m, 4H + 2H', **43a** + **43a'**), 7.35 – 7.29 (m, 1H, **43a**), 7.27 – 7.22 (m, 1H, **43a'**), 7.21 – 7.18 (m, 1H, **43a'**), 7.00 (d, *J* = 2.5 Hz, 1H, **43a**), 6.86 (dd, *J* = 2.3, 1.1 Hz, 1H, **43a**), 6.41 (dq, *J* = 1.9, 0.9 Hz, 1H, **43a'**), 3.65 (t, *J* = 6.4 Hz, 2H, **43a'**), 3.51 (ddt, *J* = 6.4 Hz, 2H, **43a**), 2.91 (td, *J* = 7.6, 2.1 Hz, 2H, **43a'**), 2.75 (td, *J* = 7.5, 1.0 Hz, 2H, **43a**), 2.24 – 2.12 (m, 2H, **43a'**), 1.95 (ddt, *J* = 8.7, 7.5, 6.4 Hz, 2H, **43a**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 133.9, 132.6, 132.6, 128.9, 128.7, 128.7, 128.6, 128.3, 127.1, 126.9, 126.4, 125.5, 124.5, 119.1 (q, $^{1}J_{C\text{-}F}$ = 260.0 Hz), 115.9,

114.3, 110.0, 44.5, 44.1, 32.4, 31.4, 22.9; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{13}ClF_3N$ [M]$^+$: 287.0689, found 287.0687.

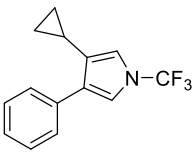
*3-(3-chloropropyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (***43a***)*: Prepared according to



general procedure A with 1-chloro-pent-4-yne the as starting alkyne. Colorless oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.56 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.33 (m, 4H), 7.36 – 7.27 (m, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 6.85 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.78 – 2.70 (m, 2H), 2.00 – 1.89 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.4, 128.8, 128.3, 127.1, 124.6, 119.1 (q, $^1J_{C\text{-}F}$ = 260.1 Hz), 115.9, 44.5, 32.5, 22.9.

3-cyclopropyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 2-cyclopropyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43b** + **43b'**): Prepared according to **general procedure A** with cyclopropylacetylene as the starting alkyne. Yield: 56%; colorless oil; crude ^{19}F NMR ratio: 94:6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.31 (s, **43b'**), -57.59 (s, **43b**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.67 – 7.58 (m, 2H, **43b**), 7.57 – 7.50 (m, 1H, **43b'**), 7.45 – 7.28 (m, 3H + 3H', **43b** + **43b'**), 7.26 – 7.21 (m, 1H, **43b'**), 7.17 (dt, *J* = 2.1, 0.8 Hz, 1H, **43b'**), 7.03 (d, *J* = 2.5 Hz, 1H, **43b**), 6.67 (dd, *J* = 2.5, 1.0 Hz, 1H, **43b**), 6.24 (dt, *J* = 1.9, 1.0 Hz, 1H, **43b'**), 1.90 (ttd, *J* = 8.6, 6.8, 4.5 Hz, 1H, **43b'**), 1.75 (ttd, *J* = 8.3, 5.2, 1.0 Hz, 1H, **43b**), 0.97 – 0.82 (m, 2H + 2H', **43b** + **43b'**), 0.78 – 0.71 (m, 2H, **43b'**), 0.64 – 0.56 (m, 2H, **43b**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 134.5, 134.1, 132.7, 129.4, 128.9, 128.9, 128.7, 128.6, 128.6, 128.4, 128.3, 128.1, 126.8, 126.7, 125.9 125.5, 125.1, 119.1 (q, *J* = 259.9 Hz), 115.4, 114.4, 114.2, 114.2, 108.2, 8.0, 7.5, 6.7; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{12}F_3N$ [M]$^+$: 251.0922, found 251.0923.

3-cyclopropyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43b**): ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.61 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.57 (m, 2H), 7.43 – 7.37 (m, 2H), 7.33 – 7.27 (m, 1H), 7.02 (d, *J* = 2.5 Hz, 1H), 6.66 (dd, *J* = 2.5, 1.0 Hz, 1H), 1.74 (ttd, *J* = 8.3, 5.2, 1.0 Hz, 1H), 0.93 – 0.82 (m, 2H), 0.64 – 0.52 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 128.9, 128.7, 128.6, 128.2, 128.1, 126.8, 125.5, 119.1 (q, *J* = 259.8 Hz); 115.4, 114.4, 8.0, 7.5, 6.7.



3-cyclopropyl-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole and 2-cyclopropyl-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole (**43c** + **43c'**): Prepared according to **general procedure A** with cyclopropylacetylene as the starting alkyne. Yield: 56%; colorless oil; crude ^{19}F NMR ratio: 91:9; ^{19}F NMR (377 MHz, $CDCl_3$) δ -54.76 (s, **43c'**), -57.05 (s, **43c**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 2H, **43c**), 7.38 – 7.32 (m, 2H, **43c'**), 7.24 – 7.18 (m, 2H, **43c'**), 7.18 – 7.14 (m, 3H, **43c'**), 7.12 (q, *J* = 0.9 Hz, 1H, **43c'**), 6.98 (d, *J* = 2.5 Hz, 1H, **43c**), 6.64 (dd, *J* = 2.5, 1.0 Hz, 1H, **43c**), 6.20 (dt, *J* = 2.0, 1.0 Hz, 1H, **43c'**), 2.39 (s, 3H, **43c'**), 2.35 (s, 3H, **43c'**), 1.73 (ttd, *J* = 8.4, 5.2, 1.0 Hz, 1H, **43c**), 0.95 – 0.81 (m, 2H, **43c**), 0.63 – 0.53 (m, 2H, **43c**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 131.5, 129.5, 129.3, 128.8, 128.7, 128.0, 125.4, 119.1 (q, $^{1}J_{C\text{-}F}$ = 259.8 Hz), 115.1, 115.1, 114.3, 21.3, 21.3, 8.0, 7.5; HRMS (EI$^+$) *m/z* calcd. for $C_{15}H_{14}F_3N$ [M]$^+$: 265.1078, found 265.1073.

3-butyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and *2-butyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (***43d** + **43d'***)*: Yield: 48%; colorless oil; Prepared according to **general procedure A** with 1-hexyne as the starting alkyne; crude ^{19}F NMR ratio: 97:3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.07 (s, **43d'**), -57.51 (s, **43d**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H, **43d'**), 7.44 – 7.34 (m, 4H + 3H**'**, **43d** + **43d'**), 7.33 – 7.28 (m, 1H, **43d**), 7.18 – 7.16 (m, 1H, **43d'**), 6.98 (d, *J* = 2.5 Hz, 1H, **43d**), 6.82 (dt, *J* = 2.3, 1.1 Hz, 1H, **43d**), 6.37 (dq, *J* = 1.9, 1.0 Hz, 2H, **43d'**), 2.75 – 2.66 (m, 2H, **43d'**) 2.60 – 2.52 (m, 2H, **43d**), 1.76 – 1.64 (m, 3H, **43d'**), 1.58 – 1.49 (m, 3H, **43d**), 1.50 – 1.43 (m, 2H, **43d'**), 1.42 – 1.30 (m, 2H, **43d**), 0.99 (t, *J* = 7.4 Hz, 3H, **43d'**), 0.90 (t, *J* = 7.3 Hz, 3H, **43d**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 134.2, 128.8, 128.6, 128.4, 128.4, 126.9, 126.7, 126.7, 125.5, 119.2 (q, $^{1}J_{C\text{-}F}$ = 259.8 Hz), 115.5, 115.5, 113.8, 113.7. 109.1, 32.0, 30.6, 26.3, 25.5, 22.7, 22.6, 14.0, 14.0; HRMS (EI$^+$) *m/z* calcd. for $C_{15}H_{16}F_3N$ [M]$^+$: 267.1235, found 267.1239.

3-butyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43d**): ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.51 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.39 (d, *J* = 1.0 Hz, 1H), 7.38 (s, 1H), 7.33 – 7.28 (m, 1H), 6.98 (d, *J* = 2.6 Hz, 1H), 6.81 (dt, *J* = 2.3, 1.1 Hz, 1H), 2.59 – 2.51 (m, 2H), 1.58 – 1.46 (m, 1H), 1.34 (dq, *J* = 14.4, 7.2 Hz, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 134.74, 128.59, 128.39, 128.35, 126.87, 126.66, 119.2 (q, $^1J_{C-F}$ = 259.8 Hz), 115.5, 115.5, 32.0, 25.5, 22.7, 14.0.

3-heptyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and *2-heptyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole* (**43e** + **43e'**): Prepared according to **general procedure B** with 1-nonyne as the starting alkyne. Yield: 36%; colorless oil; crude ^{19}F NMR ratio: 98:2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -54.54 (s, **43e'**), -56.97 (s, **43e**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H, **43e'**), 7.39 (d, *J* = 4.9 Hz, 4H + 3H', **43e**+ **43e'**), 7.33 – 7.26 (m, 1H, **43e**), 7.17 (d, *J* = 2.0 Hz, 1H, **43e'**), 6.98 (d, *J* = 2.5 Hz, 1H, **43e**), 6.81 (dd, *J* = 2.5, 1.3 Hz, 1H, **43e**), 6.38 – 6.33 (m, 1H, **43e'**), 2.69 (t, *J* = 7.8 Hz, 2H, **43e'**), 2.59 – 2.50 (m, 2H, **43e**), 1.71 (q, *J* = 7.4 Hz, 2H, **43e'**), 1.59 – 1.47 (m, 2H, **43e**), 1.38 – 1.18 (m, 8H + 8H', **43e** + **43e'**), 0.88 (t, *J* = 6.8 Hz, 3H + 3H', **43e** + **43e'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 128.9, 128.6, 128.4, 128.4, 126.9, 126.8, 126.7, 125.6, 119.2 (q, $^1J_{C-F}$ = 259.8 Hz), 115.5, 115.5, 31.9, 29.9, 29.6, 29.2, 25.8, 22.8, 14.2; HRMS (EI$^+$) *m/z* calcd. for $C_{18}H_{22}F_3N$ [M]$^+$: 309.1704, found 309.1709.

3-dodecyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 2-dodecyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43f** + **43f'**): Prepared according to **general procedure B** with 1-tetradecyne as the starting alkyne. Yield: 43%; colorless oil; crude ^{19}F NMR ratio: 94:6; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.07 (s, **43f'**), -57.51 (s, **43f**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.53 – 7.48 (m, 2H, **43f'**), 7.43 – 7.37 (m, 4H + 3H', **43f** + **43f'**), 7.35 – 7.20 (m, 1H, **43f**), 7.19 – 7.16 (m, 1H, **43f'**), 6.99 (d, *J* = 2.5 Hz, 1H, **43f**), 6.82 (dd, *J* = 2.4, 1.2 Hz, 1H, **43f**), 6.37 (dq, *J* = 1.9, 0.9 Hz, 1H, **43f'**), 2.70 (t, *J* = 7.8 Hz, 2H, **43f'**), 2.55 (t, *J* = 8.3 Hz, 2H, **43f**), 1.82 – 1.65 (m, 2H, **43f'**), 1.60 – 1.48 (m, 2H, **43f**), 1.41 – 1.13 (m, 18H + 18H', **43f** + **43f'**), 0.89 (t, 3H + 3H', **43f** + **43f'**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.96, 134.76, 134.22, 128.84, 128.59, 128.41, 128.36, 126.87, 126.74, 126.70, 125.54, 115.50, 115.46, 119.2 (q, $^1J_{C-F}$ = 259.7 Hz), 113.75, 109.07, 32.09, 29.85, 29.84, 29.81, 29.79, 29.71, 29.63, 29.55, 29.52, 25.80, 22.86, 14.27; HRMS (EI$^+$) *m/z* calcd. for $C_{23}H_{32}F_3N$ [M]$^+$: 379.2487, found 379.2490.

3-(chloromethyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 2-(chloromethyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43g** + **43g'**): Prepared according to **general procedure A** with propargyl chloride as the starting alkyne. Yield: 43%; colorless oil; crude ^{19}F NMR ratio: 87:13; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.17 (s, **43g'**), -57.74 (s, **43g**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 1H, **43g'**), 7.51 – 7.40 (m, 4H + 1H', **43g** + **43g'**), 7.40 – 7.32 (m, 1H + 2H', **43g** + **43g'**), 7.30 – 7.27 (m, 2H, **43g'**), 7.17 (d, *J* = 2.5 Hz, 1H, **43g**), 7.04 (d, *J* = 2.5 Hz, 1H, **43g**), 6.75 – 6.69 (m, 1H, **43g'**), 4.72 (s, 2H, **43g'**), 4.58 (s, 2H, **43g**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.5, 133.2, 133.1, 132.6, 130.6, 129.3, 129.0, 129.0, 128.9, 128.4, 128.1, 127.5, 127.3, 127.0, 125.6, 122.4, 120.4, 118.8 (q, $^{1}J_{C\text{-}F}$ = 259.9 Hz), 118.7, 116.9, 116.6 (q, *J* = 1.8 Hz), 115.8, 114.3, 114.3, 37.9, 36.9, 36.9; HRMS (EI$^+$) *m/z* calcd. for $C_{12}H_9ClF_3N$ $[M]^+$: 259.0376, found 259.0377.

3-(2-bromoethyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43h**): Prepared according to **general procedure A** with 1-bromo-4-butyne as the starting alkyne. Yield: 48%; pale-yellow oil; crude ^{19}F NMR ratio to **43h'**: 93:7; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.58 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.36 – 7.30 (m, 4H), 6.99 (d, *J* = 2.6 Hz, 1H), 6.94 (dd, *J* = 2.3, 1.2 Hz, 1H), 3.41 (t, *J* = 7.8 Hz, 2H), 3.14 (t, *J* = 7.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.0, 128.9, 128.4, 128.3, 128.2, 127.3, 123.0, 119.0 (q, $^{1}J_{C\text{-}F}$ = 260.4 Hz), 116.4, 115.9, 31.8, 29.5; HRMS (EI$^+$) *m/z* calcd. for $C_{13}H_{11}BrF_3N$ $[M]^+$: 317.0027, found 317.0026.

*3-(4-iodobutyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole and 2-(4-iodobutyl)-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (***43i** + **43i'***)*: Prepared according to **general procedure A** with 6-iodo-1-hexyne as the starting alkyne. Yield: 36%; colorless oil; crude ^{19}F NMR ratio: 98:2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -54.98 (s, **43i'**), -57.49 (s, **43i**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.57 – 7.48 (m, 2H, **43i'**), 7.43 – 7.36 (m, 4H + 3H', **43i** + **43i'**), 7.35 – 7.29 (m, 1H, **43i**), 7.20 – 7.16 (m, 1H, **43i'**), 6.99 (d, *J* = 2.5 Hz, 1H, **43i**), 6.84 (dt, *J* = 2.3, 1.0 Hz, 1H, **43i**), 6.40 (dq, *J* = 1.9, 1.0 Hz, 1H, **43i'**), 3.25 (t, *J* = 6.7 Hz, 2H, **43i'**), 3.15 (t, *J* = 6.9 Hz, 2H, **43i**), 2.78 – 2.70 (m, 2H, **43i'**), 2.59 (td, *J* = 7.7, 1.0 Hz, 2H, **43i**), 2.02 – 1.91 (m, 2H, **43i'**), 1.91 – 1.79 (m, 2H + 2H', **43i** + **43i'**), 1.69 – 1.59 (m, 2H,

43i); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 128.9, 128.7, 128.6, 128.4, 128.4, 127.0, 126.8, 125.7, 125.5, 119.1 (q, *J* = 260.0 Hz), 115.7, 115.6, 114.0, 33.3, 30.6, 24.8, 6.7; HRMS (EI$^+$) *m/z* calcd. for $C_{15}H_{15}F_3IN$ $[M]^+$: 393.0201, found 393.0205.

(4-phenyl-1-(trifluoromethyl)-1H-pyrrol-3-yl)methyl benzoate and (4-phenyl-1-(trifluoromethyl)-1H-pyrrol-2-yl)methyl benzoate (**43j** + **43j'**): Prepared according to **general procedure B** with propargyl benzoate as the starting alkyne. Yield: 50%; colorless oil; crude ^{19}F NMR ratio: 89:11; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.35 (s, **43j'**), -57.59 (s, **43j**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.14 – 7.90 (m, 2H + 2H', **43j** + **43j'**), 7.65 – 7.28 (m, 10H + 10H', **43j**+ **43j'**), 7.24 (d, *J* = 2.5 Hz, 1H, **43j**), 7.09 (d, *J* = 2.5 Hz, 1H, **43j**), 6.82 – 6.77 (m, 1H, **43j'**), 5.43 (s, 2H, **43j'**), 5.31 (s, 2H, **43j**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 166.2, 133.4, 133.3, 133.2, 130.2, 129.8, 129.4, 129.0, 128.9, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.3, 127.4, 127.2, 125.7, 120.4, 119.4, 119.1, 119.0 (q, $^1J_{C\text{-}F}$ = 261.2 Hz), 118.9 (q, $^1J_{C\text{-}F}$ = 261.9 Hz), 116.5, 116.5, 115.6, 58.8, 58.2; HRMS (EI$^+$) *m/z* calcd. for $C_{19}H_{14}F_3NO_2$ $[M]^+$: 345.0977, found 345.0974.

3-(3-chloropropyl)-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole and 2-(3-chloropropyl)-4-(p-tolyl)-1-(trifluoromethyl)-1H-pyrrole (**43k** + **43k'**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 60%; colorless oil; crude ^{19}F NMR ratio: 92:8; ^{19}F NMR (377 MHz, $CDCl_3$) δ -54.96 (s, **43k'**), -57.53 (s, **43k**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 2H, **43k'**), 7.33 – 7.26 (m, 2H), 7.24 – 7.18 (m, 2H + 2H', **43k** + **43k'**), 7.18 – 7.14 (m, 2H, **43k'**), 6.98 (d, *J* = 2.4 Hz, 1H, **43k**), 6.85 (dt, *J* = 2.3, 1.0 Hz, 1H, **43k**), 6.39 (dq, *J* = 1.9, 1.0 Hz, 1H, **43k'**), 3.65 (t, *J* = 6.4 Hz, 2H, **43k'**), 3.52 (t, *J* = 6.4 Hz, 2H, **43k**), 2.94 – 2.84 (m, 2H, **43k'**), 2.74 (td, *J* = 7.5, 1.0 Hz, 2H, **43k**), 2.40 (s, 3H, **43k**), 2.37 (s, 3H, **43k'**), 2.23 – 2.13 (m, 2H, **43k'**), 1.96 (ddt, *J* = 8.6, 7.4, 6.5 Hz, 2H, **43k**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 136.6, 132.4, 131.4, 131.0, 129.6, 129.4, 128.2, 128.2, 128.2, 126.4, 125.4, 124.6, 119.1 (q, *J* = 260.0 Hz), 115.8, 115.7, 113.9, 113.9, 110.0, 110.0, 44.5, 32.4, 22.9, 21.3; HRMS (EI$^+$) *m/z* calcd. for $C_{15}H_{15}ClF_3N$ $[M]^+$: 301.0845, found 301.0844.

3-(3-chloropropyl)-4-(4-methoxyphenyl)-1-(trifluoromethyl)-1H-pyrrole and 2-(3-chloropropyl)-4-(4-methoxyphenyl)-1-(trifluoromethyl)-1H-pyrrole (**43l**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 49%; colorless oil; crude ^{19}F NMR ratio to **43l'**: 90:10; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.52 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.96 – 6.91 (m, 3H), 6.83 (dt, *J* = 2.3, 1.0 Hz, 1H), 3.84 (s, 3H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.81 – 2.58 (m, 2H), 2.03 – 1.85 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 129.4, 128.6, 128.4, 128.0, 126.9, 126.8, 124.6, 119.1 (q, *J* = 259.9 Hz), 115.7, 115.5, 114.2, 55.4, 44.6, 32.4, 22.9; HRMS (Cl^+) *m/z* calcd. for $C_{15}H_{15}ClF_3NO$ $[M+H]^+$: 318.0873, found 318.0877.

3-(3-chloropropyl)-1-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole and 2-heptyl-4-phenyl-1-(trifluoromethyl)-1H-pyrrole (**43m** + **43m'**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 59%; colorless oil; crude ^{19}F NMR ratio: 95:5; ^{19}F NMR (377 MHz, $CDCl_3$) δ -55.14 (s, *N*-CF_3, **43m'**), -57.64 (s, *N*-CF_3, **43m**), -62.92 (s, **43m'**), -62.96 (s, **43m**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H, **43m**), 7.65 – 7.54 (m, 4H, **43m'**), 7.49 (dtd, *J* = 8.5, 1.9, 1.0 Hz, 2H), 7.05 (d, *J* = 2.5 Hz, 1H, **43m**), 6.89 (dt, *J* = 2.2, 1.0 Hz, 1H, **43m**), 6.43 (dq, *J* = 1.9, 0.9 Hz, 1H, **43m'**), 3.65 (t, *J* = 6.3 Hz, 2H, **43m**), 3.52 (t, *J* = 6.4 Hz, 2H, **43m**), 2.96 – 2.87 (m, 2H, **43m'**), 2.80 – 2.71 (m, 2H, **43m**), 2.18 (ddt, *J* = 8.5, 7.4, 6.4 Hz, 2H, **43m'**), 1.96 (ddt, *J* = 8.8, 7.5, 6.3 Hz, 2H, **43m**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 138.1, 129.2 (q, *J* = 32.5 Hz), 128.4, 127.0, 125.9, 125.9, 125.7 (q, *J* = 3.8 Hz), 125.6, 124.4, 123.0, 120.3, 120.2, 118.9 (q, *J* = 260.6 Hz), 116.4, 116.3, 109.8, 44.4, 32.4, 22.8; HRMS (Cl^+) *m/z* calcd. for $C_{15}H_{12}ClF_6N$ $[M+H]^+$: 356.0641, found 356.0647.

3-(3-chloropropyl)-1-(trifluoromethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (**43m**): colorless oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.64 (s, *N*-CF_3), -62.97 (s) ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 65.5, 7.9 Hz, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 2.4, 1.1 Hz, 1H), 3.52 (t, *J* = 6.3 Hz, 2H), 2.75 (td, *J* = 7.5, 1.0 Hz, 2H), 1.95 (ddt, *J* = 8.8, 7.5, 6.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 129.2 (q, *J* = 32.5 Hz), 128.4, 127.0, 125.7 (q, *J* = 3.8 Hz), 124.4, 123.0, 120.3, 118.9 (q, *J* = 260.7 Hz), 116.4, 116.3, 44.4, 32.4, 22.8.

3-(3-chloropropyl)-4-(4-fluorophenyl)-1-(trifluoromethyl)-1H-pyrrole and 2-(3-chloropropyl)-4-(4-fluorophenyl)-1-(trifluoromethyl)-1H-pyrrole (**43n** + **43n'**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 70%; colorless oil; crude ^{19}F NMR ratio: 92:8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.52 (s, **43n'**), -57.08 (s, **43n**), -115.42 to -115.59 (m, 1F, **43n**), -115.80 to -116.00 (m, 1F, **43n'**); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 8.7, 0.8 Hz, 1H, **43n'**), 7.50 – 7.39 (m, 3H, **43n'**), 7.38 – 7.32 (m, 1H, **43n**), 7.21 – 7.04 (m, 2H + 1H', **43n** + **43n'**), 6.99 (d, *J* = 2.5 Hz, 1H, **43n**), 6.87 (dt, *J* = 2.3, 1.0 Hz, 1H, **43n**), 6.37 (dq, *J* = 1.8, 0.9 Hz, 1H, **43n'**), 3.66 (t, *J* = 6.4 Hz, 2H, **43n'**), 3.53 (t, *J* = 6.4 Hz, 2H, **43n**), 2.93 (t, *J* = 7.6 Hz, 2H, **43n'**), 2.82 – 2.63 (m, 2H, **43n**), 2.19 (dq, *J* = 8.0, 6.5 Hz, 2H, **43n'**), 1.96 (ddt, *J* = 8.7, 7.4, 6.4 Hz, 2H, **43n**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.07 (d, *J* = 246.1 Hz), δ 161.9 (d, *J* = 245.5 Hz), 147.1, 133.4, 132.6, 130.2, 130.2, 129.9, 129.8, 127.3, 127.0, 126.9, 124.8, 124.5, 124.4, 124.0, 122.8, 120.2, 118.9 (q, *J* = 260.2 Hz), 119.1, 117.6, 115.8, 115.7, 115.6, 115.5, 115.4, 115.2, 115.0, 113.9, 109.8, 44.30, 32.3, 22.7; HRMS (CI^+) *m/z* calcd. for $C_{14}H_{12}ClF_4N$ $[M + H]^+$: 306.0673, found 306.0674.

*3-(3-chloropropyl)-4-(4-fluorophenyl)-1-(trifluoromethyl)-1H-pyrrole (***43n***)*: colorless oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.58 (s, *N*-CF_3), -116.04 (m, 1F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 2H), 7.14 – 7.04 (m, 2H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.84 (dt, *J* = 2.3, 1.0 Hz, 1H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.84 – 2.44 (m, 2H), 2.12 – 1.76 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, *J* = 246.1 Hz), 130.4, 130.3, 130.0, 129.9, 127.4, 124.5, 118.9 (q, *J* = 260.2 Hz), 115.9, 115.8, 115.8, 115.6, 44.5, 32.4, 22.8.

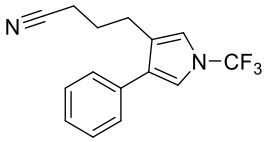
3-(3-chloropropyl)-4-(4-nitrophenyl)-1-(trifluoromethyl)-1H-pyrrole (**43o**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 27%; colorless oil; crude ^{19}F NMR ratio to **43o'**: 96:4; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.73 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.29 – 8.24 (m, 2H), 7.61 – 7.51 (m, 2H), 7.12 (d, *J* = 2.5 Hz, 1H), 6.91 (dt, *J* = 2.3, 1.0 Hz, 1H), 3.53 (t, *J* = 6.3 Hz, 2H), 2.82 – 2.73 (m, 2H), 1.96 (ddt, *J* = 8.9, 7.5, 6.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 141.3, 128.6, 126.2, 126.1, 124.4, 124.2, 118.8 (q, *J* = 261.1 Hz), 116.9, 116.7, 44.3, 32.4, 22.9; HRMS (EI^+) *m/z* calcd. for $C_{14}H_{12}ClF_3N_2O_2$ $[M]^+$: 332.0539, found 332.0538.

3-(3-chloropropyl)-1-(perfluoroethyl)-4-(p-tolyl)-1H-pyrrole and 2-(3-chloropropyl)-1-(perfluoroethyl)-4-(p-tolyl)-1H-pyrrole (**43p** + **43p'**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 51%; colorless oil; crude ^{19}F NMR ratio: 97:3; ^{19}F NMR (377 MHz, $CDCl_3$) δ -84.98 (s, -CF_3, **43p'**), -85.78 (s, -CF_3, **43p**), -96.06 (s, *N*-CF_2-, **43p'**), -98.97 (s, *N*-CF_2-, **43p**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H, **43p'**), 7.28 (d, *J* = 8.2 Hz, 2H, **43p**), 7.24 – 7.16 (m, 2H + 2H', **43p** + **43p'**), 7.06 (q, *J* = 1.0 Hz, 1H, **43p'**), 6.93 (d, *J* = 2.5 Hz, 1H, **43p**), 6.84 – 6.73 (m, 1H, **43p**), 6.42 (dt, *J* = 1.9, 0.9 Hz, 1H, **43p'**), 3.64 (t, *J* = 6.4 Hz, 2H, **43p'**), 3.51 (t, *J* = 6.4 Hz, 2H, **43p**), 2.91 – 2.83 (m, 2H, **43p'**), 2.85 – 2.62 (m, 2H, **43p**), 2.39 (s, 3H, **43p**), 2.37 (s, 3H, **43p'**), 2.22 – 2.12 (m, 2H, **43p'**), 1.96 (ddt, *J* = 8.7, 7.5, 6.4 Hz, 2H, **43p**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8, 131.3, 129.6, 129.4, 128.5, 128.2, 125.4, 124.8, 122.1 (t, *J* = 47.5 Hz), 119.3 (t, *J* = 47.4 Hz), 116.4 (q, $^1J_{C-F}$ = 47.5 Hz), 116.3, 116.2, 113.6 (q, $^1J_{C-F}$ = 47.4 Hz), 113.4 (q, *J* = 41.7 Hz), 110.8 (q, *J* = 41.7 Hz), 108.2 (q, *J* = 41.5 Hz); 44.5, 32.4, 23.0, 21.3; HRMS (EI$^+$) *m/z* calcd. for $C_{16}H_{15}ClF_5N$ $[M]^+$: 351.0813, found 351.0813.

3-(3-chloropropyl)-1-(perfluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole and 2-(3-chloropropyl)-1-(perfluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrrole (**43q** + **43q'**): Prepared according to **general procedure A** with 1-chloro-4-pentyne as the starting alkyne. Yield: 42%; colorless oil; crude ^{19}F NMR ratio: 98:2; ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.95 (CF3, **43q'**), -62.98 (CF_3, **43q**), -85.05 (-CF_3, **43q'**), -85.84 (-CF_3, **43q**), -96.33 (*N*-CF_2, **43q'**), -99.26 (*N*-CF_2, **43q**); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.67 – 7.56 (m, 4H + 4H', **43q'** + **43q'**), 7.58 (dd, *J* = 62.7, 8.1 Hz, 4H, **43q**), 7.17 – 7.13 (m, 1H, **43q'**), 7.00 (d, *J* = 2.4 Hz, 1H, **43q**), 6.84 (d, *J* = 2.4 Hz, 1H, **43q**), 6.46 (dt, *J* = 2.1, 1.0 Hz, 1H, **43q'**), 3.64 (t, *J* = 6.3 Hz, 2H, **43q'**), 3.52 (t, *J* = 6.3 Hz, 2H, **43q**), 2.89 (t, *J* = 7.4 Hz, 2H, **43q'**), 2.92 – 2.61 (m, 2H, **43q**), 2.23 – 2.13 (m, 2H, **43q'**), 1.96 (ddt, *J* = 8.8, 7.5, 6.3 Hz, 2H, **43q**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 138.0, 138.0, 129.2 (q, *J* = 32.6 Hz), 128.4, 127.2, 125.7 (q, *J* = 3.8 Hz), 124.6, 123.0, 122.0 (t, *J* = 47.1 Hz), 120.3, 119.2 (t, *J* = 47.0 Hz), 116.9, 116.9, 116.1 (t, *J* = 47.1 Hz), 113.5 (t, $^1J_{C-F}$ = 47.1 Hz), 113.4 (q, *J* = 41.7 Hz), 110.7 (q, *J* = 41.8 Hz), 108.1 (q, *J* = 41.9 Hz), 44.4, 32.4, 22.9; HRMS (EI$^+$) *m/z* calcd. for $C_{16}H_{12}ClF_8N$ $[M]^+$: 405.0531, found 405.0539.

Competitive reaction of 41a with 5-Hexynenitrile

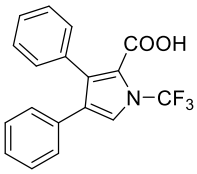
*4-(4-phenyl-1-(trifluoromethyl)-1H-pyrrol-3-yl)butanenitrile (**44**)*: Yield: 32%; colorless oil;



crude ^{19}F NMR ratio to **4'** and **5**: 63:6:31; ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.58 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.47 – 7.29 (m, 5H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.86 (dt, *J* = 2.3, 1.0 Hz, 1H), 2.84 – 2.56 (m, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 1.89 – 1.72 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.14, 128.95, 128.86, 128.26, 128.18, 127.29, 123.73, 119.48, 119.0 (q, *J* = 260.7 Hz), 116.15, 116.03, 25.39, 24.62, 16.72; HRMS (Cl^+) *m/z* calcd. for $C_{15}H_{13}F_3N_2$ $[M + H]^+$: 279.1109, found 279.1107.

Carboxylation of pyrrole 42a

*3,4-diphenyl-1-(trifluoromethyl)-1H-pyrrole-2-carboxylic acid (**46**)*: The crude mixture of **42a** + **42a'** (0.2 mmol) prepared according to **general procedure A** was dried under reduced pressure, then THF (8 mL) was added. The solution was cooled down to -78 °C and *n*-BuLi (2.5 M in hexane, 160 µL, 0.4 mmol, 2 equiv.) was added. The reaction was stirred for 30 min under nitrogen atmosphere. Then, excess of CO_2 (in the form of dry ice, approx. 2 g) was added to the reaction mixture. After 15 min of stirring, the reaction was quenched with acetic acid (1 mL). The reaction mixture was extracted with ether; the organic layer was washed with brine (3 × 20 mL). Solvent evaporation afforded pure product. Yield: 75%, white crystalline solid; ^{19}F NMR (377 MHz, $CDCl_3$) δ -53.50 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.34 – 7.28 (m, 3H), 7.23 – 7.16 (m, 5H), 7.04 – 6.97 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8, 136.4, 132.8, 132.3, 130.28, 128.45, 128.31, 127.95, 127.83, 127.15, 122.08, 118.57 (q, *J* = 264.3 Hz); HRMS (Cl^+) *m/z* calcd. for $C_{18}H_{12}F_3NO_2$ $[M + H]^+$: 331.0820, found 331.07778

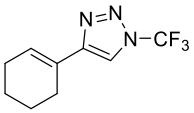


5.3 Synthesis and characterization of *N*-perfluoroalkyl triazoles

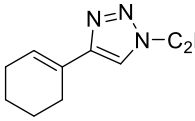
General procedure C for the synthesis of triazoles 47

Copper(I) 3-methylsalicylate (54 mg, 0.25 mmol) was placed in a 10 mL screw-cap glass tube and a cold solution of azide in THF (~6 mmol, 4-6 mL) was added. Subsequently, alkyne (5.0 mmol) in THF (1 mL) was added, and the flask was closed and stirred at rt for 18 h. The product was purified by flash column chromatography on silica gel (cyclohexane/EtOAc).

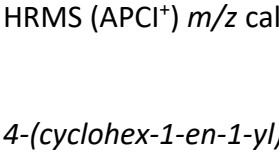
4-(cyclohex-1-en-1-yl)-1-(trifluoromethyl)-1H-1,2,3-triazole (**47a**): Prepared according to **general procedure C** with trifluoromethyl azide as the starting azide. Yield: 79% (857 mg); colorless oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.41 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.71 (tt, *J* = 4.0, 1.8 Hz, 1H), 2.44 – 2.13 (m, 4H), 1.86–1.61 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 128.2, 125.7, 117.8 (q, $^{1}J_{C\text{-}F}$ = 267.4 Hz), 115.6, 26.4, 25.4, 22.4, 22.1; HRMS (APCI$^+$) *m/z* calcd. for $C_9H_{11}F_3N_3$ $[M+H]^+$: 218.0905, found 218.0900.



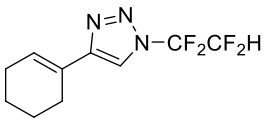
4-(cyclohex-1-en-1-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole (**47b**): Prepared according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 60% (801 mg); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.44 (s, 3F), -99.19 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.73 (tt, *J* = 4.0, 1.8 Hz, 1H), 2.37 (tdd, *J* = 6.2, 2.7, 1.8 Hz, 2H), 2.24 (ddd, *J* = 6.1, 5.0, 3.1 Hz, 2H), 1.83 – 1.76 (m, 2H), 1.74 – 1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 128.3, 125.7, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.5 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.3, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 269.9 Hz, $^{2}J_{C\text{-}F}$ = 43.0 Hz, CF_2), 26.3, 25.4, 22.3, 22.1; HRMS (APCI$^+$) *m/z* calcd. for $C_{10}H_{11}F_5N_3$ $[M+H]^+$: 268.0873, found 268.0868.



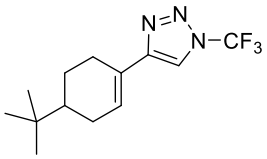
4-(cyclohex-1-en-1-yl)-1-(difluoro(phenylsulfonyl)methyl)-1H-1,2,3-triazole (**47c**): Prepared according to **general procedure C** with ((azidodifluoromethyl)sulfonyl)benzene as the starting azide. Yield: 80% (1.36 g); colorless crystals. The spectral data were in agreement with the literature.[31]



4-(cyclohex-1-en-1-yl)-1-(1,1,2,2-tetrafluoroethyl)-1H-1,2,3-triazole (**47d**): Prepared according to **general procedure C** with 1,1,2,2-tetrafluoroethyl azide as the starting azide. Yield 91% (747 mg); pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -99.4 (td, *J* = 7.8, 4.7 Hz, 2F), -137.9 (dt, *J* = 52.4, 7.9 Hz, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.67 (tt, *J* = 3.9, 1.7 Hz, 1H), 6.60 (tt, *J* = 52.4, 4.6 Hz, 1H), 2.38 – 2.31 (m, 2H), 2.23 – 2.16 (m, 2H), 1.80 – 1.71 (m, 2H), 1.66 (t, *J* = 2.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 127.9, 125.9, 115.9, 112.2 (tt, $^{1}J_{C\text{-}F}$ = 265.5 Hz, $^{2}J_{C\text{-}F}$ 29.2 Hz, CF_2), 107.8 (tt, $^{1}J_{C\text{-}F}$ = 253.5 Hz, $^{2}J_{C\text{-}F}$ 35.5 Hz, CF_2H), 26.3, 25.3, 22.3, 22.0; HRMS (ESI$^+$) *m/z* calcd. for $C_{10}H_{12}F_4N_3$ $[M+H]^+$: 250.0962, found 250.0964.

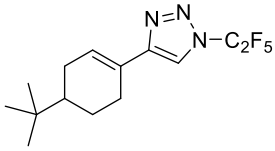


4-(4-(tert-butyl)cyclohex-1-en-1-yl)-1-(trifluoromethyl)-1H-1,2,3-triazole (**47e**): Prepared



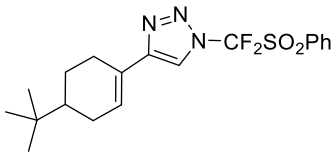
according to **general procedure C** with trifluoromethyl azide as the starting azide. Yield: 91% (1.24 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.40 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.70 (dt, *J* = 5.2, 2.4 Hz, 1H), 2.49 (ddt, *J* = 18.3, 4.8, 2.4 Hz, 1H), 2.40 – 2.22 (m, 2H), 1.98 (dddd, *J* = 14.9, 8.1, 4.4, 2.3 Hz, 2H), 1.43 – 1.25 (m, 2H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 128.4, 125.5, 121.0, 117.8 (q, $J_{C\text{-}F}$ = 267.6 Hz), 43.9, 32.4, 27.8, 27.3, 27.1, 23.8; HRMS (ESI$^+$) *m/z* calcd. for $C_{13}H_{19}F_3N_3$ $[M+H]^+$: 274.1526, found 274.1525.

4-(4-(tert-butyl)cyclohex-1-en-1-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole (**47f**): Prepared



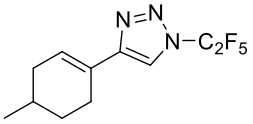
according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 82% (1.32 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.43 (s, 3F), -99.17 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.76 – 6.68 (m, 1H), 2.56 – 2.44 (m, 1H), 2.43 – 2.22 (m, 2H), 2.07 – 1.93 (m, 2H), 1.45 – 1.23 (m, 2H), 0.91 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 128.6, 125.5, 118.6 (qt, $^1J_{C\text{-}F}$ = 287.8 Hz, $^2J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.3, 111.6 (tq, $^1J_{C\text{-}F}$ = 270.0 Hz, $^2J_{C\text{-}F}$ = 43.1 Hz, CF_2), 43.9, 32.4, 27.9, 27.3, 27.2, 23.8; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{18}F_5N_3$ $[M]^+$: 323.1415, found 323.1421.

4-(4-(tert-butyl)cyclohex-1-en-1-yl)-1-(difluoro(phenylsulfonyl)methyl)-1H-1,2,3-triazole



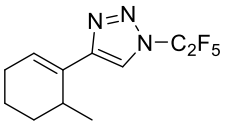
(**47g**): Prepared according to **general procedure C** with ((azidodifluoromethyl)sulfonyl)benzene as the starting azide. Yield: 83% (1.64 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -91.94 (s); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 – 7.87 (m, 2H), 7.83 (td, *J* = 7.5, 1.2 Hz, 1H), 7.79 (s, 1H), 7.68 – 7.61 (m, 2H), 6.70 (dt, *J* = 5.4, 2.5 Hz, 1H), 2.54 – 2.46 (m, 1H), 2.41 – 2.23 (m, 2H), 2.05 – 1.94 (m, 2H), 1.44 – 1.26 (m, 2H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1, 136.8, 131.1, 130.8, 130.0, 128.4, 125.6, 117.4, 116.2 (t, $J_{C\text{-}F}$ = 305.3 Hz), 43.9, 32.4, 27.8, 27.3, 27.1, 23.8; HRMS (ESI$^+$) *m/z* calcd. for $C_{19}H_{24}O_2F_2N_3S$ $[M+H]^+$: 396.1552, found 396.1553; $C_{19}H_{23}O_2F_2N_3NaS$ $[M+Na]^+$: 418.1371, found 418.1373.

4-(4-methylcyclohex-1-en-1-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole (**47h**): Prepared according



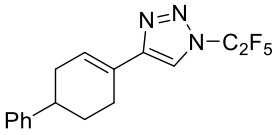
to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 64% (899 mg); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.43 (s, 3F), -99.19 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.71 (s, 1H), 6.79 – 6.45 (m, 1H), 2.57 – 2.21 (m, 3H), 1.93 – 1.82 (m, 3H), 1.46 – 1.31 (m, 1H), 1.02 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.2, 127.9, 125.4, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.8 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.3, 111.6 (tq, $^{1}J_{C\text{-}F}$ = 270.0 Hz, $^{2}J_{C\text{-}F}$ = 43.1 Hz, CF_2), 33.9, 30.5, 28.2, 26.4, 21.7; HRMS (EI$^+$) *m/z* calcd. for $C_{11}H_{12}F_5N_3$ $[M]^+$: 281.0946, found 281.0944.

4-(6-methylcyclohex-1-en-1-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole (**47i**): Prepared according



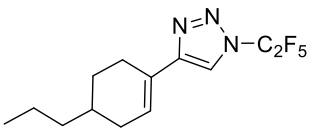
to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 76% (1.07 g); colorless oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.42 (s, 3F), -99.13 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.74 (s, 1H), 6.57 – 6.50 (m, 1H), 2.82 – 2.69 (m, 1H), 2.28 – 2.10 (m, 2H), 1.92 – 1.56 (m, 4H), 1.11 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 131.2, 128.6, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.0 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.9, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 270.7 Hz, $^{2}J_{C\text{-}F}$ = 43.0 Hz, CF_2), 29.9, 29.8, 25.8, 19.9, 17.8; HRMS (EI$^+$) *m/z* calcd. for $C_{11}H_{12}F_5N_3$ $[M]^+$: 281.0946, found 281.0946.

1-(perfluoroethyl)-4-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole (**47j**): Prepared



according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 66% (1.13 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.41 (s, 3F), -99.16 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.47 – 7.12 (m, 5H), 6.85 (tt, *J* = 3.3, 1.6 Hz, 1H), 3.04 – 2.84 (m, 1H), 2.65 – 2.54 (m, 3H), 2.50 – 2.35 (m, 1H), 2.23 – 2.11 (m, 1H), 2.05 – 1.89 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 146.3, 128.6, 127.7, 127.0, 126.4, 125.6, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.6 Hz, $^{2}J_{C\text{-}F}$ = 41.5 Hz, CF_3), 116.5, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 271.5 Hz, $^{2}J_{C\text{-}F}$ = 43.1 Hz, CF_2), 39.7, 33.5, 29.5, 27.0; HRMS (EI$^+$) *m/z* calcd. for $C_{16}H_{15}F_5N_3$ $[M]^+$: 344.1181, found 344.1181.

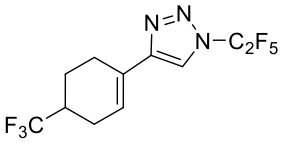
1-(perfluoroethyl)-4-(4-propylcyclohex-1-en-1-yl)-1H-1,2,3-triazole (**47k**): Prepared according



to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 78% (1.20 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.44 (s, 3F), -99.19 (s, 2F); δ 7.71 (s, 1H), 6.76 – 6.56 (m,

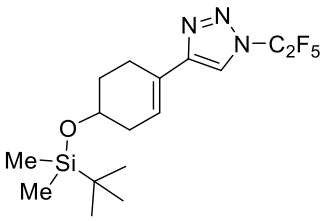
1H), 2.47 – 2.30 (m, 3H), 1.94 – 1.79 (m, 2H), 1.69 – 1.57 (m, 1H), 1.42 – 1.34 (m, 3H), 1.34 – 1.27 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.2, 127.9, 125.6, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.2 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.3, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 269.4 Hz, $^{2}J_{C\text{-}F}$ = 43.0 Hz, CF_2), 38.7, 32.9, 32.1, 28.6, 26.4, 20.1, 14.4; HRMS (ESI$^+$) *m/z* calcd. for $C_{13}H_{17}F_5N_3$ $[M+H]^+$: 310.1337, found 310.1336.

1-(perfluoroethyl)-4-(4-(trifluoromethyl)cyclohex-1-en-1-yl)-1H-1,2,3-triazole (**47l**): Prepared



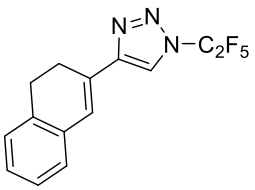
according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 75% (1.26 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -74.15 (d, *J* = 7.8 Hz, 3F), -84.41 (s, 3F), -99.18 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 6.71 – 6.62 (m, 1H), 2.73 – 2.56 (m, 1H), 2.55 – 2.25 (m, 4H), 2.24 – 2.11 (m, 1H), 1.80 – 1.64 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.2, 127.8 (q, *J* = 278.3 Hz), 125.8, 124.8, 117.1 (qt, $^{1}J_{C\text{-}F}$ = 287.5, $^{2}J_{C\text{-}F}$ = 41.4 Hz, CF_3), 116.8, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 270.6, $^{2}J_{C\text{-}F}$ = 43.2 Hz, CF_2), 38.3 (q, *J* = 27.5 Hz), 25.4, 24.4 (q, *J* = 2.9 Hz), 21.3 (q, *J* = 2.8 Hz); HRMS (ESI$^+$) *m/z* calcd. for $C_{11}H_9F_8N_3$ $[M+H]^+$: 336.0742, found 336.0743.

4-(4-((tert-butyldimethylsilyl)oxy)cyclohex-1-en-1-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole



(**47m**): Prepared according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 85% (1.69 g); yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.43 (s, 3F), -99.17 (s, 2F); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 6.58 (ddt, *J* = 5.0, 3.4, 1.6 Hz, 1H), 4.05 – 3.96 (m, 1H), 2.62 – 2.52 (m, 1H), 2.51 – 2.35 (m, 2H), 2.28 – 2.15 (m, 1H), 1.97 – 1.88 (m, 1H), 1.83 – 1.72 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 125.4, 125.1, 116.9 (qt, $^{1}J_{C\text{-}F}$ = 287.0 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 116.3, 110.0 (tq, $^{1}J_{C\text{-}F}$ = 270.9 Hz, $^{2}J_{C\text{-}F}$ = 43.1 Hz, CF_2), 66.8, 34.9, 30.9, 25.7, 24.7, 18.1, -4.8; HRMS (ESI$^+$) *m/z* calcd. for $C_{16}H_{25}OF_5N_3Si$ $[M+H]^+$: 398.1687, found 398.1683.

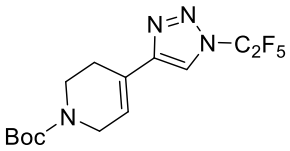
4-(3,4-dihydronaphthalen-2-yl)-1-(perfluoroethyl)-1H-1,2,3-triazole (**47n**): Prepared



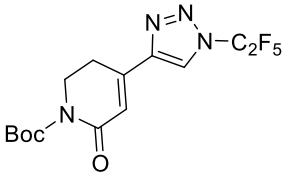
according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 72% (1.13 g); colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.35 (s, 3F), -99.12 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.38 (d, *J* = 1.6 Hz, 1H), 7.24 – 7.04 (m, 4H), 2.99 (dd, *J* = 9.2, 7.2 Hz, 2H), 2.75 (ddd, *J* = 9.5, 7.3, 1.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 135.2, 133.5, 128.1,

127.6, 127.3, 127.0, 126.6, 126.2, 117.1 (qt, $^{1}J_{C\text{-}F}$ = 288.4 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_3), 117.4, 110.3 (tq, $^{1}J_{C\text{-}F}$ = 270.4 Hz, $^{2}J_{C\text{-}F}$ = 43.1 Hz, CF_2), 27.6, 25.0; HRMS (ESI$^+$) *m/z* calcd. for $C_{14}H_{11}F_5N_3$ $[M+H]^+$: 316.0873, found 316.0867.

tert-butyl 4-(1-(perfluoroethyl)-1H-1,2,3-triazol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**47o**): Prepared according to **general procedure C** with pentafluoroethyl azide as the starting azide. Yield: 15%; colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.41, -99.19; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 6.65 – 6.60 (m, 1H), 4.15 – 4.09 (m, 2H), 3.69 – 3.62 (m, 2H), 2.56 – 2.48 (m, 2H), 1.5 (d, *J* = 1.6 Hz, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 148.9, 124.7, 117.2 (qt, $^{1}J_{C\text{-}F}$ = 287.7 Hz, $^{2}J_{C\text{-}F}$ = 41.4 Hz, CF_3), 110.3 (tq, $^{1}J_{C\text{-}F}$ = 271.2 Hz, $^{2}J_{C\text{-}F}$ = 43.2 Hz, CF_2), 116.9, 80.1, 28.60, 28.56, 27.1, 26.4; HRMS (APCI$^+$) *m/z* calcd. for $C_{14}H_{18}F_5N_4O_20$ $[M+H]^+$: 369.13444, found 369.13458.



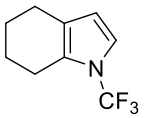
tert-butyl 6-oxo-4-(1-(perfluoroethyl)-1H-1,2,3-triazol-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (**47o'**): Oxidized **47o**. Colorless crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.31, -99.15; ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.16 (s, 1H), 6.58 (t, *J* = 1.5 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 2.94 (ddd, *J* = 7.6, 6.2, 1.5 Hz, 2H), 1.6 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.5, 152.4, 145.9, 141.5, 122.5, 120.4, 117.0 (qt, $^{1}J_{C\text{-}F}$ = 288.9 Hz, $^{2}J_{C\text{-}F}$ = 40.9 Hz, CF_3), 110.2 (tq, $^{1}J_{C\text{-}F}$ = 271.7 Hz, $^{2}J_{C\text{-}F}$ = 43.3 Hz, CF_2), 83.5, 43.3, 28.2, 25.8; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{15}F_5N_4O_3Na$ $[M+Na]^+$: 405.09565, found 405.09555.



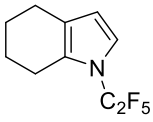
General procedure D for transannulation of triazoles 47

N-(per)fluoroalkyl-triazole **47** (0.20 mmol) and bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)] $Rh_2(esp)_2$ (1 mol%, 1.5 mg) were dissolved in dry DCE (2 mL) in a 10 mL microwave tube. The vial was flushed with nitrogen, capped and heated at 100 °C for 30 min in a microwave reactor. The resulting mixture was filtered through a pad of alumina, the solvent was evaporated under nitrogen flow or under vacuum. If necessary, purification using flash chromatography using silica gel (cyclohexane/EtOAc) was performed.

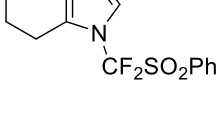
1-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indole **(48a)**: Prepared according to **general procedure D**. ^{19}F NMR yield: 64%. To obtain NMR spectra, the reaction was repeated in $CDCl_3$ and worked up by filtering through alumina. ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 – 6.79 (m, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 2.65 (t, *J* = 6.0 Hz, 2H), 2.46 (t, *J* = 6.1 Hz, 2H), 1.86 – 1.78 (m, 2H), 1.77 – 1.68 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.5, 121.9, 119.5 (q, $J_{C\text{-}F}$ = 260.1 Hz), 116.6, 110.7, 23.02, 23.00, 22.97, 22.3–22.1 (m); HRMS (EI^+) *m/z* calcd. for $C_9H_{10}F_3N$ $[M]^+$: 189.0765, found 189.0760.



1-(perfluoroethyl)-4,5,6,7-tetrahydro-1H-indole (**48b**): Prepared according to **general procedure D**. ^{19}F NMR yield: 92%, isolated yield: 10%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (s, 3F), -96.3 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (ddt, *J* = 3.4, 1.7, 0.9 Hz, 1H), 6.08 (d, *J* = 3.3 Hz, 1H), 2.64 (t, *J* = 6.1 Hz, 2H), 2.48 (t, *J* = 6.1 Hz, 2H), 1.86 – 1.66 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.5, 122.2, 118.1 (qt, $^{1}J_{C\text{-}F}$ = 288.2, $^{2}J_{C\text{-}F}$ = 48.3 Hz, CF_3), 117.5 (t, *J* = 2.8 Hz), 111.9 (tq, $^{1}J_{C\text{-}F}$ = 263.3 Hz, $^{2}J_{C\text{-}F}$ = 41.6 Hz, CF_2), 111.5, 23.3, 23.24, 23.20, 23.0; HRMS (EI^+) *m/z* calcd. for $C_{10}H_{10}F_5N$ $[M]^+$: 239.0728, found 239.0733.



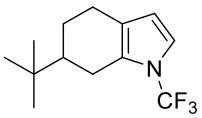
1-(difluoro(phenylsulfonyl)methyl)-4,5,6,7-tetrahydro-1H-indole (**48c**): Prepared according to **general procedure D**. Yield: 42%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -87.3 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.86 (m, 2H), 7.76 (ddt, *J* = 8.8, 7.3, 1.3 Hz, 1H), 7.65 – 7.54 (m, 2H), 6.71 (d, *J* = 3.3 Hz, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 2.56 – 2.41 (m, 4H), 1.76 – 1.60 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 132.8, 130.7, 129.6, 129.2 (t, *J* = 1.3 Hz), 122.6 – 122.4 (m), 118.7 (t, *J* = 2.9 Hz), 118.3 (t, *J* = 298.6 Hz), 112.0, 23.3, 23.2 – 23.0 (m), 22.9, 22.9 – 22.7 (m); HRMS (ESI^+) *m/z* calcd. for $C_{15}H_{16}O_2F_2NS$ $[M+H]^+$: 312.0864, found 312.0866, $C_{15}H_{15}O_2F_2NNaS$ $[M+Na]^+$: 334.0689, found 334.0686.



1-(1,1,2,2-tetrafluoroethyl)-4,5,6,7-tetrahydro-1H-indole (**48d**): Prepared according to **general procedure D** (microwave heating to 140 °C for 30 min). Yield: 54%; pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -94.9 (t, *J* = 5.6 Hz, 2F), -134.8 (dt, *J* = 53.4, 6.1 Hz, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 6.73 (d, *J* = 3.1 Hz, 1H), 6.06 (d, *J* = 3.2 Hz, 1H), 5.96 (tt, $^{2}J_{HF}$ = 53.4, $^{3}J_{HF}$ = 2.4 Hz, 1H), 2.66 (t, *J* = 5.8 Hz, 2H), 2.49 (t, *J* = 5.9 Hz, 2H), 1.88

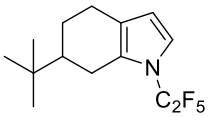
– 1.67 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 127.8, 121.8, 117.1, 113.8 (tt, $^1J_{C\text{-}F}$ = 258.8 Hz, $^2J_{C\text{-}F}$ = 29.0 Hz, CF_2), 110.9, 108.9 (tt, $^1J_{C\text{-}F}$ = 253.6 Hz, $^2J_{C\text{-}F}$ = 46.9 Hz, CF_2H), 23.3, 23.2, 23.11, 23.05; HRMS (APCI$^+$) *m/z* calcd. for $C_{10}H_{12}F_4N$ [M+H]$^+$: 222.0906, found 222.0901.

6-(tert-butyl)-1-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indole (**48e**): Prepared according to



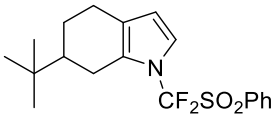
general procedure D. Isolated yield: 62%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.5 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 – 6.76 (m, 1H), 6.02 (d, *J* = 3.3 Hz, 1H), 2.72 (dd, *J* = 16.1, 4.6 Hz, 1H), 2.56 (ddd, *J* = 14.1, 5.1, 1.8 Hz, 1H), 2.46 – 2.29 (m, 2H), 1.97 (dtd, *J* = 10.8, 3.4, 1.6 Hz, 1H), 1.56 – 1.44 (m, 1H), 1.36 – 1.17 (m, 1H), 0.95 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.2, 122.5–121.4 (m), 119.6 (q, $^1J_{C\text{-}F}$ = 260.1 Hz), 117.0 (q, *J* = 2.3 Hz), 110.3, 45.2, 32.7, 27.5, 24.8, 23.7, 23.7 (q, *J* = 1.9 Hz); HRMS (EI$^+$) *m/z* calcd. for $C_{13}H_{18}F_3N$ [M]$^+$: 245.1386, found 245.1387.

6-(tert-butyl)-1-(perfluoroethyl)-4,5,6,7-tetrahydro-1H-indole (**48f**): Prepared according to



general procedure D. ^{19}F NMR yield: 99%, isolated yield: 58%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.1 (s, 3F), -95.6 (d, ^2J = 222.4 Hz, 1F), -96.5 (d, ^2J = 222.4 Hz, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 – 6.68 (m, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 2.76 – 2.68 (m, 1H), 2.62 – 2.53 (m, 1H), 2.48 – 2.24 (m, 2H), 2.01 – 1.89 (m, 1H), 1.59 – 1.40 (m, 1H), 1.36 – 1.13 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6 – 128.7 (m), 122.2, 118.1 (qt, $^1J_{C\text{-}F}$ = 288.2, $^2J_{C\text{-}F}$ = 48.4 Hz, CF_3), 111.9 (tq, $^1J_{C\text{-}F}$ = 262.9 Hz, $^2J_{C\text{-}F}$ = 41.8 Hz, CF_2), 118.0–117.5 (m), 111.1, 45.3, 32.7, 27.5, 24.7, 24.6–24.3 (m), 23.9; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{18}F_5N$ [M]$^+$: 295.1354, found 295.1361.

6-(tert-butyl)-1-(difluoro(phenylsulfonyl)methyl)-4,5,6,7-tetrahydro-1H-indole (**48g**):



Prepared according to **general procedure D**. ^{19}F NMR yield: 58%, isolated yield: 58%; pale yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -86.6 (d, ^2J = 187.7 Hz, 1F), -87.3 (d, ^2J = 187.6 Hz, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.3 Hz, 2H), 7.75 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.58 (ddd, *J* = 8.9, 7.7, 1.5 Hz, 2H), 6.72 (d, *J* = 3.3 Hz, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 2.57 – 2.48 (m, 2H), 2.42 – 2.31 (m, 1H), 2.13 – 1.98 (m, 1H), 1.93 – 1.74 (m, 1H), 1.31 (tdd, *J* = 11.5, 5.1, 1.9 Hz, 1H), 1.15 (qd, *J* = 12.2, 5.1 Hz, 1H), 0.88 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 132.7, 130.7, 129.9, 129.5, 122.4, 119.1 (t, *J* = 2.8 Hz),

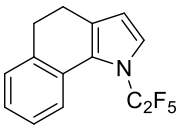
118.3 (t, $J_{C\text{-}F}$ = 298.6 Hz), 111.6, 45.1, 32.6, 27.5, 24.5, 24.2 (t, *J* = 3.6 Hz), 23.9.; HRMS (EI$^+$) *m/z* calcd. for $C_{19}H_{23}F_2NO_2S$ [M]$^+$: 367.1412, found 367.1413.

6-methyl-1-(perfluoroethyl)-4,5,6,7-tetrahydro-1H-indole (**48h**): Prepared according to **general procedure D**. ^{19}F NMR yield: 99%, isolated yield: 38%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (s, 3F), -95.8 (d, ^2J = 222.4 Hz, 1F), -96.7 (d, ^2J = 222.5 Hz, 1F); ^{1}H NMR (401 MHz, $CDCl_3$) 6.73 (d, *J* = 3.2 Hz, 1H), 6.08 (d, *J* = 3.3 Hz, 1H), 2.80 – 2.70 (m, 1H), 2.59 – 2.42 (m, 2H), 2.27 – 2.16 (m, 1H), 1.97 – 1.76 (m, 2H), 1.46 – 1.22 (m, 1H), 1.08 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 128.5–128.2 (m), 121.7, 118.0 (qt, $^1J_{C\text{-}F}$ = 288.3, $^2J_{C\text{-}F}$ = 48.4 Hz, CF_3), 117.6 (t, *J* = 3.3 Hz), 111.7 (tq, $^1J_{C\text{-}F}$ = 263.0 Hz, $^2J_{C\text{-}F}$ = 42.0 Hz, CF_2), 111.2, 31.2, 31.1–31.0 (m), 29.5, 22.6, 21.6; HRMS (EI$^+$) *m/z* calcd. for $C_{11}H_{12}F_5N$ [M]$^+$: 253.0884, found 253.0890.

1-(perfluoroethyl)-4,5-dihydro-1H-benzo[g]indole (**48j**): Prepared according to **general procedure D**. ^{19}F NMR yield: 80%, isolated yield: 65%; pale yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (s, 3F), -95.8 (d, ^2J = 222.7 Hz, 1F), -96.7 (d, ^2J = 222.7 Hz, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.30 (m, 2H), 7.30 – 7.26 (m, 2H), 7.26 – 7.22 (m, 1H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.14 (d, *J* = 3.3 Hz, 1H), 3.07 – 2.94 (m, 2H), 2.83 – 2.67 (m, 1H), 2.67 – 2.60 (m, 2H), 2.13 – 2.02 (m, 1H), 1.91 (ddt, *J* = 13.0, 11.6, 8.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 128.7, 128.4 – 127.9 (m), 127.1, 126.6, 122.0, 118.1 (qt, $^1J_{C\text{-}F}$ = 288.2, $^2J_{C\text{-}F}$ = 48.1 Hz, CF_3), 118.3 – 117.7 (m), 111.7 (tq, $^1J_{C\text{-}F}$ = 263.4 Hz, $^2J_{C\text{-}F}$ = 41.8 Hz, CF_2), 111.4, 41.2, 31.5–30.8 (m), 30.3, 23.3; HRMS (EI$^+$) *m/z* calcd. for $C_{16}H_{14}F_5N$ [M]$^+$: 315.1041, found 315.1043.

1-(perfluoroethyl)-6-propyl-4,5,6,7-tetrahydro-1H-indole (**48k**): Prepared according to **general procedure D**. ^{19}F NMR yield: 64%, isolated yield: 61%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.2 (s, 3F), -95.8 (d, ^2J = 222.4 Hz, 1F), -96.6 (d, ^2J = 222.4 Hz, 1F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 – 6.70 (m, 1H), 6.07 (d, *J* = 3.3 Hz, 1H), 2.75 (d, *J* = 16.3 Hz, 1H), 2.58 – 2.38 (m, 2H), 2.27 – 2.14 (m, 1H), 1.94 – 1.68 (m, 2H), 1.46 – 1.25 (m, 5H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.3 – 126.0 (m), 123.2 – 121.0 (m), 118.1 (qt, $^1J_{C\text{-}F}$ = 288.2, $^2J_{C\text{-}F}$ = 48.3 Hz, CF_3), 117.9 – 117.3 (m), 111.9 (tq, $^1J_{C\text{-}F}$ = 263.6 Hz, $^2J_{C\text{-}F}$ = 41.8 Hz, CF_2), 111.3, 38.5, 34.4, 29.4, 29.4–29.2 (m), 22.7, 20.3, 14.4; HRMS (EI$^+$) *m/z* calcd. for $C_{13}H_{16}F_5N$ [M]$^+$: 281.1197, found 281.1200.

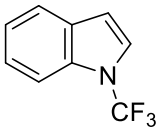
1-(perfluoroethyl)-4,5-dihydro-1H-benzo[g]indole (**48n**): Prepared according to **general procedure D**. ^{19}F NMR yield: 58%, isolated yield: 38%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -83.3 (s, 3F), -89.3 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 1H), 7.26 – 7.19 (m, 2H), 7.20 – 7.09 (m, 1H), 6.96 – 6.90 (m, 1H), 6.28 (d, *J* = 3.3 Hz, 1H), 2.88 – 2.81 (m, 2H), 2.63 – 2.57 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 130.9–129.8 (m), 128.7, 128.5–128.2 (m), 128.2, 126.7, 126.2, 123.1 (t, *J* = 8.4 Hz), 121.9–120.8 (m), 118.1 (qt, $^{1}J_{C\text{-}F}$ = 288.4, $^{2}J_{C\text{-}F}$ = 45.8 Hz), 112.0 (tq, $^{1}J_{C\text{-}F}$ = 263.0 Hz, $^{2}J_{C\text{-}F}$ = 41.3 Hz, CF_2), 111.7, 30.7, 22.6.; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{10}F_5N$ [M]$^+$: 287.0728, found 287.0727.



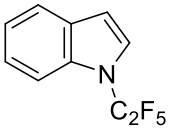
General procedure E for the synthesis of indoles 49

DDQ (91 mg, 0.40 mmol, 2 equiv.) was added to the crude reaction mixture of **48a-48o** in dry DCE (2 mL) in a 10 mL microwave tube. The vial was flushed with nitrogen, capped, and heated at 100 °C for 30 min in a microwave reactor. The resulting mixture was filtered through a pad of alumina, the solvent was evaporated under nitrogen flow or under vacuum. If necessary, purification using flash chromatography on silica gel (cyclohexane/EtOAc) was performed.

1-(trifluoromethyl)-1H-indole (**49a**): Prepared according to **general procedure E**. ^{19}F NMR yield: 93%. To obtain the NMR spectra, the reaction was performed in $CDCl_3$ and worked up by filtering through alumina. ^{19}F NMR (377 MHz, $CDCl_3$) δ -56.7 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.73 – 7.51 (m, 2H), 7.39 – 7.20 (m, 3H), 6.66 (dd, *J* = 3.7, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.9, 129.9, 124.3, 123.2 – 123.0 (m), 122.7, 121.6, 119.5 (q, $J_{C\text{-}F}$ = 260.1 Hz), 112.0 (q, *J* = 2.5 Hz), 107.2 – 106.3 (m); HRMS (EI$^+$) *m/z* calcd. for $C_9H_6F_3N$ [M]$^+$: 185.0447, found 185.0447.

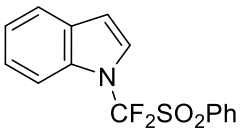


1-(perfluoroethyl)-1H-indole (**49b**): Prepared according to **general procedure E**. ^{19}F NMR yield: 87%, isolated yield: 50%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.0 (s, 3F), -97.8 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.64 (ddd, *J* = 7.7, 1.5, 0.8 Hz, 1H), 7.58 (dtt, *J* = 8.2, 2.0, 1.1 Hz, 1H), 7.36 – 7.19 (m, 2H), 7.22 (d, *J* = 3.5 Hz, 1H), 6.71 (dd, *J* = 3.7, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 130.0–129.9 (m), 124.3, 123.6 (t, *J* = 2.9 Hz), 122.6, 121.6, 118.3 (qt, $^{1}J_{C\text{-}F}$ = 289.2, $^{2}J_{C\text{-}F}$ = 48.6 Hz, CF_3), 112.6–112.5 (m),

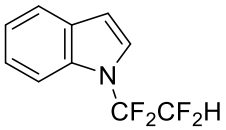


112.2 (tq, $^{1}J_{C\text{-}F}$ = 208.2 Hz, $^{2}J_{C\text{-}F}$ = 42.3 Hz, CF_2), 107.6–107.4 (m); HRMS (APCI$^+$) *m/z* calcd. for $C_{10}H_6F_5N$ [M]$^+$: 235.0415, found 235.0416.

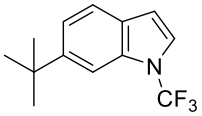
1-(difluoro(phenylsulfonyl)methyl)-1H-indole (**49c**): Prepared according to **general procedure E**. ^{19}F NMR yield: 90%, isolated yield: 75%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -88.3 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.88 – 7.81 (m, 2H), 7.75 – 7.66 (m, 1H), 7.61 – 7.55 (m, 1H), 7.54 – 7.46 (m, 3H), 7.24 – 7.17 (m, 2H), 7.17 – 7.11 (m, 1H), 6.66 (dd, *J* = 3.6, 0.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 135.0, 132.5, 130.7, 129.8, 129.6, 124.5 (t, *J* = 2.6 Hz), 124.2, 122.7, 121.3, 118.6 (t, $J_{C\text{-}F}$ = 299.3 Hz), 113.1 (t, *J* = 4.7 Hz), 107.9; HRMS (APCI$^+$) *m/z* calcd. for $C_{15}H_{11}O_2F_2NS$ [M]$^+$: 307.0473, found 307.0475.



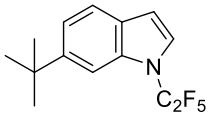
1-(1,1,2,2-tetrafluoroethyl)-1H-indole (**49d**): Prepared according to **general procedure E**. ^{19}F NMR yield: 79%, isolated yield: 46%; pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -96.9 (ddd, *J* = 8.0, 6.0, 1.9 Hz, 2F), -134.9 (dt, *J* = 53.2, 6.1 Hz, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 1H), 7.62 – 7.57 (m, 1H), 7.35 – 7.21 (m, 3H), 6.70 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.11 (tt, $^{2}J_{HF}$ = 53.2, $^{3}J_{HF}$ = 2.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 130.0, 124.0, 123.6, 122.3, 121.6, 114.3 (tt, $^{1}J_{C\text{-}F}$ = 259.8 Hz, $^{2}J_{C\text{-}F}$ = 29.3 Hz, CF_2), 112.4 (t, *J* = 4.2 Hz), 180.8 (tt, $^{1}J_{C\text{-}F}$ = 254.0 Hz, $^{2}J_{C\text{-}F}$ = 47.0 Hz, CF_2H), 106.8; HRMS (APCI$^+$) *m/z* calcd. for $C_{10}H_7F_4N$ [M]$^+$: 217.0509, found 217.0510.



6-(tert-butyl)-1-(trifluoromethyl)-1H-indole (**49e**): Prepared according to **general procedure E**, yield: 62%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.6 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 0.7 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.25 (d, *J* = 3.6 Hz, 1H), 6.61 (dd, *J* = 3.6, 0.7 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 134.1, 127.4, 122.7 (q, *J* = 1.5 Hz), 120.8, 120.7, 119.0 (q, $J_{C\text{-}F}$ = 259.8 Hz), 108.1 (q, *J* = 2.6 Hz), 107.1 – 105.4 (m), 35.0, 31.7; HRMS (EI$^+$) *m/z* calcd. $C_{13}H_{14}F_3N$ [M]$^+$: 241.1073, found 241.1075.

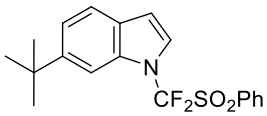


6-(tert-butyl)-1-(perfluoroethyl)-1H-indole (**49f**): Prepared according to **general procedure E**.



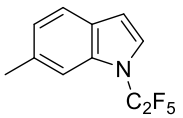
^{19}F NMR yield: 99%, isolated yield: 70%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.8 (s, 3F), -97.4 (s, 2F); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.35 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.18 (d, *J* = 3.7 Hz, 1H), 6.71 – 6.59 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 134.9, 127.6, 123.3 (t, *J* = 2.9 Hz), 120.9, 120.8, 118.5 (qt, $^{1}J_{C\text{-}F}$ = 289.3, $^{2}J_{C\text{-}F}$ = 48.7 Hz, CF_3), 112.3 (tq, $^{1}J_{C\text{-}F}$ = 263.4 Hz, $^{2}J_{C\text{-}F}$ = 42.4 Hz, CF_2), 109.9–108.0 (m), 107.1, 35.2, 31.8.; HRMS (EI$^+$) *m/z* calcd. for $C_{14}H_{14}F_5N$ [M]$^+$: 291.1041, found 291.1049.

6-(tert-butyl)-1-(difluoro(phenylsulfonyl)methyl)-1H-indole (**49g**): Prepared according to



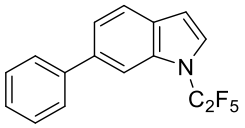
general procedure E, yield: 42%; pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -88.2 (s); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 2H), 7.68 – 7.62 (m, 1H), 7.50 – 7.43 (m, 3H), 7.39 – 7.36 (m, 1H), 7.26 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12 (d, *J* = 3.7 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 135.8, 135.3, 132.6, 130.6, 129.5, 127.3, 124.2 (t, *J* = 2.5 Hz), 120.8, 120.6, 118.6 (t, $J_{C\text{-}F}$ = 299.1 Hz), 109.4 (t, *J* = 5.0 Hz), 107.5, 35.0, 31.7; HRMS (EI$^+$) *m/z* calcd. $C_{19}H_{19}F_2NO_2S$ [M]$^+$: 363.1099, found 363.1101.

6-methyl-1-(perfluoroethyl)-1H-indole (**49h**): Prepared according to **general procedure E**,



yield: 45%; pale-yellow oil; ^{19}F NMR (376 MHz, $CDCl_3$) δ -84.9 (s, 3F), -97.6 (s, 2F); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 1H), 7.37 – 7.35 (m, 1H), 7.14 (d, *J* = 3.4 Hz, 1H), 7.08 (dd, *J* = 8.1, 0.8 Hz, 1H), 6.64 (dd, *J* = 3.6, 0.6 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.0, 134.3, 127.7, 124.2, 123.0–122.8 (m), 121.1, 118.4 (qt, $^{1}J_{C\text{-}F}$ = 289.3, $^{2}J_{C\text{-}F}$ = 48.7 Hz, CF_3), 112.8–112.4 (m), 112.2 (tq, $^{1}J_{C\text{-}F}$ = 263.9 Hz, $^{2}J_{C\text{-}F}$ = 42.3 Hz, CF_2), 107.3, 22.1; HRMS (EI$^+$) *m/z* calcd. for $C_{11}H_8F_5N$ [M]$^+$: 249.0571, found 249.0570.

1-(perfluoroethyl)-6-phenyl-1H-indole (**49j**): Prepared according to **general procedure E**, yield:



75%; pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -84.8 (s, 3F), -97.6 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 1H), 7.73 – 7.69 (m, 1H), 7.68 – 7.60 (m, 2H), 7.57 – 7.44 (m, 3H), 7.43 – 7.32 (m, 1H), 7.29 – 7.18 (m, 1H), 6.79 – 6.65 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 141.6, 137.9, 135.1, 128.9, 127.6, 127.2, 123.9 (t, *J* = 2.9 Hz), 122.4, 121.6, 118.3 (qt, $^{1}J_{C\text{-}F}$ = 289.2, $^{2}J_{C\text{-}F}$ = 48.4 Hz, CF_3),

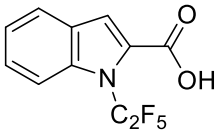
112.1 (tq, $^{1}J_{C\text{-}F}$ = 264.2 Hz, $^{2}J_{C\text{-}F}$ = 42.4 Hz, CF_2), 111.5–110.6 (m), 107.3; HRMS (EI^+) *m/z* calcd. $C_{16}H_{10}F_5N$ $[M]^+$: 311.0728, found 311.0729.

(E)-3-(1-(perfluoroethyl)-1H-indol-6-yl)acrylaldehyde (**49k'**): DDQ (1.2 mmol, 6 equiv.) was added to the crude reaction mixture of **48k** in dry DCE (2 mL) in a 10 mL microwave tube. The vial was flushed with nitrogen, capped, and heated at 100 °C for 30 min in a microwave reactor, then left at room temperature overnight to ensure full oxidation. The resulting mixture was filtered through a pad of alumina, the solvent was evaporated under vacuum. Purified using flash chromatography on silica gel (cyclohexane/EtOAc). Yield 50%, pale-yellow crystals; ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.0 (s, 3F), -97.9 (s, 2F); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 15.9 Hz, 1H), 7.53 – 7.50 (m, 1H), 7.34 – 7.31 (m, 1H), 6.78 (dd, *J* = 15.9, 7.7 Hz, 1H), 6.77 – 6.73 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.7, 153.4, 134.8, 132.4, 130.5, 128.3, 126.1–126.0 (m), 122.35, 122.28, 118.2 (qt, $^{1}J_{C\text{-}F}$ = 289.3, $^{2}J_{C\text{-}F}$ = 48.0 Hz), 113.7–113.5 (m), 112.0 (tq, $^{1}J_{C\text{-}F}$ = 264.9 Hz, $^{2}J_{C\text{-}F}$ = 42.5 Hz, CF_2), 107.8; HRMS (EI^+) *m/z* calcd. $C_{13}H_8F_5NO$ $[M]^+$: 289.0521, found 289.0520.

1-(perfluoroethyl)-1H-benzo[g]indole (**49n**): Prepared according to **general procedure E**, yield: 38%; pale-yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -82.0 (s, 3F), -87.1 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.8 Hz, 1H), 7.97 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.71 (q, *J* = 8.5 Hz, 2H), 7.60 (ddd, *J* = 8.7, 6.9, 1.5 Hz, 1H), 7.55 – 7.45 (m, 1H), 7.41 (tt, *J* = 4.0, 1.2 Hz, 1H), 6.84 (d, *J* = 3.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.4, 129.8 (t, *J* = 2.2 Hz), 129.5, 128.5, 126.4 (t, *J* = 1.8 Hz), 125.3, 124.6, 123.9 (td, *J* = 4.1, 2.0 Hz), 122.4 (t, *J* = 11.3 Hz), 122.1, 120.3, 118.2 (qt, $^{1}J_{C\text{-}F}$ = 288.3, $^{2}J_{C\text{-}F}$ = 44.8 Hz, CF_3), 112.5 (tq, $^{1}J_{C\text{-}F}$ = 261.5 Hz, $^{2}J_{C\text{-}F}$ = 41.4 Hz, CF_2), 108.8–108.0 (m); HRMS (EI^+) *m/z* calcd. $C_{14}H_8F_5N$ $[M]^+$: 285.0577, found 285.0572.

Carboxylation of indole 49b

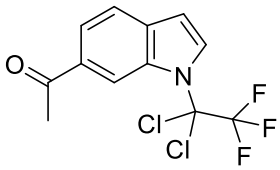
1-(perfluoroethyl)-1H-indole-2-carboxylic acid (**52**): Indole **49a** (0.2 mmol), prepared



according to **general procedure E**, was dried under nitrogen flow, then THF (8 mL) was added. The solution was cooled down to -78 °C and *n*-BuLi (2.5 M in hexane, 160 µL, 0.4 mmol, 2 equiv.) was added. The reaction was stirred for 30 min under nitrogen atmosphere. Then, an excess of CO_2 (in the form of dry ice, approx. 2 g) was added to the reaction mixture. After 15 min of stirring, the reaction was quenched with acetic acid (1 mL). The reaction mixture was extracted with ether; the organic layer was washed with brine (3 × 20 mL). Solvent evaporation afforded the pure product. Yield: 91%; colorless crystals; ^{19}F NMR (377 MHz, $CDCl_3$) δ -83.2 (s, 3F), -90.2 (s, 2F); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.63 (s, 1H), 7.65 – 7.60 (m, 1H), 7.46 (ddd, *J* = 8.6, 7.2, 1.2 Hz, 1H), 7.32 (ddd, *J* = 7.9, 7.1, 0.7 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 138.5, 128.2, 128.0, 127.2, 123.6, 123.2, 120.4, 118.4 (qt, $^{1}J_{C\text{-}F}$ = 289.0, $^{2}J_{C\text{-}F}$ = 47.1 Hz), 114.7–114.0 (m), 112.5 (tq, $^{1}J_{C\text{-}F}$ = 271.3 Hz, $^{2}J_{C\text{-}F}$ = 43.6 Hz); HRMS (ESI^-) *m/z* calcd. for $C_{11}H_5F_5NO_2$ $[M\text{-}H]^+$: 278.0246, found 278.0247.

Acylation of indole 49f

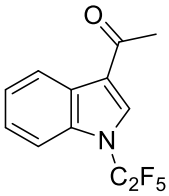
1-(1-(1,1-dichloro-2,2,2-trifluoroethyl)-1H-indol-6-yl)ethan-1-one (**53**): To a mixture of $AlCl_3$



(0.6 mmol, 3 equiv.) and acetyl chloride (0.6 mmol) in DCM at 0 °C, indole **49b** (0.2 mmol) in DCM (2 mL) was added dropwise. The solution was allowed to reach room temperature and was stirred for 16 h. The resulting mixture was poured into ice water and extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and purified using flash chromatography on silica gel. Yield: 42%; colorless crystals; ^{19}F NMR (377 MHz, $CDCl_3$) δ -77.2 (s, 3F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.48 – 8.37 (m, 1H), 8.08 – 8.04 (m, 1H), 8.04 - 7.69 (m, 1H), 7.44 – 7.37 (m, 2H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.3, 132.6, 124.9, 124.6, 123.4, 123.0 (q, *J* = 287.2 Hz, CF_3) 115.1, 91.4, 38.3.

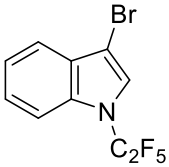
Acylation of indole 49b

1-(1-(perfluoroethyl)-1H-indol-3-yl)ethan-1-one (**54**): To $FeCl_3$ (1.2 mmol, 6 equiv.) in DCM (2 mL) was added acetic anhydride (0.6 mmol) at 0 °C; then, indole **49b** (0.2 mmol) in DCM (2 mL) was added, the solution was allowed to reach room temperature and was stirred for 16 h. The resulting mixture was poured into ice water and extracted with DCM (3 × 10 mL). The combined organic phases were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and purified using flash chromatography on silica gel. Yield: 89%; colorless crystals; ^{19}F NMR (377 MHz, $CDCl_3$) δ -84.4 (s, 3F), -98.1 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 8.43 (dt, *J* = 5.6, 3.3 Hz, 1H), 7.84 (s, 1H), 7.60 – 7.51 (m, 1H), 7.44 – 7.35 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.2, 134.8, 129.4 (t, *J* = 3.3 Hz), 126.8, 125.6, 124.5, 123.2, 121.3, 117.9 (qt, $^{1}J_{C\text{-}F}$ = 289.0, $^{2}J_{C\text{-}F}$ = 47.0 Hz), 112.7–111.9 (m), 111.7 (tq, $^{1}J_{C\text{-}F}$ = 266.7 Hz, $^{2}J_{C\text{-}F}$ = 42.9 Hz, CF_2), 27.8; HRMS (EI^+) *m/z* calcd. $C_{12}H_8F_5NO$ $[M]^+$: 277.0521, found 277.0518.



Bromination of indole 49b

3-bromo-1-(perfluoroethyl)-1H-indole (**55**): Prepared according to an established procedure:[51] NBS (0.25 mmol, 1.2 equiv.) was slowly added to a mixture of indole **49b** (0.2 mmol) and 2,4,6-trimethylaniline (0.56 µL, 2 mol%, 0.004 mmol) in DCM (2 mL). The reaction was stirred overnight at room temperature. Evaporated on silica. Purified using flash chromatography on silica gel (cyclohexane/EtOAc); yield: 64%; yellow oil; ^{19}F NMR (377 MHz, $CDCl_3$) δ -85.0 (s, 3F), -98.0 (s, 2F); ^{1}H NMR (401 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 1H), 7.58 – 7.53 (m, 1H), 7.37 (pd, *J* = 7.2, 1.4 Hz, 2H), 7.29 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.1, 129.0, 125.5, 123.3, 122.3 (t, *J* = 3.1 Hz), 120.3, 118.2 (qt, $^{1}J_{C\text{-}F}$ = 289.0, $^{2}J_{C\text{-}F}$ = 48.1 Hz, CF_3), 112.7 (t, *J* = 4.6 Hz), 111.9 (tq, $^{1}J_{C\text{-}F}$ = 265.6 Hz, $^{2}J_{C\text{-}F}$ = 42.5 Hz, CF_2), 97.8; HRMS ($APCI^+$) *m/z* calcd. $C_{10}H_5F_5NBr$ $[M]^+$: 312.9520, found 312.9519.



Crystallographic data

Single-crystal diffraction data of **52** were collected using Bruker D8 VENTURE system equipped with a Photon 100 CMOS detector, a multilayer monochromator, and a CuKα Incoatec microfocus sealed tube (λ = 1.54178 Å) at 180 K. The frames were integrated with the with Bruker SAINT[52] software package. The structure was solved by direct methods with SIR92[53] and refined by full-matrix least-squares on F with CRYSTALS.[54] The positional and anisotropic thermal parameters of all non-hydrogen atoms were refined. All hydrogen atoms were located in a difference Fourier map, but those attached to carbon atoms were repositioned geometrically. They were initially refined with soft restraints on the bond lengths and angles to regularise their geometry, then their positions were refined with riding constraints.

1-(perfluoroethyl)-1H-indole-2-carboxylic acid (**52**) (colorless, 0.090 × 0.137 × 0.254 mm):

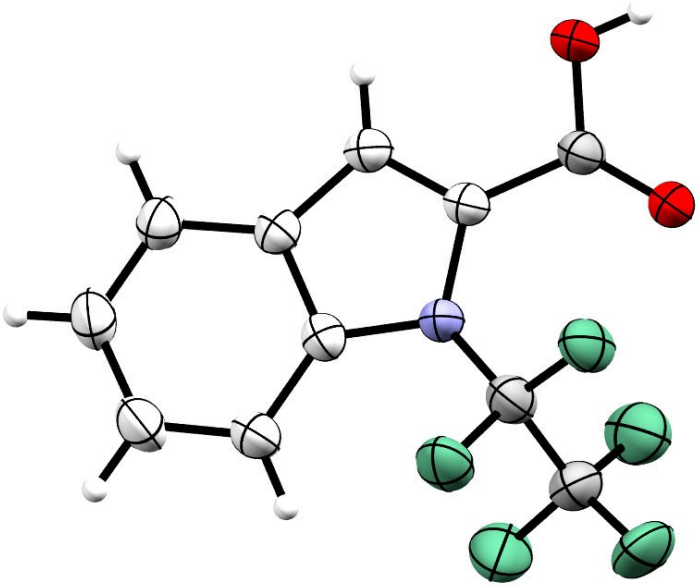


Figure 7. ORTEP diagram of **52**, displacement ellipsoids shown with 50 % probability.

$C_{11}H_6F_5N_1O_2$, triclinic, space group *P*-1, *a* = 7.6612(3) Å, *b* = 8.6533(3) Å, *c* = 8.7731(3) Å, α = 107.8102(12)°, *β* = 94.3444(13)°, γ = 95.6658(13)°, *V* = 547.57(3) Å^3, *Z* = 2, *M* = 279.16, 15955 reflections measured, 2004 independent reflections. Final *R* = 0.044, *wR* = 0.055, *GoF* = 1.010 for 1887 reflections with $I > 2\sigma(I)$ and 173 parameters. CCDC 2291313.

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