SYNTHETIC AND METHODOLOGICAL STUDIES IN COPPER AND PALLADIUM–CATALYZED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION

A Dissertation

Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Ilja Popovs

May 2014

SYNTHETIC AND METHODOLOGICAL STUDIES IN COPPER AND PALLADIUM–CATALYZED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION

Ilja Popovs

APPROVED

Dr. Olafs Daugulis, Chairman

Dr. Ramanan Krishnamoorti

Dr. Arnold M. Guloy

Dr. Jeremy A. May

Dr. Randolph P. Thummel

Dean, College of Natural Sciences and Mathematics

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This work is dedicated to the memory of Gerson Ivan Franko Santos.

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ABSTRACT

Carbon-hydrogen bond functionalization of arenes using transition metal catalysis has experienced a renaissance in recent decade. This powerful approach offers the most straightforward way to build up molecular complexity and streamline the synthesis of otherwise difficult to access organic compounds. In this dissertation, general methods for rapid introduction of fluorinated substituents via copper catalysis have been developed.

A broadly applicable method for deprotonative, copper-catalyzed C-H arylation of 1*H*-perfluoroalkanes with aryl iodides was developed. Unparalleled reaction scope with respect to aryl iodides and fluorinated counterparts allows rapid access to multitude of structurally related molecules. Additionally, a method for the direct introduction of trifluoromethylsulfenyl group onto aromatic ring via removable auxiliary directed, copper-catalyzed C-H bond activation of carboxylic acid derivatives was developed.

Finally, copper-promoted palladium-catalyzed C-H arylation of polyfluoroarenes bearing sensitive functional groups with aryl iodides was applied to the synthesis of precursors for the supramolecular assemblies and functional materials such as HOFs and MOFs. These materials are anticipated to have unique adsorption and binding properties.

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LIST OF ABBREVIATIONS

Ac	acetyl
Bn	benzyl
Boc	*tert*-butyl carbonyl
BOM	benzyloxymethyl
dba	dibenzalacetone
DCE	1,2-dichloroethane
DMAC	N,N-dimethylacetamide
DMI	1,3-dimethyl-2-imidazolinone
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
Et	ethyl
Me	methyl
MeCN	acetonitrile
MOF	metal organic framework
MOM	methoxymethyl
NMP	N-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
phen	1,10-phenanthroline
Piv	pivaloyl
RT	room temperature

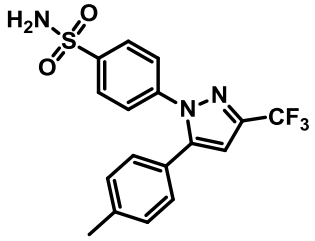
t-Bu	*tert*-butyl
t-Bu-bpy	4,4’-di-*tert*-butyl-2,2’bipyridyl
Tf_2N	bis(trifluoromethylsulfonyl)imide
TFA	trifluoroacetic acid
TfO^-	trifluoromethylsulfonate
THF	tetrahydrofurane
TMP	2,2,6,6-tetramethylpiperidine
TMSA	trimethylsilylacetylene

CHAPTER 1 COPPER-PROMOTED PERFLUOROALKYLATIONS OF AROMATIC COMPOUNDS

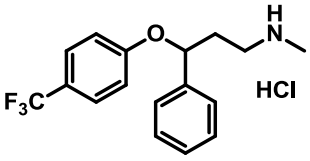
Introduction

Introduction of the fluorinated moieties in organic compounds drastically alters physical properties of these molecules. The relatively small size and high electronegativity of the fluorine atom, combined with low polarizability, renders most of perfluorinated substituents more lipophilic than their unsubstituted analogs. These and other desirable properties of fluorinated organic molecules have found extensive applications in many aspects of modern medicinal chemistry and materials science.[1] Additionally, introduction of fluorine-containing groups into biologically active molecules increases their biological stability and bioavailability. Many pharmaceuticals[2] and agrochemicals[3] contain fluorinated moieties (Scheme 1.1.).

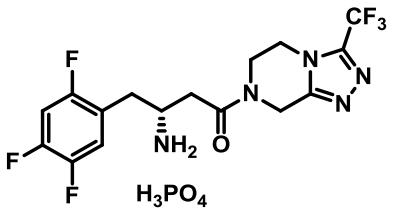
Scheme 1.1. Biologically relevant molecules bearing $-CF_3$ groups



Celecoxib (Celebrex®)



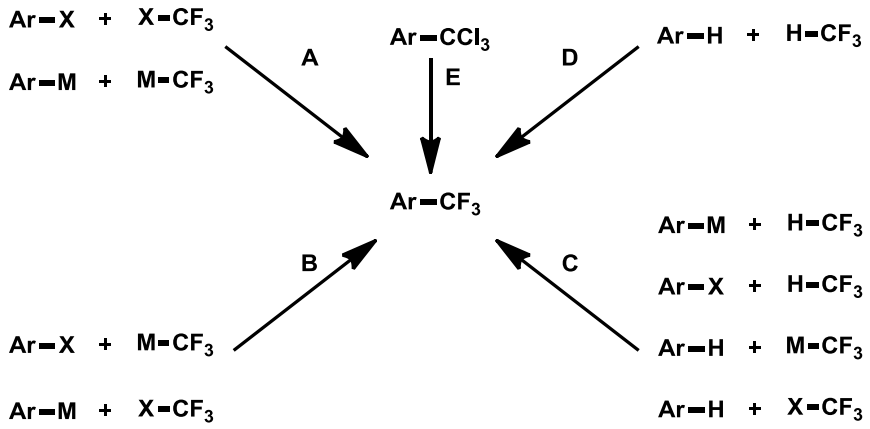
Fluoxetine (Prozac®)



Sitagliptin (Januvia®)

Direct introduction of perfluorinated residues onto organic molecules still represents a substantial challenge, though the toolbox of the reactions available to organic chemists is expanding very rapidly (Scheme 1.2.).

Scheme 1.2. Methods for the introduction of-trifluoromethyl group



Direct reductive cross-coupling between two electrophilic reagents or oxidative coupling between two nucleophilic reagents (Pathway A), represents one of the most widely used methods for the introduction of trifluoromethyl group onto an aromatic ring. These reactions are typically performed with superstoichiometric amount of transition-metal reductant or oxidant. Coupling reaction between aryl halide and nucleophilic trifluoromethylating reagent or aryl metal and electrophilic reagent (Pathway B) is gaining prominence, since it allows good control of regio- as well as homo- versus heterocoupling selectivity. Unfortunately, both of the reaction pathways require prefunctionalization of both starting materials, increasing the environmental impact and labor intensity of the reactions. On the other hand, employing abundant carbon-hydrogen bonds as coupling partners in either of the starting materials would substantially increase

overall practicality of the coupling reactions (Pathway C). Consequently, these reactions have been extensively investigated recently. The most atom-economical, direct dehydrogenative trifluoromethylation of arene C-H bonds has not yet been reported (Pathway D).[4] The strong Lewis acid-promoted exchange of the chlorine atoms in the trichloromethyl group with fluorine atoms is called a Swarts reaction (Pathway E). This reaction is still widely used in industry, despite being neither environmentally benign nor functional group tolerant.

The main focus of the following literature review is to provide coverage of the state-of-the-art introduction of trifluoromethyl and other perfluoroalkyl group-containing substituents onto aromatic rings using copper catalysis. Formal coupling reactions in which a metal catalyst acts as a radical initiator will not be discussed.

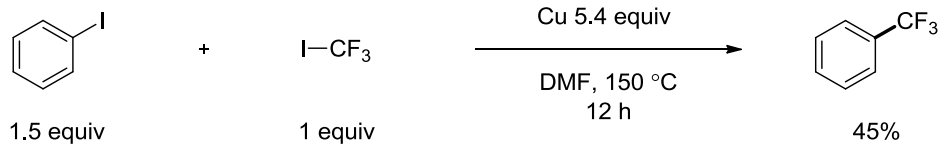
II. Copper-promoted polyfluoroalkylation of carbon-heteroatom bond

II.1. Cross-coupling with electrophilic polyfluoroalkylating reagents

Pioneering work on metal-mediated introduction of perfluoroalkyl groups onto aromatic rings using cross-coupling approach was performed by McLoughlin and Thrower.[5] Polyfluoroalkyl iodides were coupled with aryl iodides using super stoichiometric amounts of copper metal to provide arylperfluoroalkanes in good yields (Scheme 1.3). This was a breakthrough in fluorine chemistry, since it allowed for the first time to have selective introduction of perfluorinated residues onto aromatic compounds. However, in some cases Ullmann coupling byproducts were also observed. The authors

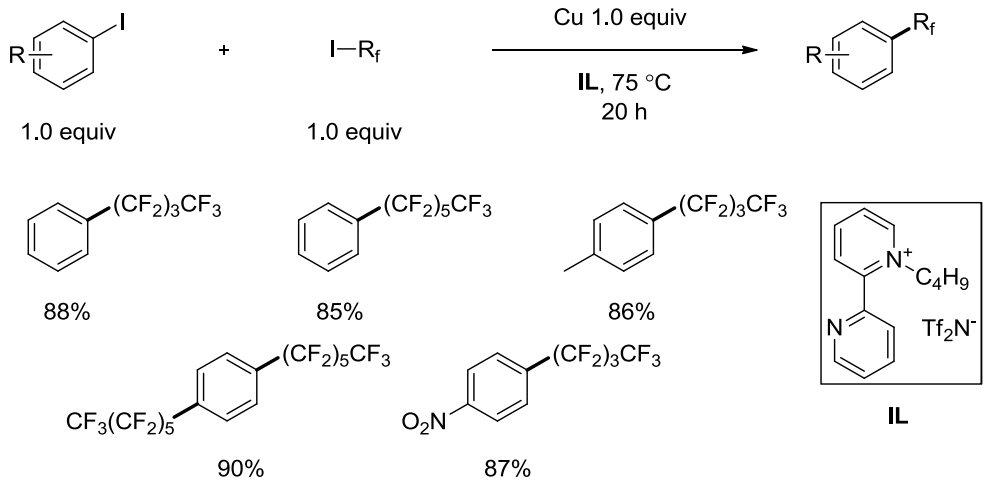
postulated the formation of the active perfluoroaryl copper intermediates in the reaction mixture and were able study them in solution.[5]

Scheme 1.3. Direct cross-coupling mediated by copper



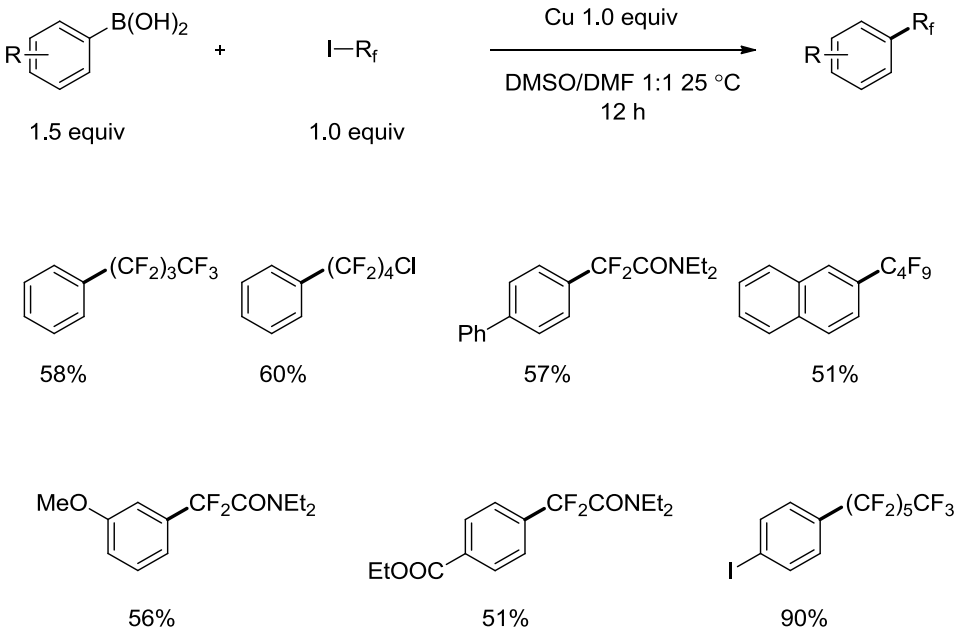
After the initial discovery, other examples of the McLoughlin-Thrower reaction were reported.[6] A major improvement of the method was reported by Shreeve and coworkers.[7] Using room-temperature ionic liquid as a solvent, the amount of copper and perfluoroalkyl iodide used could be decreased considerably, while increasing reaction yields and overall synthetic utility. Additionally, the ionic liquid solvent can be reused up to 5 times without decreasing the yield. Some sensitive functional groups were tolerated during the reaction, affording products in good to excellent yields (Scheme 1.4.).

Scheme 1.4. Copper mediated cross-coupling in ionic liquid



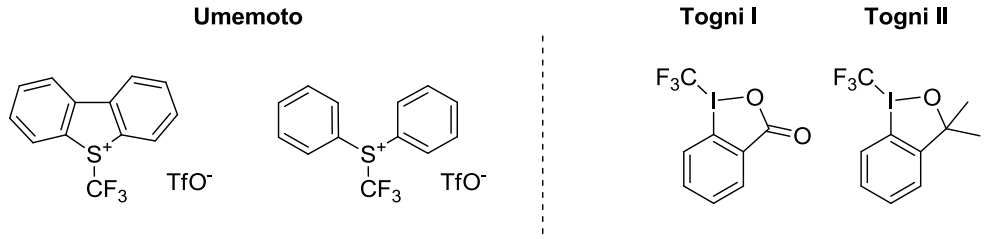
Modification of the protocol allowed researchers to develop a selective method for the perfluoroalkylation of boronic acids.[8] When aryl boronic acid is treated with stoichiometric amount of perfluoroalkyl iodide and copper under dry air atmosphere, the cross-coupling product is obtained. Reaction conditions are very mild, allowing for a wide array of substituted boronic acids and perfluoroalkyl iodides to engage in the reaction. An unprecedented degree of functional group tolerance highlights the overall practicality of this method. The mechanism of this reaction is not well understood, but the authors proposed involvement of perfluoroalkyl copper intermediate which oxidatively couples with boronic acid (Scheme 1.5.).

Scheme 1.5. Perfluoroalkylations of aryl boronic acids



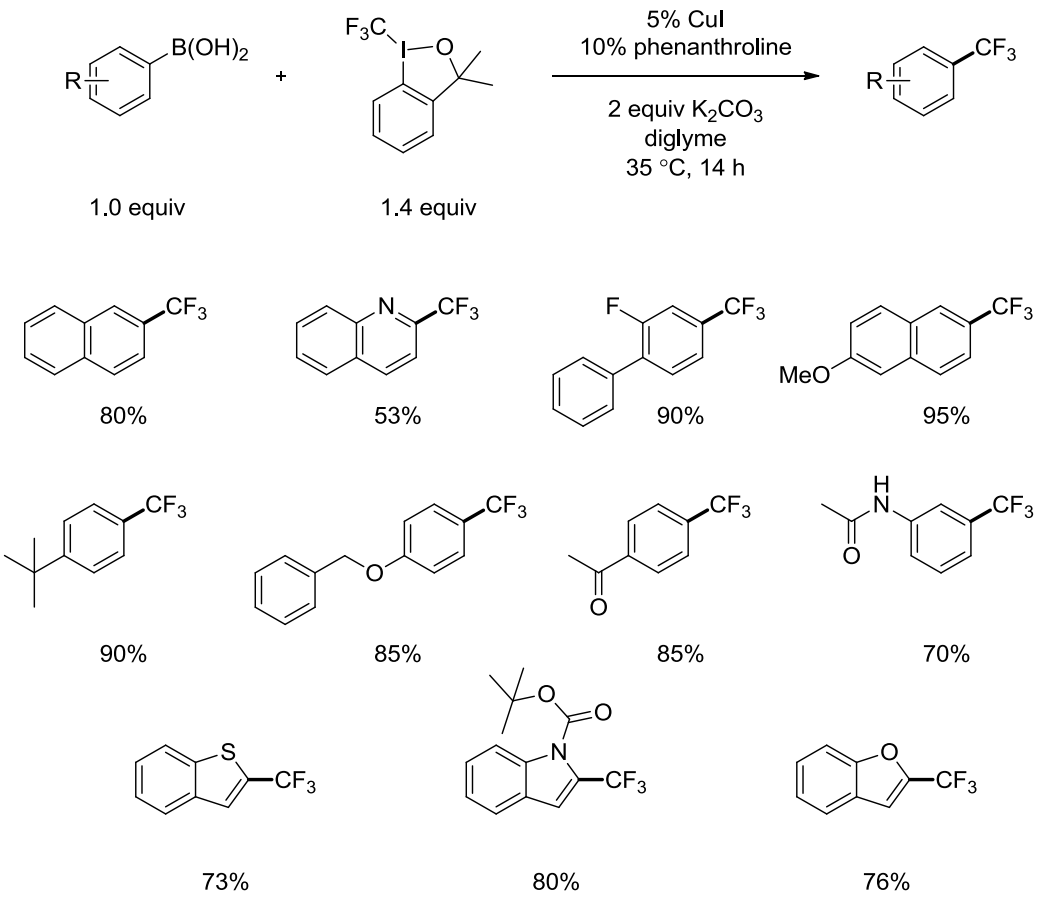
Impressive progress has been made in the functionalization of aryl iodides and boronic acids using perfluoroalkyl halides. However, the development of more user friendly electrophilic reagents has allowed even further broadening of the scope and applicability of such transformations. A number of solid non-volatile electrophilic perfluoroalkylating reagents were developed by the Umemoto and Togni groups (Scheme 1.6.).[9] Both classes of these reagents possess varying degrees of electrophilicity. Thus, an appropriate reagent can be used for the particular application.

Scheme 1.6. Solid electrophilic trifluoromethylating reagents



Liu and Shen have reported a cross-coupling reaction between boronic acids and Togni's reagent.[10] Employing catalytic amounts of a copper salt and bidentate phenanthroline ligand in diglyme solvent, a number of structurally diverse boronic acids engaged in the reaction to afford the desired products in good to excellent yields (Scheme 1.7).

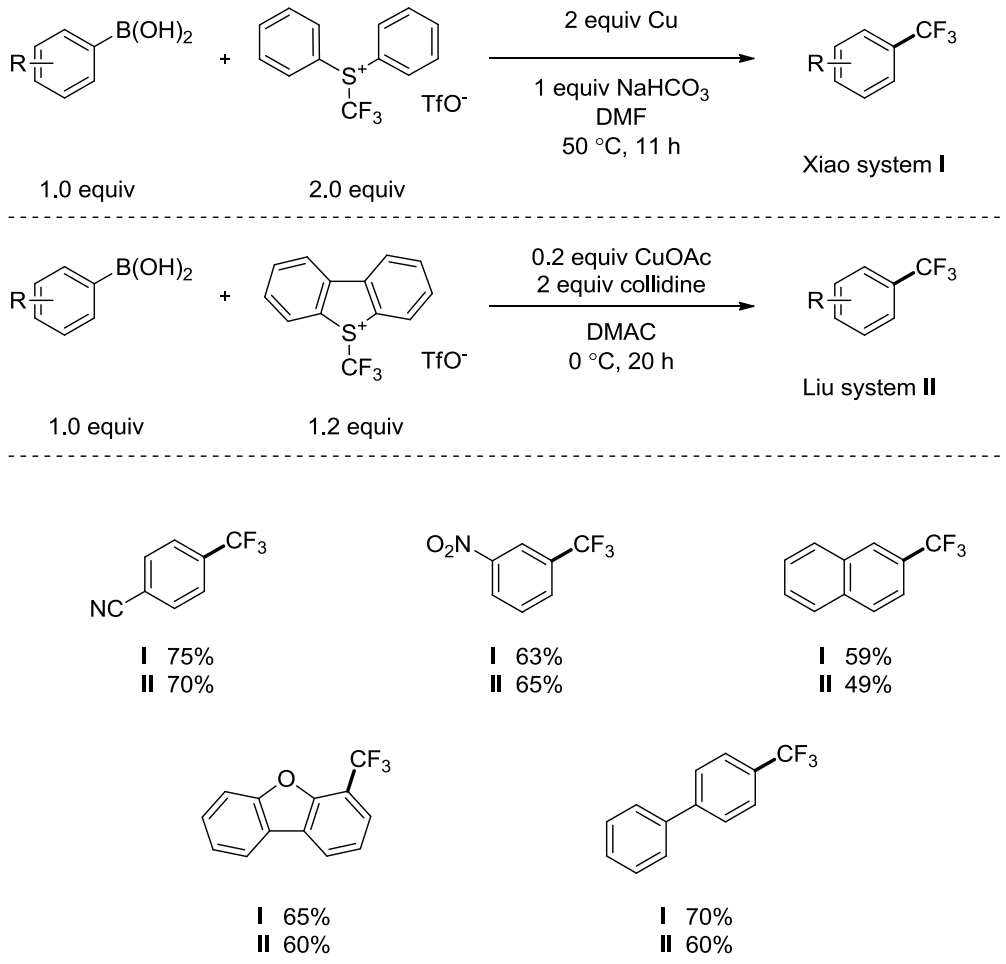
Scheme 1.7. Trifluoromethylation of boronic acids using Togni reagent



Significantly, the concept of cross-coupling of aryl boronic acids could be extended to other types of electrophilic trifluoromethylating reagents. Reports on trifluoromethylation of aryl boronic acids with both types of Umemoto reagent appeared almost simultaneously. In the report by Xiao and coworkers,[11] boronic acids were coupled with a diphenylsulfide based reagent. Liu and coworkers[12] reported coupling with a dibenzothiophene-based electrophilic trifluoromethylating reagent. Remarkably, despite the seemingly similar reagents employed, the reaction conditions in both reports differ drastically. The procedure developed by Xiao and coworkers required

stoichiometric amounts of copper and was performed at 50 °C, while the method of Liu required 0 °C and only catalytic amounts of copper. Regardless of the method used, the overall reaction scope and yields are comparable for both protocols (Scheme 1.8.)

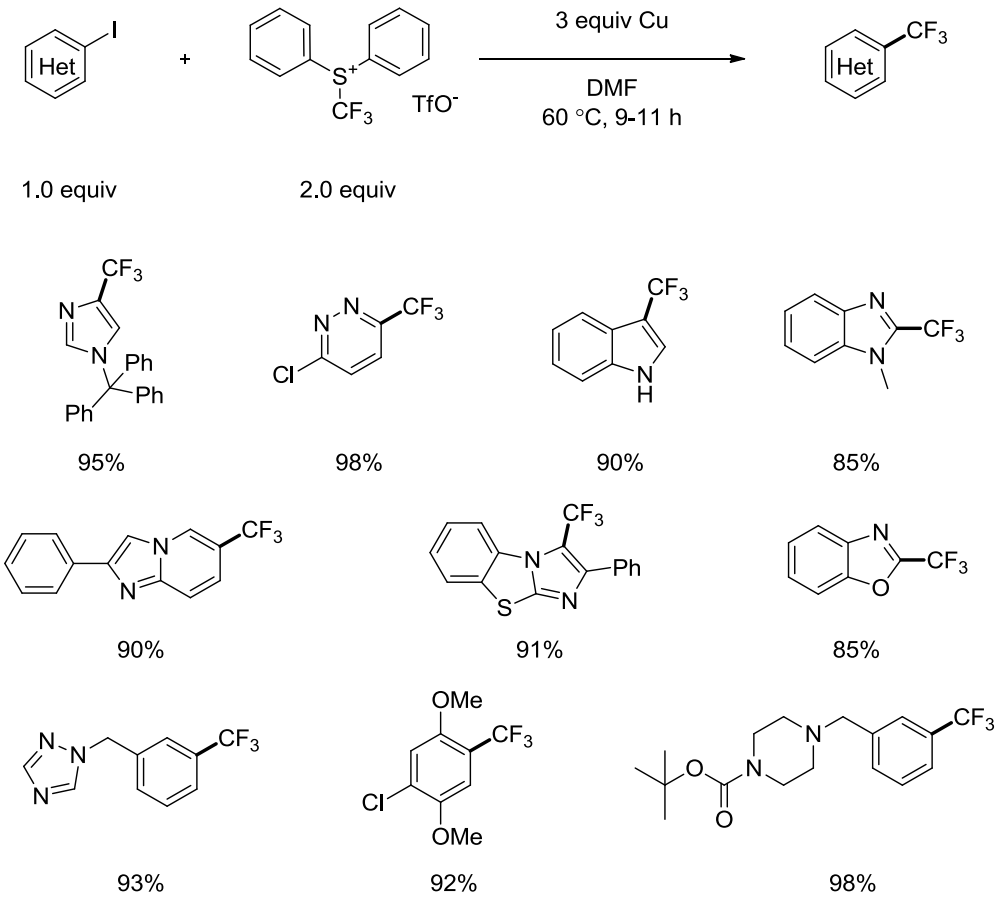
Scheme 1.8. Trifluoromethylation of boronic acids using Umemoto reagents



Similarly, electrophilic trifluoromethylating reagents can be cross-coupled with aryl iodides under copper catalysis. Xiao and coworkers described another method employing a diphenylsulfide-derived electrophilic trifluoromethylating reagent and different aryl iodides using stoichiometric amount of copper as both reducing agent and

promoter.[13] Remarkably, the yields of the reactions are uniformly high. Most of the substrates reported are heteroaryl iodides (Scheme 1.9.).

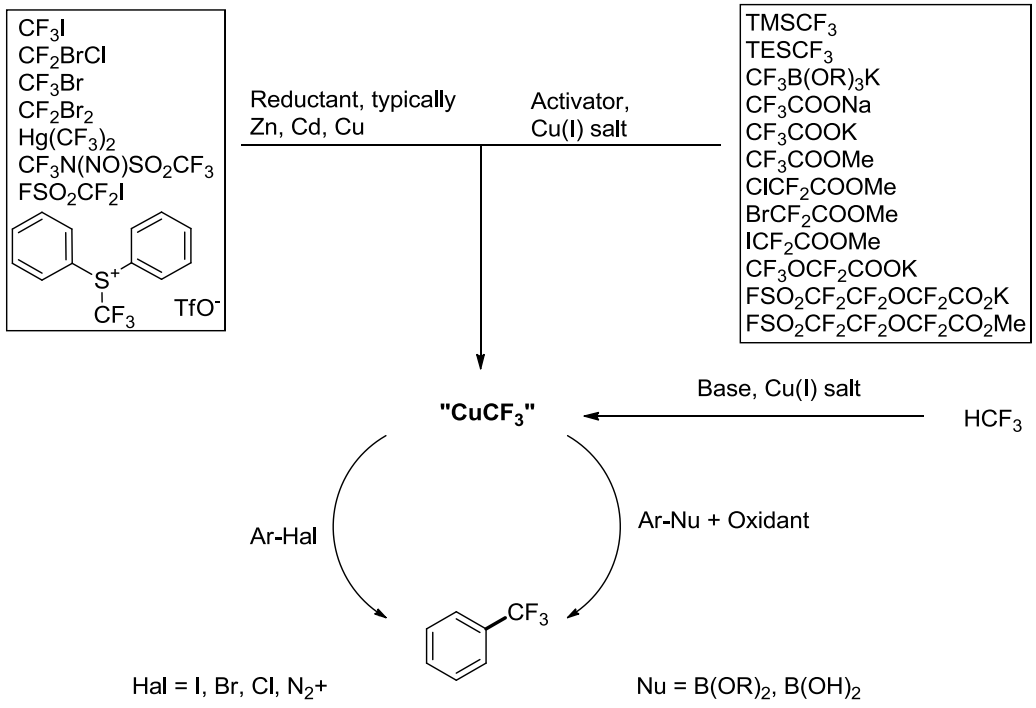
Scheme 1.9. Trifluoromethylation of aryl iodides using Umemoto reagent



II.2. Cross-coupling with nucleophilic polyfluoroalkylating reagents

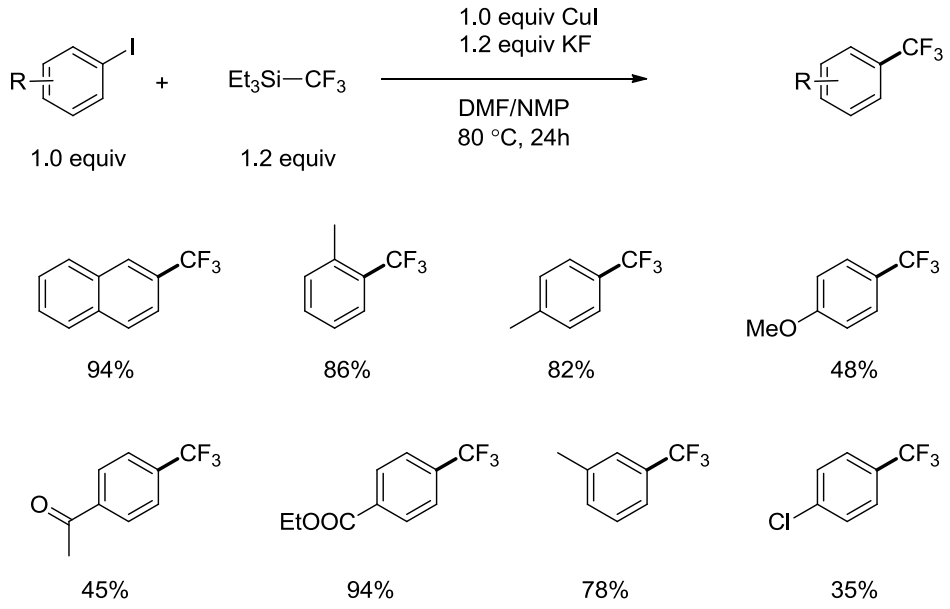
Many nucleophilic trifluoromethylating reagents have been developed and successfully applied for the synthesis of trifluoromethylated arenes (Scheme 1.10.). The most prominent is trifluoromethyltrimethylsilane $TMSCF_3$ (Ruppert-Prakash reagent).[14] The silicon-carbon bond is polarized, so that upon attack of the nucleophile on the silicon atom, a trifluoromethyl anion equivalent is formed, which can be transferred to an electrophilic species. Oftentimes transition metal ions, such as copper or palladium ions can accept trifluoromethyl group and form corresponding metal complexes. Resulting metal species can engage in a number of reactions with electrophiles or undergo reductive elimination.[1]

Scheme 1.10 Reported methods that generate trifluoromethyl copper species



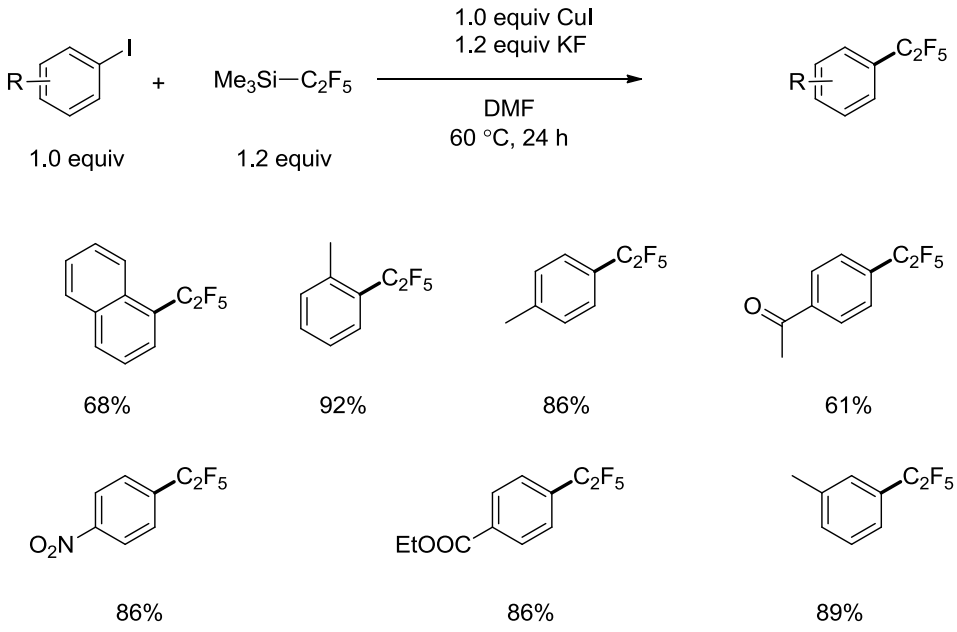
In 1991, Urata and Fuchikami[15] pioneered the application of trialkylsilyltrifluoromethane and trialkylsilylpentafluoroethane in the copper-promoted perfluoroalkylation of aryl iodides. In the presence of stoichiometric amounts of copper iodide and potassium fluoride in DMF/NMP solvent mixture, a number of substituted aryl iodides provided cross-coupling products. Reaction conditions are very mild and sensitive functional groups are well tolerated (Scheme 1.11.).

Scheme 1.11. Perfluoroalkylation using TES-CF_3



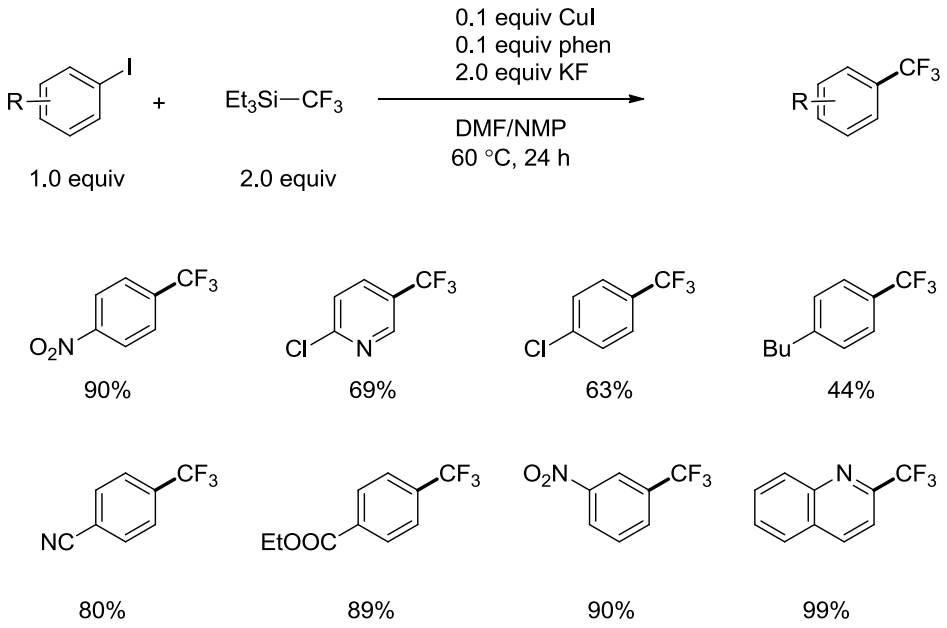
Remarkably, the reaction temperature was lower for the pentafluoroethylation of aryl iodides. Efficiency of the reaction did not suffer, and pentafluoroethylated products were obtained in comparable yields (Scheme 1.12)

Scheme 1.12. Pentafluoroethylation using TMS-C_2F_5



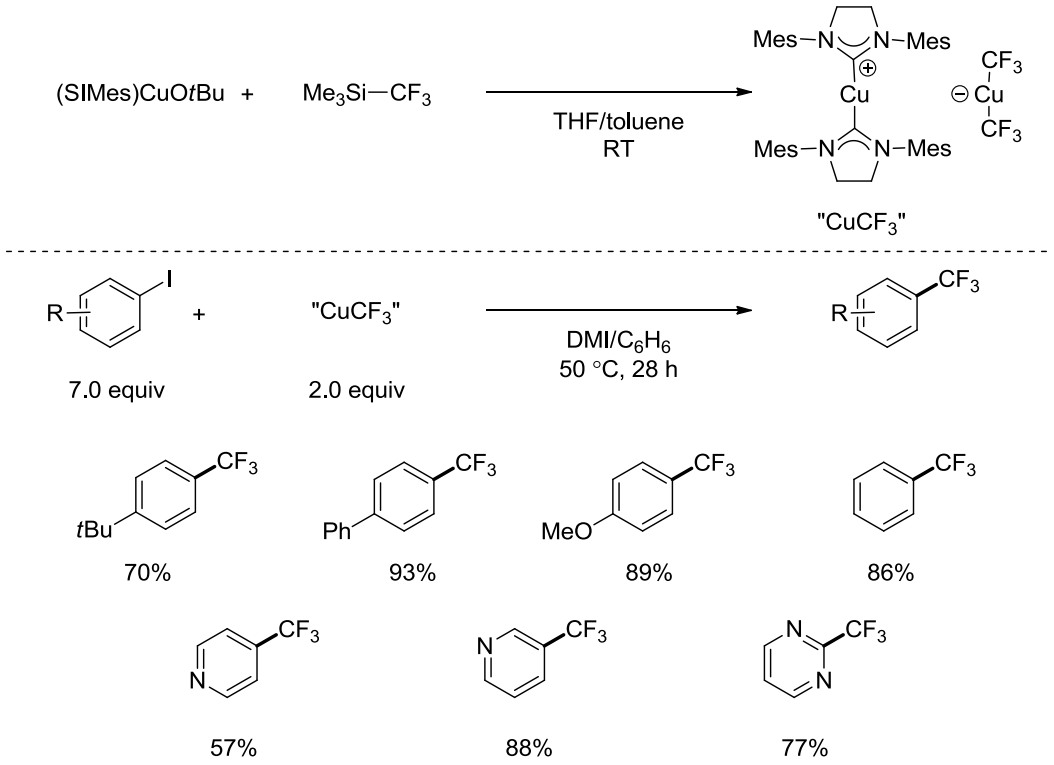
Amii and coworkers[16] made a major breakthrough, when they developed catalytic version of Urata and Fuchikami reaction. The addition of the bidentate nitrogen-based ligand allowed one to considerably lower the amount of copper used (Scheme 1.13.).

Scheme 1.13. Amii catalytic trifluoromethylation



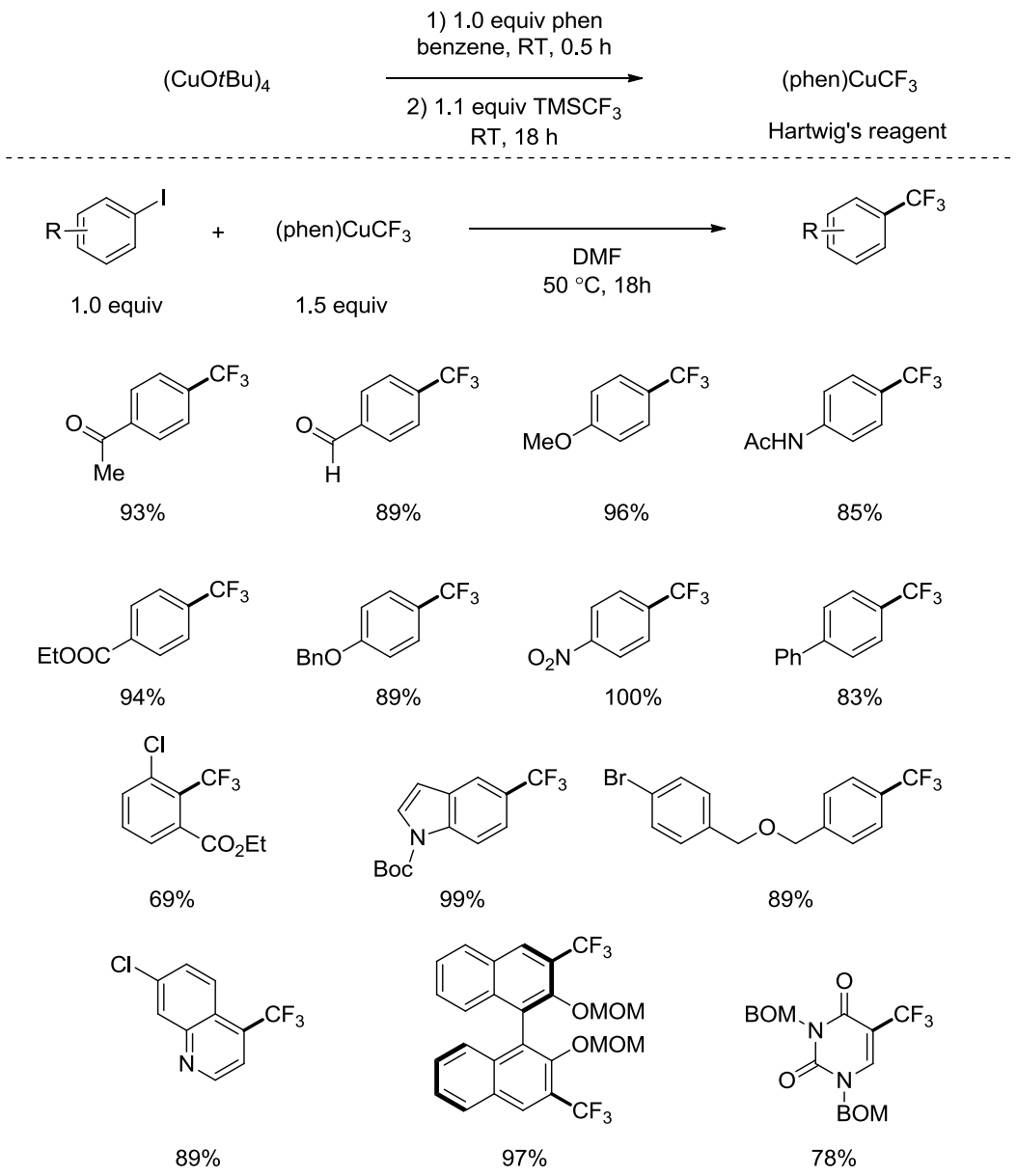
Vicic and coworkers[17] have reported preparation of the first well-defined, structurally characterized trifluoromethyl copper species ligated by N-heterocyclic carbene. Researchers were able to demonstrate competence of this species as a trifluoromethylating reagent when employed in the reaction with number of aryl iodides (Scheme 1.14).

Scheme 1.14. Vicic cross-coupling protocol

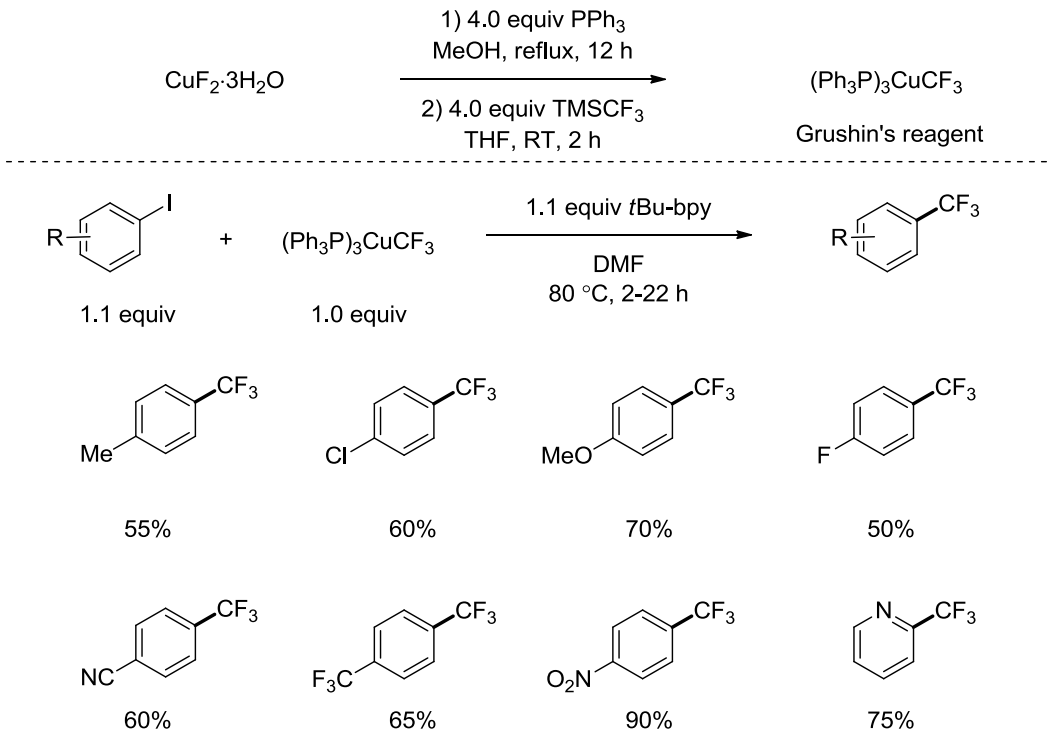


Several years later, groups of Hartwig[18] and Grushin[19] nearly simultaneously reported preparation of other stable copper-based trifluoromethylating reagents. Both reagents are derived from the Rupert-Prakash reagent in the presence of stoichiometric copper salt (Scheme 1.15 and 1.16). A wide variety of aryl iodides could be cross-coupled with the reagents providing high yields of the products and excellent functional group tolerance.

Scheme 1.15 Hartwig's trifluoromethylation



Scheme 1.16. Grushin's trifluoromethylation



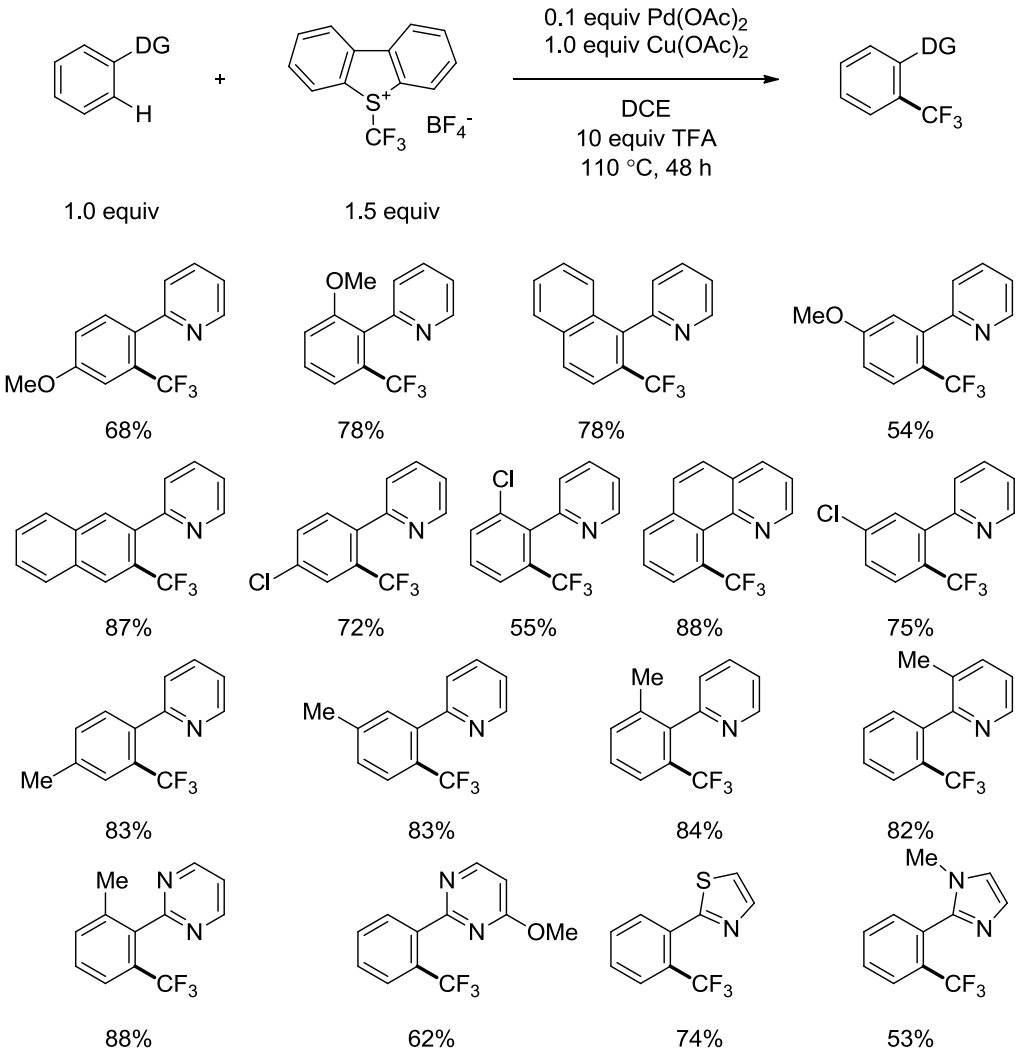
In order to improve the scope and the applicability of the devised reactions, researchers are developing novel reagents for trifluoromethylation and perfluoroalkylation based on stoichiometric amounts of copper, Rupert-Prakash reagent,[14] and additional ligands. Even though it is a step back in terms of moving to catalytic processes, overall scope of the trifluoromethylation has improved.[1]

III. Copper-promoted polyfluoroalkylation of arene C-H Bonds

III.1. Carbon-hydrogen bond polyfluoroalkylation

In 2010 Yu and coworkers[20] reported the first directed regioselective trifluoromethylation of unactivated aryl C-H bonds using palladium catalysis. Substrates possessing a range of directing groups are successfully trifluoromethylated *ortho*- to the heteroarene substituent. The reaction requires use of electrophilic trifluoromethylating Umemoto reagent[9] and stoichiometric amount of copper salt as a promoter. A number of functional groups are well tolerated under reaction conditions (Scheme 1.17). Only mono trifluoromethylation products were observed under reaction conditions. Unfortunately, the presence of non-removable directing group in the substrate has decreased overall utility of the method.

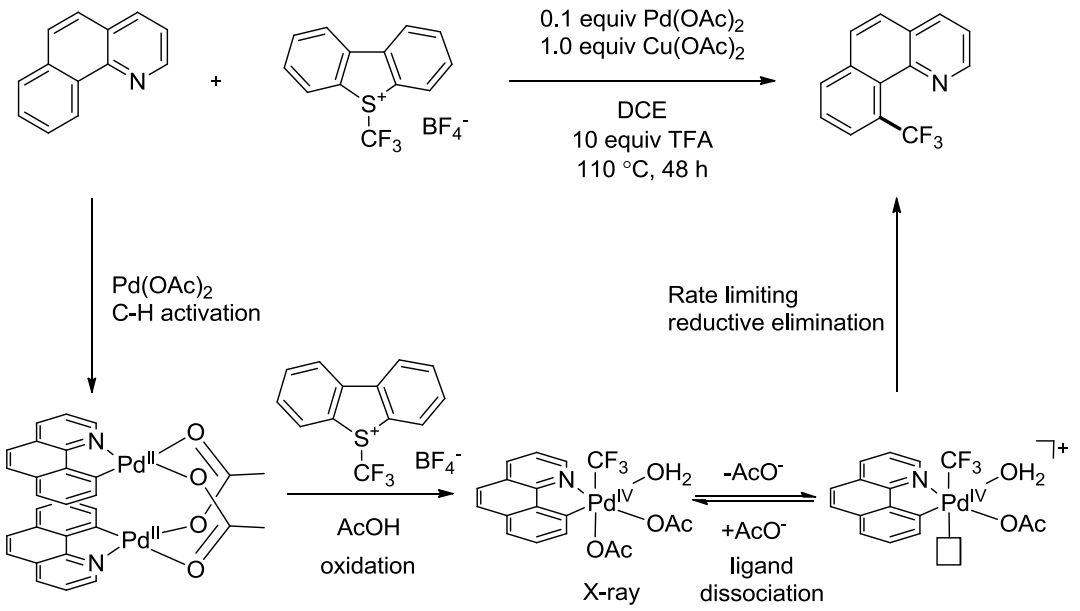
Scheme 1.17. Trifluoromethylation of aryl C-H bonds



In order to address underlying mechanistic intricacies, Sanford and coworkers have performed detailed, in-depth mechanistic studies using Yu's system.[21] According to their study, both copper (II) acetate and trifluoroacetic acid are necessary for the reaction, and appear to have an overall positive effect on mass balance and rate of the reaction. Based on kinetic data combined with the stoichiometric reactions and isolation of

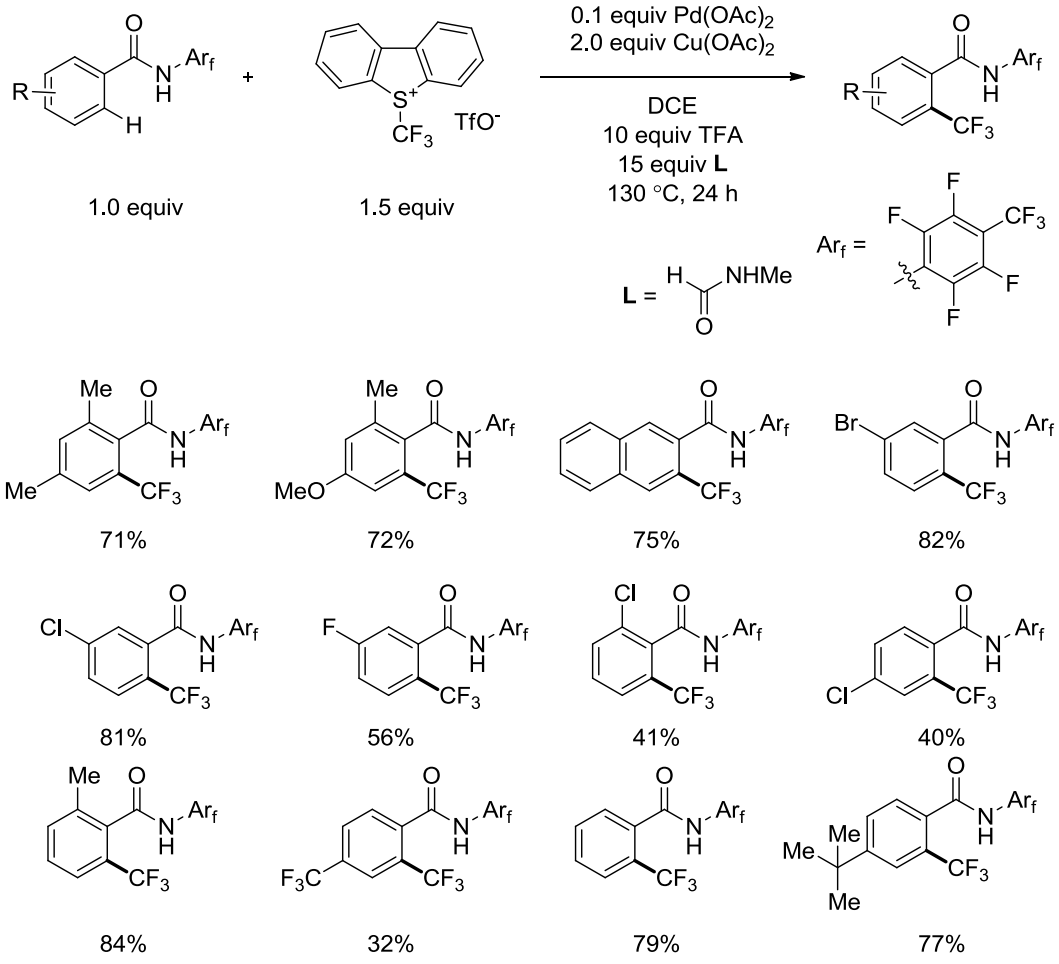
putative reaction intermediates, they have provided a possible reaction mechanism (Scheme 1.18).

Scheme 1.18. Proposed mechanism for C-H trifluoromethylation



Subsequently, Yu and coworkers have developed a method for *ortho*-functionalization of benzoic acid derivatives.[22] The incoming trifluoromethyl group is installed *ortho*- to the removable benzamide auxiliary, thus substantially increasing overall utility of the transformation. Remarkably, no trifluoromethylation was observed without added copper salt, highlighting the role of copper as an important promoter of the reaction. The substrate scope was substantially increased, compared to the previous report (Scheme 1.19).

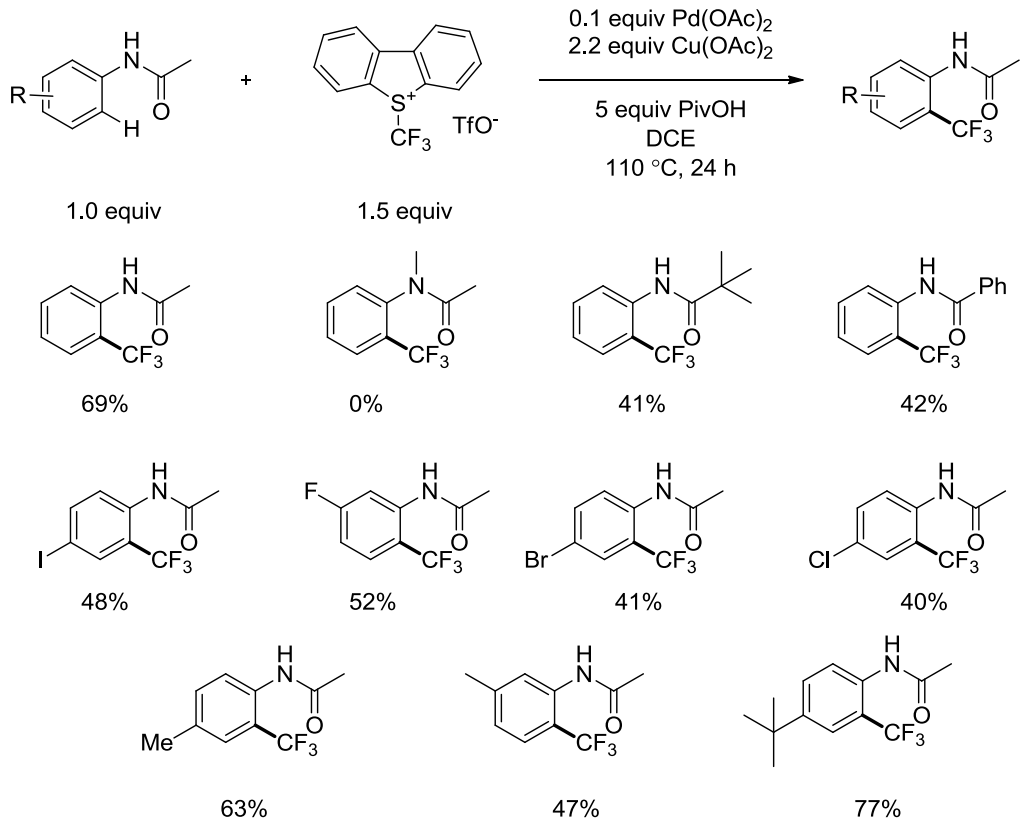
Scheme 1.19. Catalytic trifluoromethylation of benzoic acid derivatives



Subsequently, Shi and coworkers have reported copper-promoted, palladium-catalyzed protocol for selective trifluoromethylation of arene C-H bonds *ortho*- to an acetamido group.[23] Applying essentially the same conditions as those developed by Yu and coworkers,[20,22] they were able to trifluoromethylate a wide array of the acetanilides bearing a number of sensitive functional groups. Similarly to previous reports, a copper promoter was essential to obtain conversion to the product. Remarkably, N-methyl

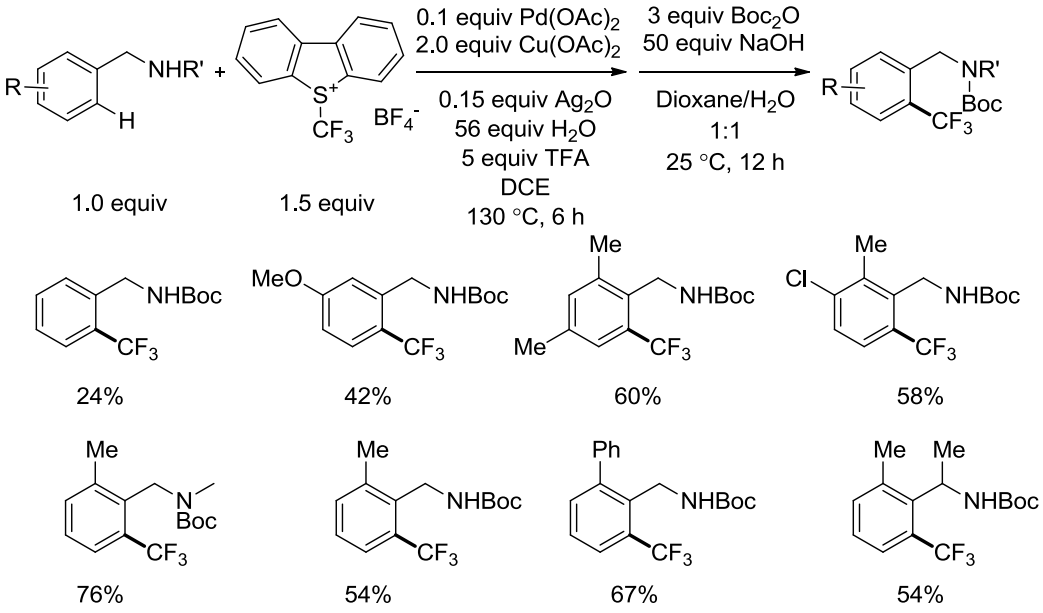
substituted acetanilide did not provide any product, and bulkier benzanilides and pivaloylanilides afforded much lowered yields. (Scheme 1.20.)

Scheme 1.20. Trifluoromethylation of acetanilides



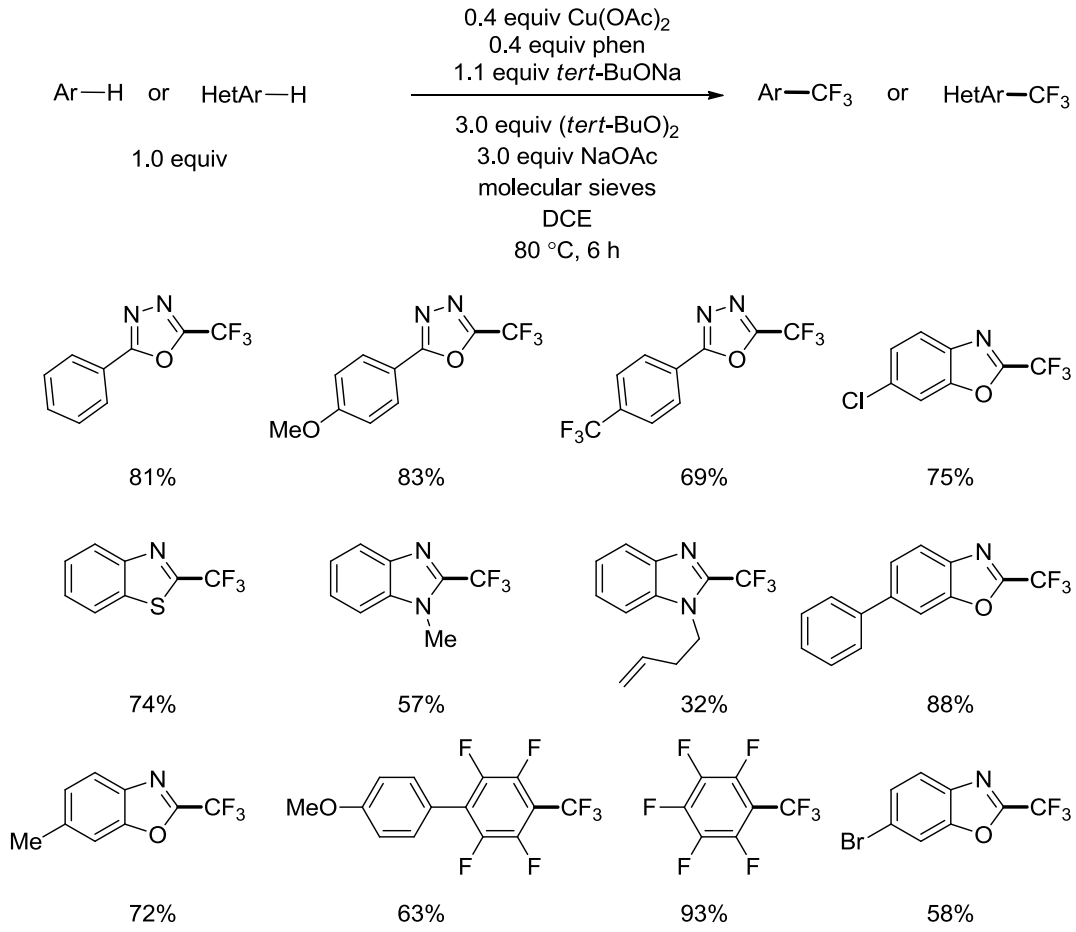
Yu and coworkers have reported on a method for the *ortho*-trifluoromethylation of unprotected benzylamines.[24] After applying minor changes to their previously described protocols, they were able to successfully expand the scope of the reaction to include benzylamine derivatives. Copper salt is an integral component of the method (Scheme 1.21).

Scheme 1.21. Trifluoromethylation of unprotected benzylamines



Qing and coworkers have reported on a copper-catalyzed method for the trifluoromethylation of heterocycles and electron-poor arenes (Scheme 1.22.).[25] One of the prerequisites of this transformation is the presence of a relatively acidic arene or heteroarene carbon-hydrogen bond. Trifluoromethylation occurs at the most acidic position of the arene or heteroarene.

Scheme 1.22. Trifluoromethylation of electron-poor arenes and heterocycles



VI. Catalytic trifluoromethylsulfenylation of arenes

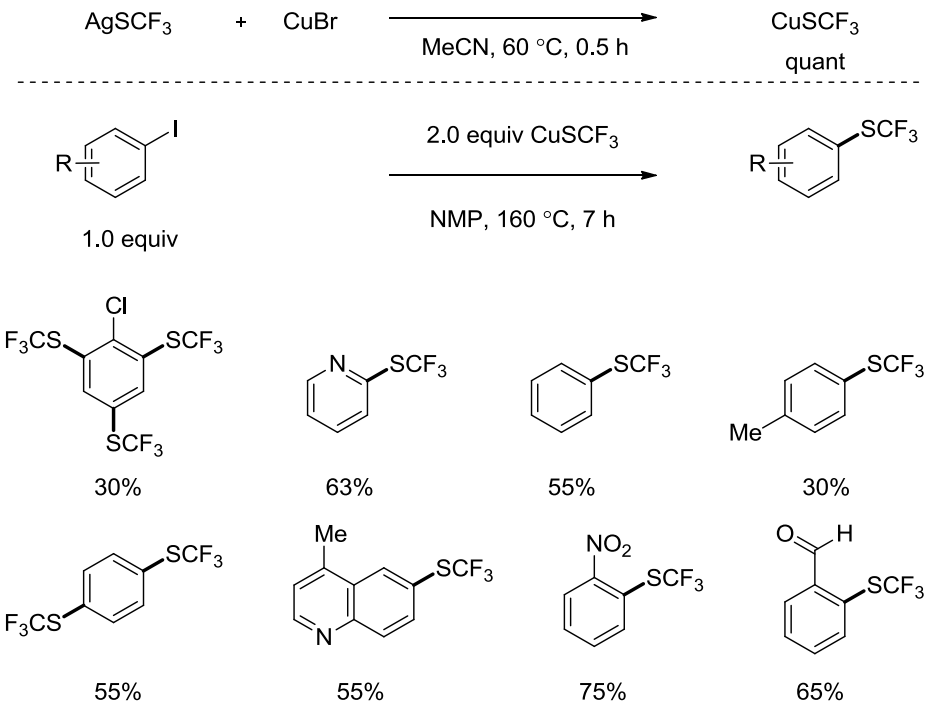
VI.1. Trifluoromethylsulfenylation of carbon-heteroatom bonds

The direct introduction of trifluoromethylsulfenyl group has attracted a substantial amount of attention from synthetic organic chemists.[26] Low polarity and increased lipophilicity of SCF_3 moiety are desirable properties in biologically relevant compounds.

Historically, copper was the first metal that has been shown to promote cross-coupling reaction between an SCF_3 containing nucleophile and aryl iodides. Thus, it is not a surprise that most of the methods that exist in the literature are based on copper-promoted introduction of trifluoromethylsulfenyl group.[1]

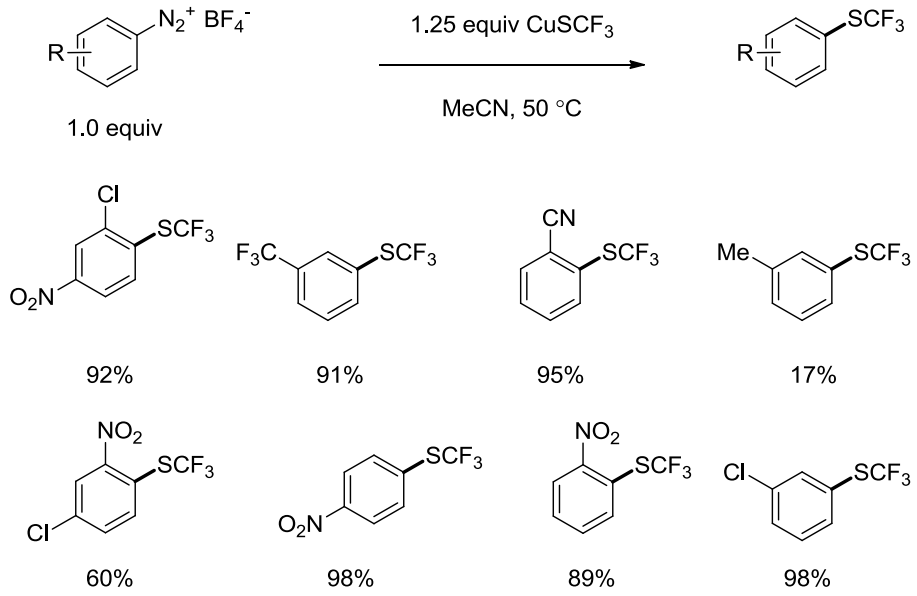
Pioneering example of direct introduction of SCF_3 group using copper was reported by Yagupolskii and coworkers.[28] Trifluoromethylthiocopper reagent was prepared from trifluoromethylthiosilver by anion exchange in dry MeCN. Copper species bearing SCF_3 substituent were subsequently cross-coupled with a variety of aryl iodides using polar aprotic solvents and rather high reaction temperatures. (Scheme 1.23.). Several functional groups were tolerated and yields ranged from fair to good. Subsequently, others have contributed to the expansion of the method by introducing other sources of $CuSCF_3$.[29]

Scheme 1.23. Yagupolskii reaction



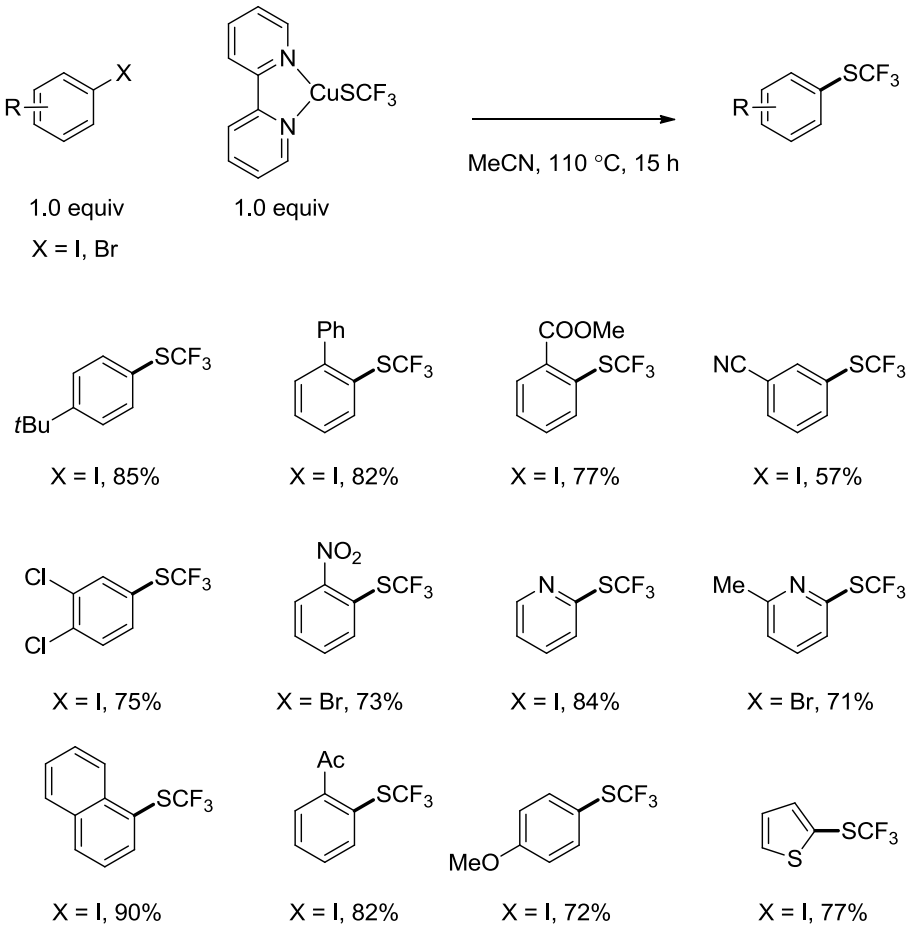
Clark and coworkers have reported trifluoromethylsulfenylation of aryl diazonium salts using $CuSCF_3$ reagent.[30] Even though the reaction temperature was much lower compared to Yagupolskii protocol, only diazonium salts bearing electron-withdrawing substituents afforded cross-coupling products in good yields (Scheme 1.24.).

Scheme 1.24. Trifluoromethylsulfenylation of aryl diazonium salts



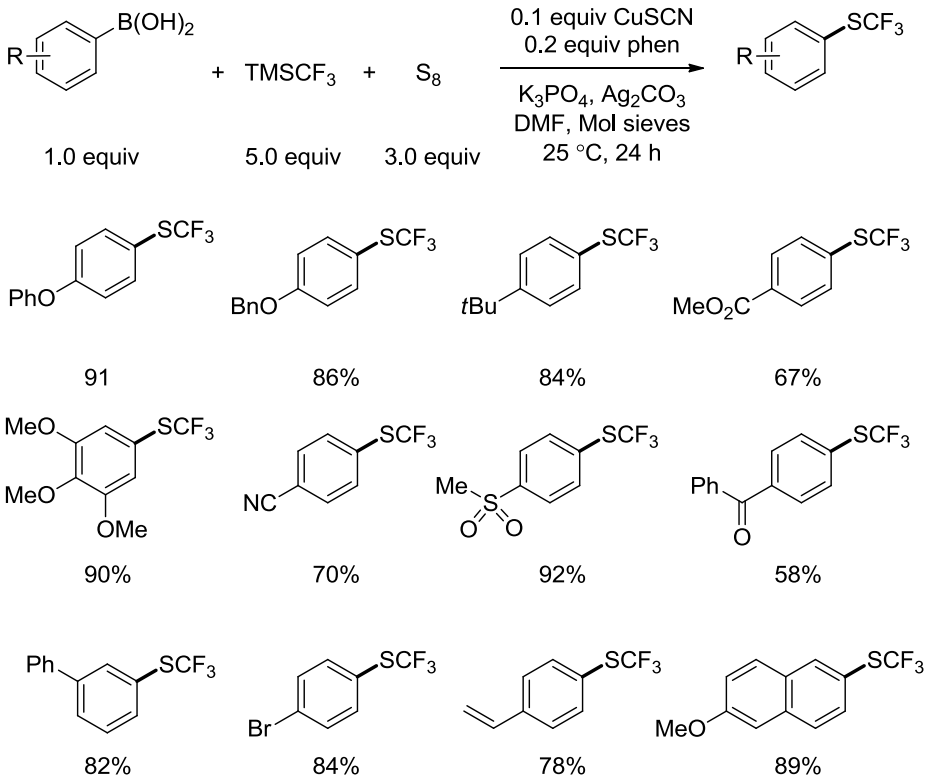
Huang and coworkers reported cross-coupling reaction of aryl iodides and select aryl bromides with $CuSCF_3$ species complexed with a bidentate bipyridine ligand.[31] Using this copper species, reaction temperature could be significantly reduced compared to the original report by Yagupolskii. Furthermore, reaction scope was greatly expanded to include two examples of aryl bromides (Scheme 1.25.).

Scheme 1.25. Trifluoromethylsulfenylation of aryl iodides and bromides



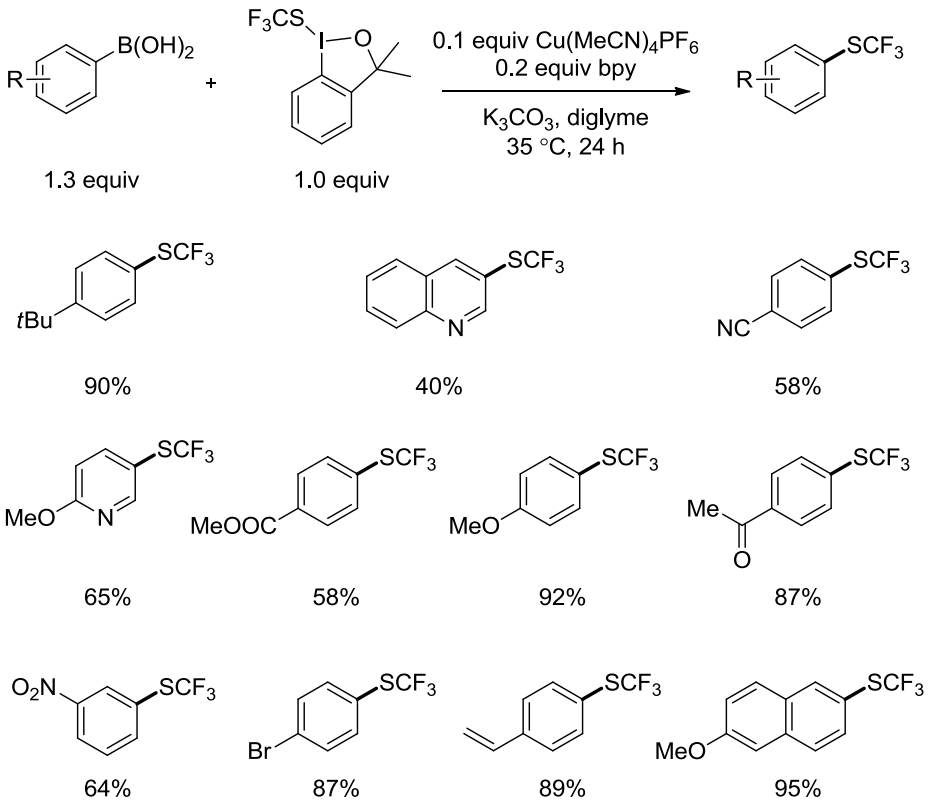
Very recently, new methods for direct, copper-promoted introduction of the trifluoromethylsulfenyl moiety using aryl pronucleophiles under oxidative conditions have been reported. Qing and coworkers have disclosed a direct introduction of the SCF_3 group using oxidative copper-catalyzed cross-coupling of aryl boronic acids.[31] In the presence of elemental sulfur, potassium triphosphate, and Rupert-Prakash reagent, boronic acids are converted to trifluoromethylsulfenyl-substituted arenes with silver carbonate acting as a terminal oxidant (Scheme 1.26).

Scheme 1.26. Oxidative trifluoromethylsulfenylation of aryl boronic acids



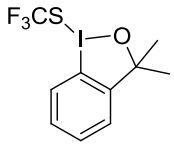
A similar, oxidative approach for trifluoromethylsulfenylation of aryl boronic acids was reported by Lu and Shen group.[33] The authors were able to utilize a Togni-type reagent as a source of SCF_3 as well as an oxidant. Various aryl boronic acids took part in the reaction and provided products in good to excellent yields (Scheme 1.27). The substrate scope and reported yields are very similar to those reported by Qing and coworkers.[32]

Scheme 1.27. Electrophilic trifluoromethylsulfenylation or aryl boronic acids

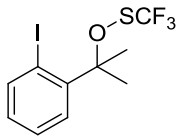


Recently Buchwald and coworkers have revised the structure of the electrophilic trifluoromethylsulfenylating reagent used by Shen.[34] Applying analytical tools such as ^{1}H NMR spectroscopy and X-ray diffraction studies, they revealed that SCF_3 substituent is attached to an oxygen atom and not to an iodine atom as previously assumed (Scheme 1.28). Nonetheless, structural reevaluation of the reagent did not change the conclusions of previous reports.

Scheme 1.28. Proposed and revised structure of electrophilic SCF_3 reagent



Proposed



Revised

IV. Conclusions

Despite significant progress in the field of direct copper-catalyzed or promoted introduction of perfluoroalkyl or trifluoromethylsulfenyl substituents, there is still substantial room for improvement. Perfluoroalkylation or trifluoromethylsulfenylation of arene C-H bonds is lagging far behind. Relatively slow progress is explained by the lack of solid mechanistic considerations and relatively small pool of available reagents, as well as difficulties in reductive elimination of aryl/perfluoroalkyl groups from a metal center. Further studies should be focused on the development of mild, user friendly methods for the direct functionalization of non-activated carbon-hydrogen bonds in arenes and alkanes.

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CHAPTER 2 METHODS FOR COPPER-CATALYZED DIRECT INTRODUCTION OF PERFLUOROALKYL- AND TRIFLUOROMETHYLSULFENYL- GROUPS ONTO ARENES

I. Introduction

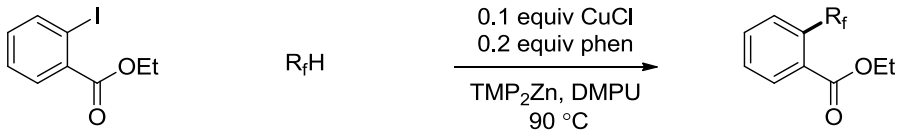
As shown in Chapter 1, there are relatively few methods for direct copper-catalyzed introduction of perfluoroalkyl and trifluoromethylsulfenyl groups onto an aromatic ring.[1] The use of copper would have a beneficial effect on the overall cost of the reaction, since it avoids use of expensive second and third row transition metals. Furthermore, reactions need to have broad scope and reliability in order to be useful. This includes easily accessible substrates, high fidelity, and predictability of the reaction, as well as the possibility of facile scale up. In order to achieve these goals, we have attempted to develop direct copper-catalyzed arylation of easily accessible 1*H*-perfluoroalkanes using aryl iodides, and a method for regioselective trifluoromethylsulfenylation of aromatic carbon-hydrogen bonds of benzamide derivatives using bidentate directing group.

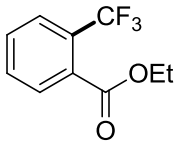
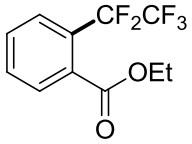
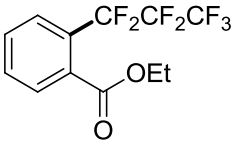
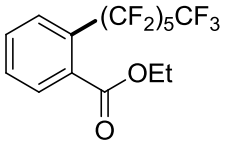
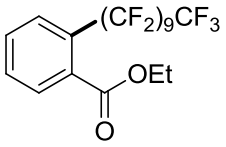
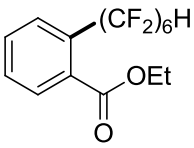
II. Results and discussions

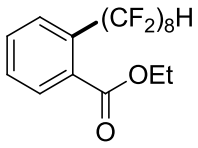
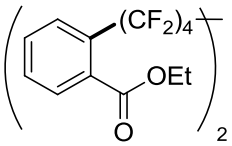
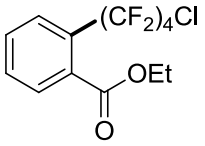
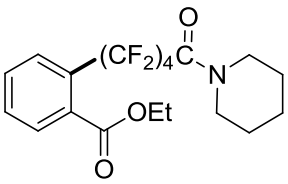
II.1. Arylation of 1*H*-perfluoroalkanes with aryl iodides

We began our investigation by selecting the target substrates for initial optimization. From the very beginning it became clear that ionic bases like alkali metal phosphates, carbonates, or alkoxides are not viable for this reaction, since they in most cases lead to decomposition of 1*H*-perfluoroalkanes. The bulky zinc amide base TMP_2Zn was identified as a suitable base.[2] Bis(tetramethylpiperidino)zinc base is sufficiently strong to be able to deprotonate relatively weakly acidic[3] C-H 1*H*-perfluoroalkanes, yet mild enough not to interfere with the subsequent reactions or cause decomposition of any other reagent. There are also strict requirements with respect to reaction concentration, temperature, and identity of the solvent. It was discovered that only by using dry DMPU solvent at 90 °C in fairly concentrated solutions can products be produced in the good to excellent yields. We hypothesized that a zinc base acts not only just a spectator, but indeed acts as a metalating agent producing perfluoroalkyl zinc intermediates *in situ*.[4] Therefore, a zinc reagent acts as a reservoir for the perfluoroalkyl anion equivalents which would otherwise be too unstable to persist long enough in the reaction mixture to be efficiently cross-coupled under copper catalysis. The reaction scope with respect to different 1*H*-perfluoroalkanes is summarized in Table 2.1.

Table 2.1 Direct arylation of 1*H*-perfluoroalkanes[a]



Entry	1*H*-Perfluoroalkane	Product	Yield (%)
1[b]	CF_3H		51
2	CF_3CF_2H		96
3	$CF_3CF_2CF_2H$		83
4	$CF_3(CF_2)_4CF_2H$		87
5	$CF_3(CF_2)_9CF_2H$		81
6	$H(CF_2)_6H$		79

7	$H(CF_2)_8H$		84
8[c]	$H(CF_2)_8H$		63
9	$Cl(CF_2)_4H$		94
10[d]	$C_5H_{10}NCO(CF_2)_4H$		62

[a] TMP_2Zn (0.75 mmol), R_fH (1.5–5 mmol), DMPU, ArI (0.5 mmol), phenanthroline (0.1 mmol), CuCl (0.05 mmol), 90 °C. [b] Phenanthroline (1 mmol) [c] TMP_2Zn (1 mmol), R_fH (0.5 mmol), DMPU, ArI (4 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol). [d] TMP_2Zn (0.5 mmol), R_FH (0.5 mmol), DMPU, ArI (1.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol

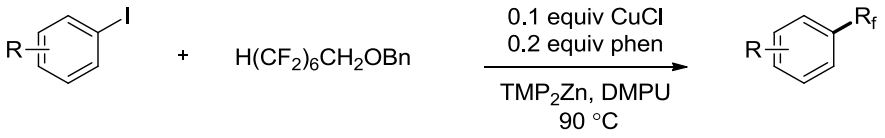
Perfluoroalkylation of ethyl 2-iodobenzoate shows unprecedented scope with respect to 1*H*-perfluoroalkanes. Simple 1*H*-perfluoroalkanes such as trifluoromethane (entry 1) and pentafluoroethane (entry 2) as well as higher homologues (entries 3-5) can be arylated in moderate (entry 1) to excellent (entries 2-5) yields. The lower yield of trifluoromethylation arises from the fact that corresponding trifluoromethyl copper and zinc intermediates are very thermally sensitive, and at higher reaction temperatures are prone to decomposition. This protocol allows selective mono- or diarylation of substrates possessing two acidic carbon hydrogen bonds (entries 6, 7, 8), depending on the reaction

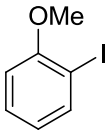
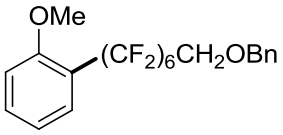
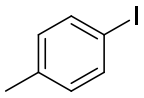
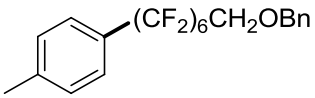
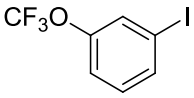
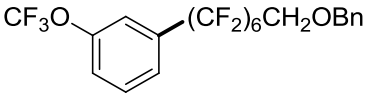
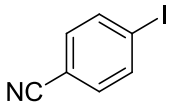
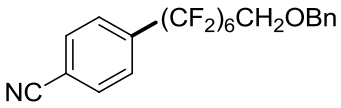
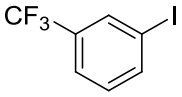
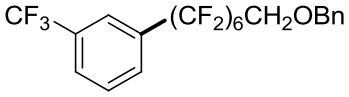
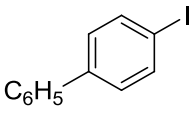
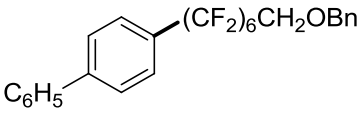
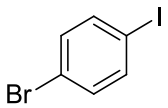
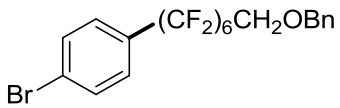
conditions and stoichiometry of the reaction. Remarkably, our protocol also allows installation of the polyfluoroalkyl moieties containing functional groups such as perfluoroalkyl chloride (entry 9) or perfluorocarboxylic acid amide (entry 10). The reaction is very clean and no decomposition is observed.

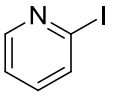
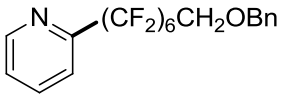
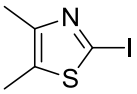
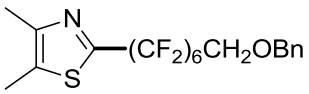
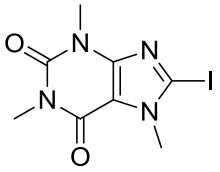
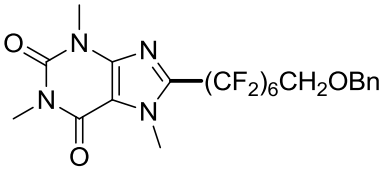
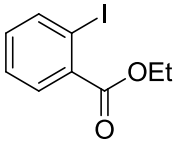
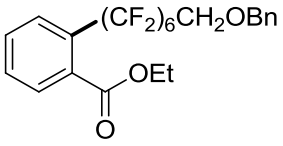
II.2. Arylation of 1*H*-perfluoroalkanes with aryl iodides

We turned our attention towards establishing the reaction scope with respect to aryl iodides. Towards this end, we had to design the 1*H*-perfluoroalkane substrate, since the simple representatives shown in Table 1 afforded products that have physical properties similar to their corresponding aryl iodide starting materials, hindering efficient purification. Additionally, the high volatility of some of the aryl substituted perfluoroalkanes hindered their recovery from the reaction mixture. Benzylated α,α,ω-trihydroperfluoroheptanol was identified as a satisfactory substrate, since its arylated derivatives were non-volatile and more polar than corresponding aryl iodides, which allowed facile recovery and separation of the products. The reaction scope with respect to aryl iodides is presented in Table 2.2.

Table 2.2. Reaction scope with respect to aryl iodides[a]



Entry	Aryl iodide	Product	Yield (%)
1			51
2			51
3			55
4[b]			83
5			61
6			62
7			53

8			85
9 [b]			63
10 [b]			94
11 [b]			92

[a] TMP_2Zn (0.5 mmol), R_FH (0.5 mmol), DMPU, then ArI (1.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol), 90 °C. [b] TMP_2Zn (0.75 mmol), R_FH (1.5 mmol), DMPU, then ArI (0.5 mmol), phenanthroline (0.1 mmol), and CuCl (0.05 mmol)

Perfluoroalkylation of electron-rich aryl iodides such as 2-iodoanisole and 4-iodotoluene afforded products in moderate yields (entries 1 and 2). In contrast, reactions with electron-poor aryl iodides provide products in much higher yields (entries 3–5, 7, 11). A broad scope of functional groups such as trifluoromethoxy (entry 3), nitrile (entry 4), bromide (entry 7), and ester (entry 11) is tolerated. Gratifyingly, different heteroaryl iodides such as 2-iodopyridine, 2-iodo-4,5-dimethylthiazole, and 8-iodocaffeine provide the product in good (entry 9) to excellent yield (entries 8 and 10).

Some limitations with respect to coupling partners were observed and are as follows. Electron-rich 2,6-disubstituted aryl iodides do not afford the coupling product,

and unactivated electron-rich or electron-neutral aryl bromides are unreactive under reaction conditions. Similarly, aryl chlorides are inert under reaction conditions.

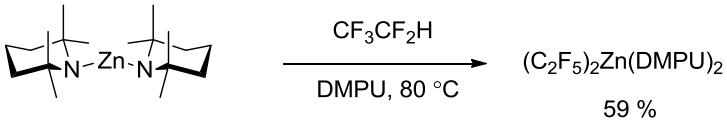
II.3. Mechanistic considerations

The perfluoroalkylation reaction can be divided into several elementary steps: deprotonation/zincation, transmetalation with copper (I) salt, and perfluoroalkylation of the aryl iodide. A series of stoichiometric experiments were performed in order to clarify reactivity of proposed intermediates. Relative rates of presumed elementary steps will be discussed in more detail.

II.3.1. Base-mediated deprotonation/zincation step

It is well established that 1*H*-perfluoroalkanes are weak acids, with pKa values on the order of 29-31 pKa units.[3] TMP_2Zn is known to be a competent base for the substrates of comparable C-H acidity to 1*H*-perfluoroalkanes. However, reactivity of TMP_2Zn with 1*H*-perfluoroalkanes has never been established.[5] We were able to estimate approximate qualitative reaction parameters for the direct deprotonative zincation reaction, which is the first step in the overall catalytic reaction sequence (Scheme 2.1.).

Scheme 2.1. Deprotonation/zincation of pentafluoroethane



It was established through experimentation that at room temperature the deprotonation reaction is very sluggish. Increasing reaction temperature allowed

deprotonation/zincation of pentafluoroethane to take place, providing homoleptic pentafluoroethyl zinc species complexed by two molecules of DMPU in the solid state, as was revealed by single crystal X-ray analysis (Figure 2.1). To the best of our knowledge, this was the first perfluoroalkyl zinc complex that has been crystallographically characterized.[6]

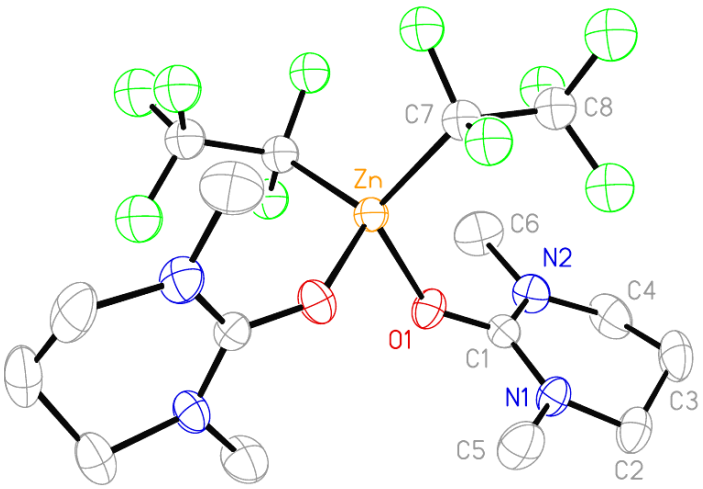
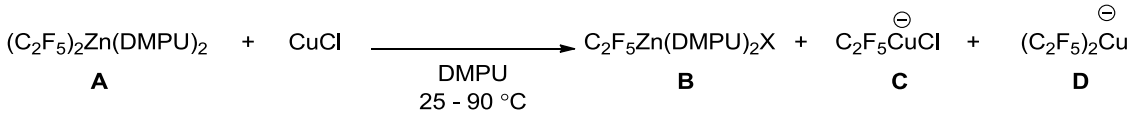


Figure 2.1. Structural view (40% ellipsoids) of $(C_2F_5)_2Zn(DMPU)_2$ complex showing partial atom numbering scheme.

II.3.2. Transmetalation from zinc to copper

We envisioned studying transmetalation reaction between pentafluoroethyl zinc and copper salt employing ^{19}F NMR. A solution of perfluoroalkyl zinc reagent was allowed to react with copper (I) chloride in DMPU solvent at various temperatures. Qualitative parameters and observed products are summarized in Table 2.3.

Table 2.3. Transmetalation of copper halide and perfluoroalkyl zinc



Entry	Temperature (°C)	Observed Products
1	25	Only **A**
2	45	Mostly **A**, minor **B**+**C**
3	90	Less **A**, more **B**+**C**+**D**

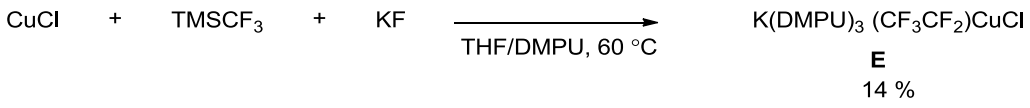
It is clear that in the transmetalation between perfluoroalkylzinc and copper chloride, several pentafluoroethyl group containing species are formed. Temperature dependence was established and no transmetalation reaction took place at room temperature. Heating to 45 °C increased the rate of the transmetalation and perfluoroalkyl copper species **B** and **C** began to appear. Raising the reaction temperature further to 90 °C allowed us to considerably increase the rate of the reaction and to observe new species **D**. New products were tentatively assigned as corresponding monopentafluoroethyl zinc species **B**, which was formed roughly at the same pace and in the same ratio as heteroleptic cuprate species **C** at 45°C, and homoleptic cuprate species **D**, which

appeared later in the reaction and at much higher temperature. To our knowledge, this is the first example of the transmetalation studies involving perfluoroalkyl zinc complexes and copper (I) halide.

II.3.3. Synthesis of heteroleptic cuprate salt

In order to probe intermediacy of cuprates versus neutral copper species in the arylation reaction, we prepared and fully structurally characterized first pentafluoroethyl chlorocuprate species **E** (Scheme 2.2.).[7]

Scheme 2.2. Synthesis of pentafluoroethyl chlorocuprate



Anionic copper complex **E** was prepared in low yield by reaction of CuCl, KF, and $TMSCF_3$. Complex **E** exists as a temperature, moisture, and air sensitive colorless solid that slowly decomposes at 25 °C under an argon atmosphere over the course of several hours. It is stable for at least 4 weeks at −35 °C under an inert atmosphere. When compound **E** is dissolved in DMPU and ^{19}F NMR spectrum is acquired, the position of the fluorine signals is identical to that of species **C**. This implies that both species **C** and **E** have the same anion composition.

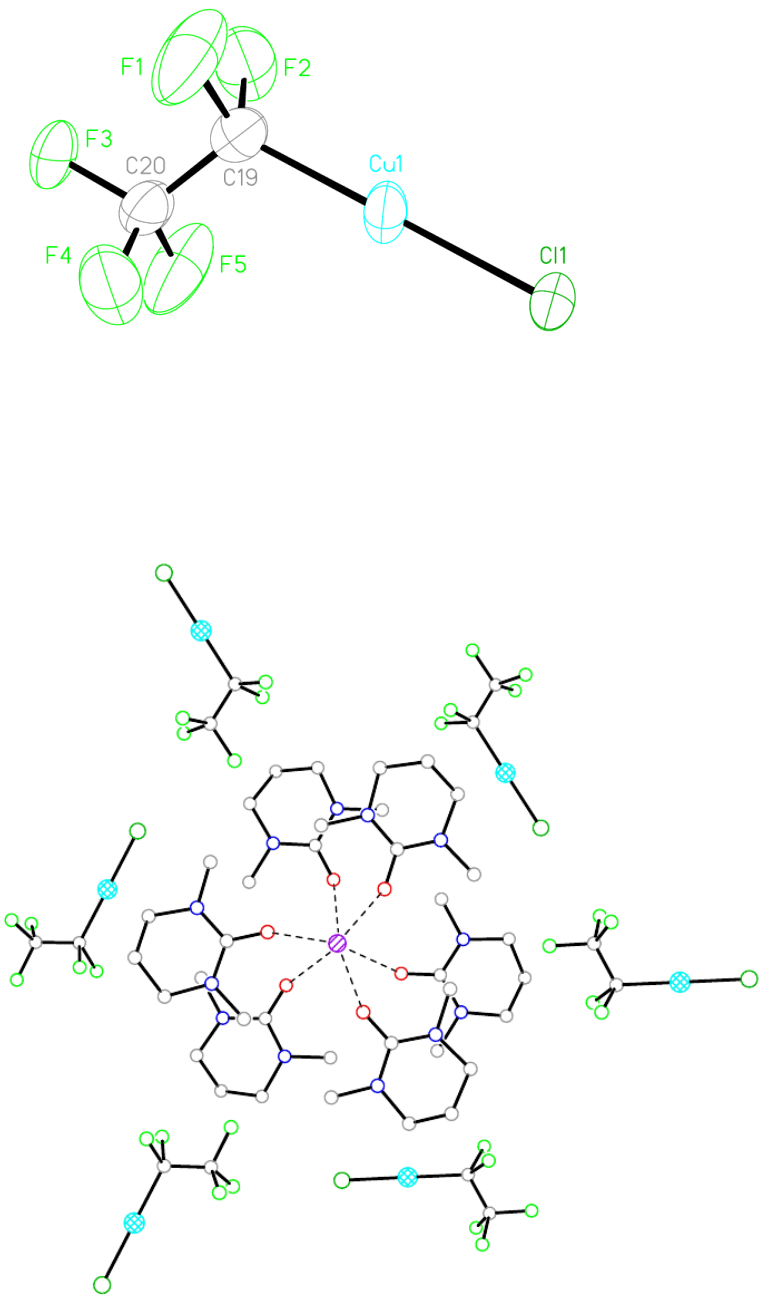
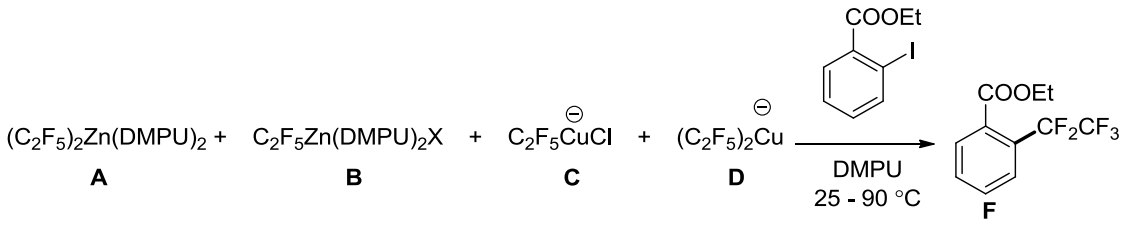


Figure 2.2. Structural view (40% ellipsoids) of $(C_2F_5)CuCl\ K(DMPU)_3$ complex showing partial atom numbering scheme.

II.3.4. Cuprate reaction with aryl iodides

In order to probe the reactivity of the cuprates and to test the corresponding relative rates of transmetalation and arylation reactions, the following experiments were performed. Pregenerated mixture of zinc and copper reaction intermediates in the presence of excess of the parent pentafluoroethyl zinc reagent was subjected to the reaction with substoichiometric amounts of 2-ethyl iodobenzoate. Reaction temperature and observed species are indicated in the Table 2.4.

Table 2.4. Stoichiometric reaction between cuprates and aryl iodide



Entry	Temperature (°C)	Observations
1	25	Consumption of **C** and **D** Formation of **F**
2	40	Further consumption of **C** and **D**
3	60	Disappearance of **C** and **D** Increase of [**B**] and decrease of [**A**]
4	90	Complete consumption of ArI Reappearance of **C** and **D**

Addition of the aryl iodide to the mixture of cuprates and excess zinc reagent consumes copper species at the temperatures from 25 °C to 40 °C. Only after increasing the temperature to 60 °C, did some transmetalation takes place concurrently with arylation. Only after increasing the temperature to 90 °C and complete consumption of the aryl iodide, did reappearance of the cuprate species **C** and **D** takes place. It can be concluded that under the reaction conditions, the rate of transmetalation is much slower than the corresponding reaction between copper species and the aryl iodide. Furthermore, homoleptic species **D** reacts faster with ethyl 2-iodobenzoate than the corresponding heteroleptic species **C**. Additional experiments with **D** and **E** showed that regardless the preparation procedures of the anionic copper species, both cuprates are reactive towards aryl iodides providing the product of pentafluoroethylation reaction. The evidence supports intermediacy of the anionic cuprates as being active catalytic species in the copper catalyzed perfluoroalkylation reaction. However, ligand dissociation and the formation of neutral perfluoroalkyl copper species prior to the reaction with aryl iodides cannot be ruled out at this point.

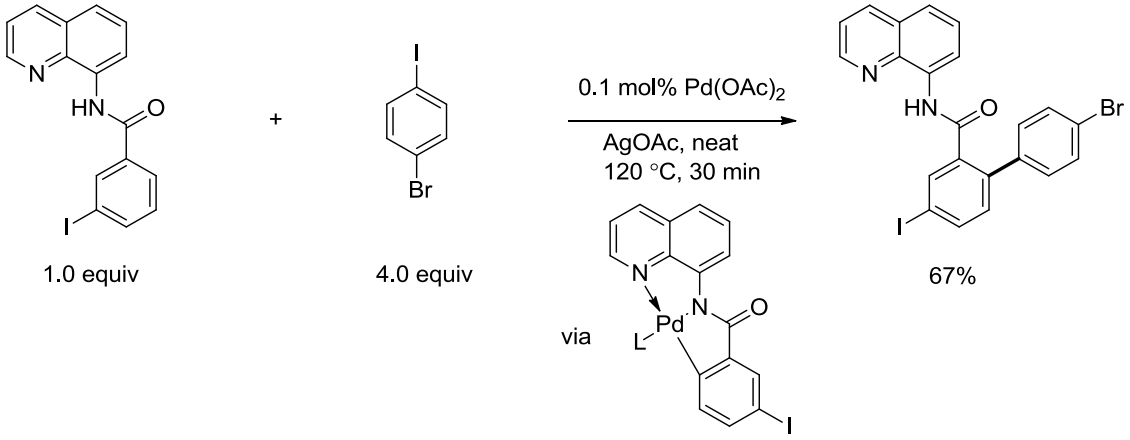
In conclusion, the first general method for the direct arylation of readily available 1*H*-perfluoroalkanes with aryl iodides was discovered. An unprecedented substrate scope for both 1*H*-perfluoroalkanes and aryl iodides was observed. Multiple intermediates were observed in solution and several were structurally characterized in the solid state by single crystal X-ray diffraction studies. Mechanistic investigations point out the complex mixture of intermediates present in the reaction mixture, among which homoleptic and heteroleptic anionic perfluoroalkyl copper species are likely to be catalytically competent

entities. Furthermore, it was established that under stoichiometric reaction conditions transmetalation is slower than the corresponding reaction between perfluoroalkyl copper species and aryl iodide.

II.4. Trifluoromethylsulfenylation of arene C-H bonds

Based on the groundbreaking chelation-assisted methodology for palladium-catalyzed arylation and alkylation of bezamide *ortho*- C-H bonds pioneered by our group we envisioned that other transformations could be promoted using cheaper and more abundant first row transition metals (Scheme 2.3).[8]

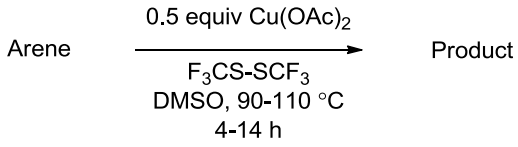
Scheme 2.3. 8-Aminoquinoline amide directed *ortho*-arylation

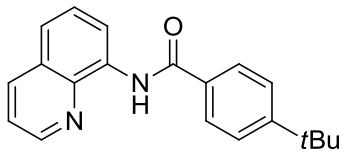
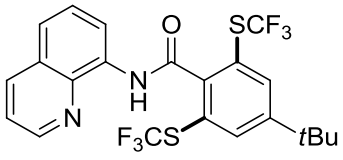
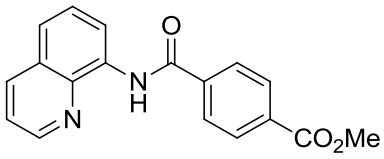
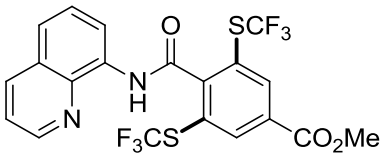
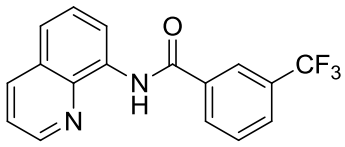
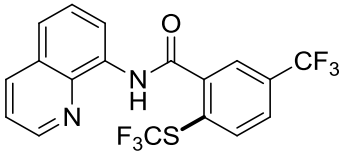
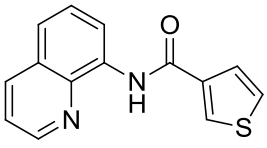
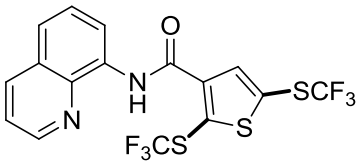


Thus, employing 8-aminoquinoline auxiliary and substoichiometric amount of copper (II) acetate in the presence of trifluoromethyl disulfide, *ortho*- positions of benzoic acid were cleanly trifluoromethylsulfenylated. The partial reaction scope is shown in Table 2.5. Importantly, the reaction provides disubstituted reaction products if both of the *ortho*- positions in the substrate are available. A thiophene derivative was

reactive under reaction conditions and provided product in synthetically useful yield (Entry 4).

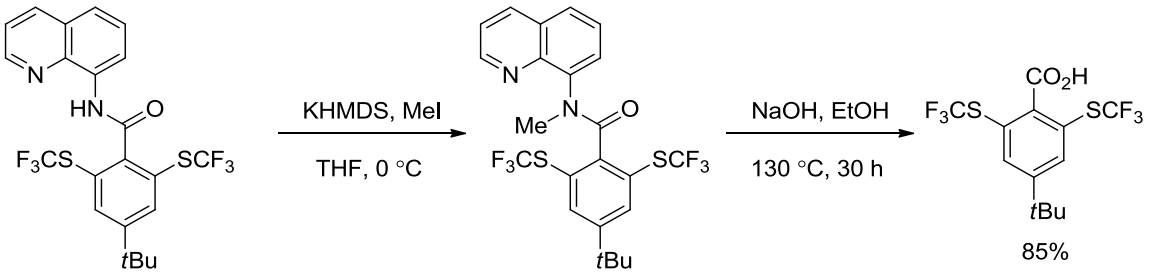
Table 2.5. Trifluoromethylsulfenylation of benzamides



Entry	Arene	Product	Yield (%)
1			76
2			72
3			52
4			56

Trifluoromethylsulfenylated benzamides can be cleanly converted to corresponding carboxylic acids via two step, one pot reaction– methylation followed by hydrolysis under basic conditions (Scheme 2.4)

Scheme 2.4. Removal of auxiliary



In summary, we have developed the first copper-catalyzed method for direct chelate-assisted functionalization of non-acidic arene C-H bonds *ortho*- to an amide moiety. The method employs removable 8-aminoquinoline amide auxiliary and introduces pharmaceutically important *SCF_3* substituent starting from ubiquitous carbon-hydrogen bonds.

III. Conclusions

In conclusion, we have developed a general method for arylation of readily available 1*H*-perfluoroalkanes. The method employs aryl iodide and 1*H*-perfluoroalkane reagents, a DMPU solvent, a TMP_2Zn base, and a copper chloride/phenanthroline catalyst. Additionally, we have developed a method for direct, auxiliary-assisted sulfenylation of β-sp^2 C-H bonds of benzoic acid derivatives and γ-sp^2 C-H bonds of benzylamine derivatives. The reaction employs catalytic or stoichiometric $Cu(OAc)_2$,

disulfide reagent, and DMSO solvent at elevated temperatures. The utilization of inexpensive copper acetate and removable directing group are significant advantages that allow for an increased usefulness of the reaction. The reaction shows high generality, excellent selectivity toward *ortho*- C-H bonds, as well as good functional group tolerance. This method provides a novel and straightforward way for the preparation of aryl trifluoromethyl thioethers.

IV. Experimental section

Arylation of 1H-perfluoroalkanes with aryl iodides

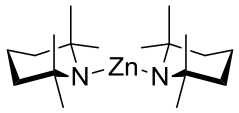
General considerations. All the reactions were performed in flame- or oven-dried glassware. Schlenk flasks or 1-dram vials with PTFE/Liner caps were used for the pre-generation of the perfluoroalkylzinc reagents. THF, Et_2O and pentane were used directly from the solvent purification system. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Preparative plate chromatography was performed on Analtech silica gel plates, 2000 micron thickness, with UV-254 indicator. Purification by HPLC was performed on Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GCMS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H and ^{19}F NMR spectra were recorded on a JEOL ECA-500 or ECX-400P spectrometer using TMS or residual solvent peak as a standard. Melting points are uncorrected. Hexafluorobenzene (1% in C_6D_6, δ = -164.9) was employed as an external standard or α, α, α-trifluorotoluene (δ = -63.72) as

an internal standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on Fluka silica gel/TLC plates with fluorescent indicator 254 nm.

Materials. The following starting materials were obtained from commercial sources and were used without further purification. Caffeine, K_3PO_4, phenanthroline, 4-iodobromobenzene and 4-iodotoluene were obtained from Acros. DMPU and n-BuLi (2.5 M solution in hexane) were purchased from Aldrich. CuCl and $ZnCl_2$ were from Alfa Aesar. 2,2,6,6-Tetramethylpiperidine, 1-iodo-3-(trifluoromethyl)benzene, 4,5-dimethylthiazole, 4-iodobiphenyl, 3-(trifluoromethoxy)iodobenzene, ethyl-2-iodobenzoate and 2-iodoanisole were obtained from Matrix Scientific. Trifluoromethane, pentafluoroethane, 1*H*-heptafluoropropane, 1*H*,4*Cl*-perfluorobutane, 1*H*-perfluorohexane, 1*H*,6*H*-perfluorohexane, 1*H*,8*H*-perfluorooctane, 1*H*-perfluorodecane, 1*H*,1*H*,7*H*-dodecafluoroheptanol and ethyl 5*H*-perfluoropentanoate were bought from SynQuest. 2-Iodopyridine and NBu_4I were bought from TCI America. Iodocaffeine and 2-iodo-4,5-dimethylthioazole were prepared from the caffeine and 4,5-dimethylthiazole[9] by following previously described procedures.

Synthesis of the starting materials:

Preparation of TMP_2Zn



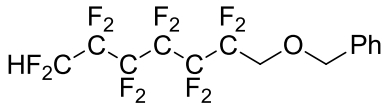
All manipulations were done using standard Schlenk techniques. Reaction mixtures and product should be protected from air and moisture. TMP_2Zn is extremely water and air sensitive; all manipulations with it should be carried out inside an inert gas-filled glovebox. TMP_2Zn can be stored inside a nitrogen-filled glovebox at room temperature with <1ppm of oxygen for at least 2 months without decomposition.

Needles and cannulas were dried in oven for 24 h at 200 °C. All glassware, Celite® and $ZnCl_2$ were flame-dried under vacuum before the reaction. $ZnCl_2$ should be fused for best results.

To the cooled solution (0 ^oC, ice bath) of 2,2,6,6-tetramethylpiperidine (260 mmol, 36.7 g) in pentane (300 mL), *n*-BuLi in hexane (250 mmol, 100 mL of a 2.5 M solution) was added over 10 min. After the addition was over, the yellow to dark yellow solution was allowed to warm to room temperature. The reaction mixture was allowed to stir at least for 12 h under positive pressure of Ar. All solvents and excess of TMPH were removed under vacuum. The yellow solid (LiTMP) was dried under vacuum at room temperature for 5 h. Freshly dried $ZnCl_2$ (133 mmol, 18.1 g) was dissolved in dry Et_2O (200 mL). Flask with solid TMPLi was refilled with Ar and cooled to -95 °C (liquid

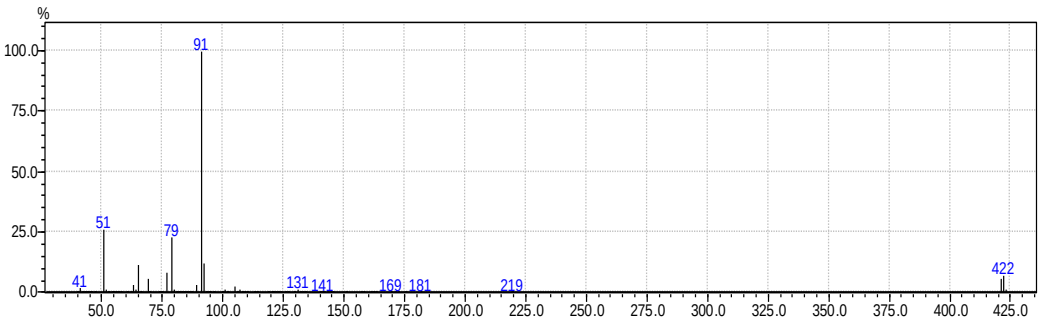
nitrogen/acetone bath). Subsequently, the solution of $ZnCl_2$ in dry Et_2O was slowly added via cannulas to the solid TMPLi over 15-20 min. followed by additional dry Et_2O (200 mL). Reaction was allowed to warm to room temperature and stirred under positive pressure of Ar for at least 14 h. Stirring was discontinued and LiCl was allowed to settle. Liquid was removed from the flask by Schlenk filtration through the plug of Celite® under Ar. Solid residue that was left in the reaction flask was rinsed with dry Et_2O (200 mL). LiCl was allowed to settle and liquid was subjected to Schlenk filtration through the plug of Celite® and combined with the first filtrate. Et_2O was removed in vacuum. The obtained residue usually is yellow to orange oil or solid. Pentane (about 50 mL) was added and mixture was gently heated to dissolve the product. The pentane solution was subjected to the Schlenk filtration through the plug of Celite® under Ar and solvent was removed in vacuum. The residue was dried in vacuum at 50 °C for 5h to give a light tan to light orange solid, generally obtained in high purity (^{1}H NMR in C_6D_6). Typical yields are >95%. Usually >42 g of the product was obtained.

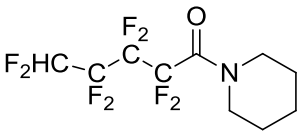
NOTE: It is ***essential*** to make TMP_2Zn free of LiCl or other Li salts. Purity of the TMP_2Zn prepared by the described method is sufficient for obtaining reproducible yields in the catalytic reaction.



((2,2,3,3,4,4,5,5,6,6,7,7-Dodecafluoroheptyloxy)methyl)benzene:

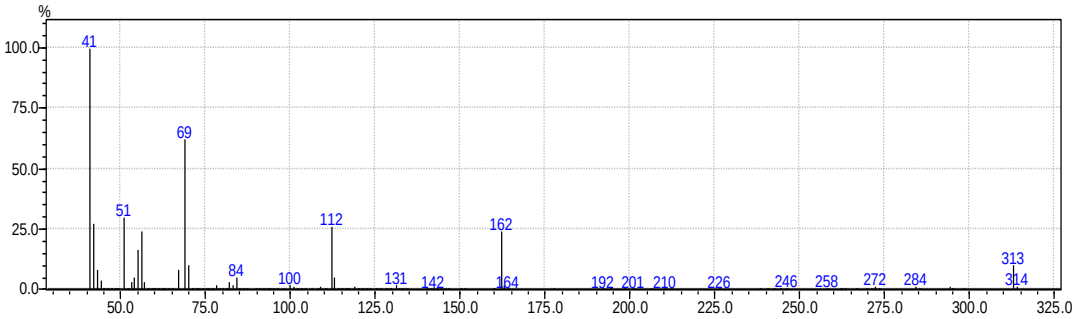
Inside the glovebox an oven-dried 500 ml Schlenk flask equipped with a magnetic stir bar was charged with K_3PO_4 (63 g, 297 mmol), NBu_4I (3 g, 8 mmol) and dry DMF (300 mL). The sealed flask was taken out of the glovebox. To this mixture BnBr (60 g, 351 mmol) and $H(CF_2)_6CH_2OH$ (75 g, 226 mmol) were added. Reaction mixture was allowed to stir at RT for 16 h. Reaction mixture was quenched with concentrated aqueous ammonia (100 mL). After stirring for 2 h, the mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x500 mL). Combined organic layers were washed with 2N HCl (2x300 mL), saturated $NaHCO_3$ (2x100 mL; **caution**! gas evolution), and brine. After drying over anhydrous $MgSO_4$ and filtration the solvent was evaporated in vacuum. After column chromatography (gradient 10%-40% CH_2Cl_2 in hexanes) 83.9 g (88%) of colorless oil was obtained. R_f=0.55 (SiO_2, CH_2Cl_2/hexanes 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.92 (t, *J*=14.0 Hz, 2H), 4.65 (s, 2H), 5.99 (tt, *J*=5.2 and 52.0 Hz, 2H), 7.26-7.40 (m, 5H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -138.1 (d, *J*=5.2 Hz, 2F), -130.7- -130.5 (m, 2F), -124.6- -124.4 (m, 2F), -124.4- -124.2 (m, 2F), -123.4- -123.0 (m, 2F), -120.5- -120.3 (m, 2F). FT-IR (neat, cm^{-1}) υ 1197, 1140. Anal calcd for $C_{14}H_{10}F_{12}O$ (422.21 g/mol): C, 39.83; H, 2.39; Found. C, 39.62; H, 2.35.



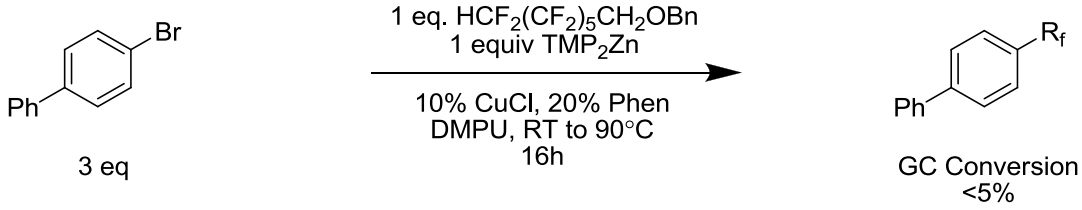


2,2,3,3,4,4,5,5-Octafluoro-1-(piperidin-1-yl)pentan-1-one:

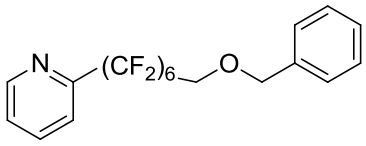
A 100 ml round bottom flask equipped with a magnetic stir bar was charged with ethyl 5-H-perfluoropentanoate (6.85 g, 25 mmol) followed by slow addition of piperidine (1.87 g, 22 mmol). An exothermic reaction ensued. The reaction mixture was stirred at RT for 3 h. After column chromatography (gradient 40%-70% CH_2Cl_2 in hexanes), 6.0 g (87%) of colorless oil was obtained. R_f=0.39 (SiO_2, AcOEt/hexanes 1/9). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.60-1.76 (m, 6H), 3.57-3.65 (m, 4H), 6.34 (tt, *J*=5.6 and 52.4 Hz, 1H). ^{19}F NMR (470.56 MHz, $CDCl_3$) δ -138.8- -138.5 (m, 2F), -129.6- -129.4 (m, 2F), -125.0- -124.9 (m, 2F), -112.6- -112s.5 (m, 2F). FT-IR (neat, cm^{-1}) υ 1677, 1450, 1164, 1121. Anal calcd for $C_{10}H_{11}F_8NO$ (313.19 g/mol): C, 38.35; H, 3.54; N, 4.47; Found. C, 38.05; H, 3.49; N, 4.44.



Attempted reaction with ArBr



Inside the glovebox an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with TMP_2Zn (173 mg, 0.50 mmol), $H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), 4-bromobiphenyl (350 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), and DMPU (0.30 mL). The sealed vial was taken out of the glovebox and placed in oil bath at RT. The temperature of the bath was increased to 60 °C and reaction mixture was stirred for 30 min. The temperature of the oil bath was then increased to 90 °C and the reaction mixture was stirred at this temperature for 16 h. GC analysis revealed <5% conversion to the product.



2-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)pyridine (Entry 8, Table 2.2.)

General procedure **A** was followed:

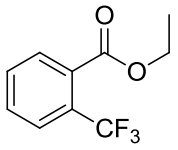
$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 2-iodopyridine (308 mg, 1.5 mmol), with or without phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 1 h at 60 °C, then 13 h at 90 °C. Conversion in both cases was determined to be >95% based on the limiting reagent using ^{19}F NMR with $PhCF_3$ as an internal standard.

A. General procedure for reaction R_fH with ArI with pre-generation of $Zn(R_f)_2$.

Inside the glovebox an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with TMP_2Zn (0.50-1.0 mmol), followed by R_fH (0.50-1.5 mmol) and DMPU (0.25-0.40 ml). The sealed vial was taken out of the glovebox and placed in oil bath at RT. After that, the temperature of the bath was increased to 40-60 °C followed by stirring of the reaction mixture for indicated time. The reaction mixture was allowed to cool to room temperature and placed inside the glovebox, the vial was uncapped and ArI (0.50-4.0 mmol) was added, followed by phenanthroline (0.2 equiv.) and CuCl (0.1 equiv.), and in some cases additional amount of DMPU (0.10-0.50 ml). The sealed vial was taken out of the glovebox and placed in the oil bath at RT. The temperature of the bath was increased to 90 °C and reaction mixture was stirred for indicated time. Reaction mixture was quenched with 1M HCl (20 mL), extracted with AcOEt (3x30 mL), washed with brine, and dried over anhydrous $MgSO_4$. Filtration was followed by flash chromatography on silica gel, or preparative plate chromatography, or HPLC. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield the pure product.

B. General procedure for reaction of R_fH with ArI without pre-generation of $Zn(R_f)_2$.

Inside the glovebox an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with TMP_2Zn (0.50-0.75 mmol), R_fH (0.50-1.5 mmol), ArI (0.50-1.5 mmol), phenanthroline (0.2 equiv.), CuCl (0.1 equiv.), and DMPU (0.30-0.50 ml). The compounds should be mixed in the specified order. The sealed vial was taken out of the glovebox and placed in oil bath at RT. The temperature of the bath was increased to 60 °C and reaction mixture was stirred for indicated time. The temperature of the oil bath was then increased to 90 °C and the reaction mixture was stirred at this temperature for rest of the time. Reaction mixture was quenched with 1M HCl (20 mL), extracted with AcOEt (3x30 mL), washed with brine, dried over anhydrous $MgSO_4$, and filtered. Flash chromatography on silica gel, preparative plate chromatography, or HPLC purification, followed by concentrating the fractions containing the product and drying of the residue under reduced pressure yielded pure product.

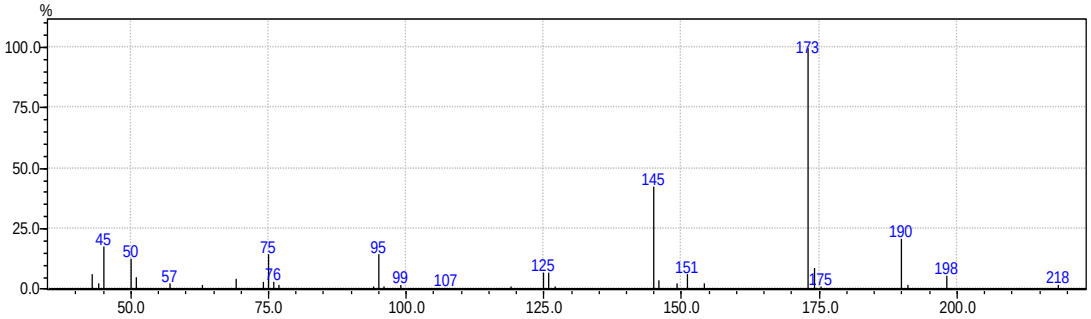


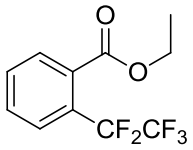
Ethyl 2-(trifluoromethyl)benzoate (Entry 1, Table 2.1.)

Inside the glovebox an oven-dried 1-dram vial equipped with a magnetic stir bar was charged with TMP_2Zn (259 mg, 0.75 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol),

phenanthroline (180 mg, 1.0 mmol), CuCl (5.0 mg, 0.05 mmol), and DMPU (0.40 mL) in the listed order. The vial was capped with septum and the empty balloon was connected to vial through the septum by 21G syringe needle. The vial and balloon were taken out of the glovebox and placed in the oil bath. The CF_3H was added by the needle via vial septum from the tank, inflating the attached balloon to approximately 100 ml volume. The temperature of the oil bath was increased to 65 °C and reaction mixture was allowed to stir for 24 h at that temperature. During the reaction time the volume of the balloon decreased, indicating the consumption of CF_3H. Reaction mixture was quenched with 1M HCl (20 mL), extracted with AcOEt (3x30 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated. Crude material possessed <5% of ethyl 2-perfluoroethylbenzoate impurity.

After column chromatography (gradient 30%-60% CH_2Cl_2 in hexanes), followed by preparative HPLC (2% of EtOAc in hexanes) 56 mg (51%) of the colorless oil was obtained. R_f=0.39 (SiO_2, CH_2Cl_2/hexanes 1/3). This compound is known. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.37 (t, *J*=7.2 Hz, 3H), 4.39 (q, *J*=7.2 Hz, 2H), 7.55-7.63 (m, 2H), 7.70-7.79 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -59.2 (s, 3F).



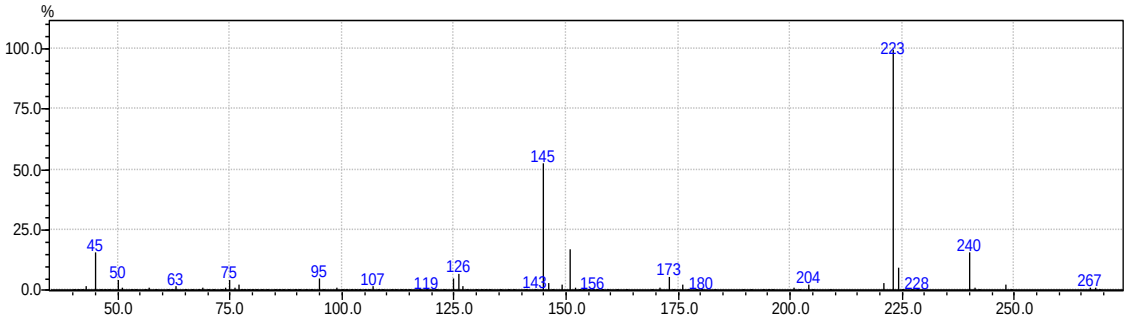


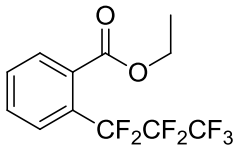
Ethyl 2-(perfluoroethyl)benzoate (Entry 2, Table 2.1.)

Inside the glovebox an oven-dried 10 ml Schlenk flask equipped with a magnetic stir bar was charged with TMP_2Zn (259 mg, 0.75 mmol) and DMPU (0.30 mL). The Schlenk flask was capped with septum and the empty balloon was connected to flask through the septum by 21G syringe needle. The flask and balloon were taken out of the glovebox and placed in the oil bath. The C_2F_5H was added by the needle via flask septum from the tank, inflating the attached balloon to approximately 100 ml volume (ca. 10 equiv of CF_3CF_2H). The temperature of the bath was increased to 70 °C (from RT) and the reaction mixture was allowed to stir at this temperature for 15 h. During this time the volume of the balloon decreased indicating the consumption of the CF_3CF_2H. After the pre-generation was complete the reaction mixture was allowed to cool to RT and the installed balloon was detached. The reaction mixture was evacuated and placed inside the glovebox. The residue from the Schlenk flask was suspended in additional amount of DMPU (0.20 mL). The reaction mixture was transferred via syringe to a 1-dram vial equipped with magnetic stirrer. Ethyl 2-iodobenzoate (138 mg, 0.50 mmol) was added to the zinc reagent solution, followed by phenanthroline (18 mg, 0.10 mmol) and CuCl (5.0 mg, 0.05 mmol) in the stated order. The sealed vial was taken out of the glovebox and placed in the oil bath at RT. The temperature of the bath was increased to 90 °C and reaction mixture was stirred for 11 h. Reaction mixture was quenched with 1M HCl (20

mL), extracted with AcOEt (3x30 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered and dry-adsorbed on silica gel.

After column chromatography (gradient 20%-40% CH_2Cl_2 in hexanes), 129 mg (96%) of a colorless oil was obtained. R_f=0.39 (SiO_2, CH_2Cl_2/hexanes 1/3). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.36 (t, *J*=7.2 Hz, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 7.55-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -109.5 (s, 2F), -84.1 (s, 3F). FT-IR (neat, cm^{-1}) υ 1739, 1299, 1282, 1206, 1153, 1111, 1075. Anal calcd for $C_{11}H_9F_5O_2$ (268.18 g/mol): C, 49.26; H, 3.38; Found. C, 49.30; H, 3.38.

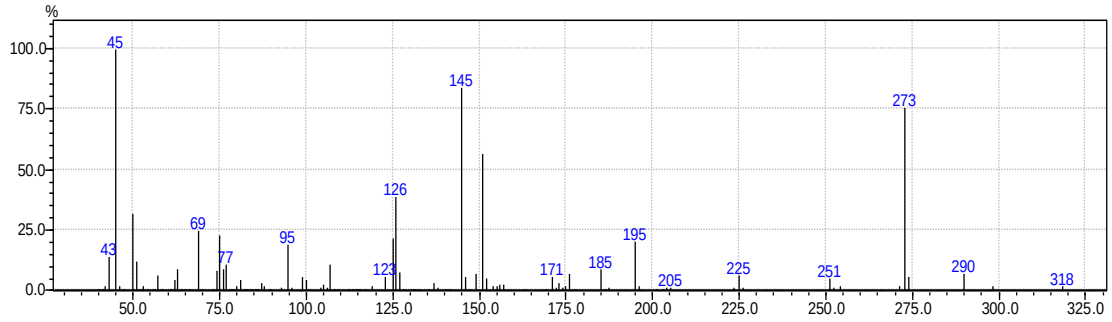


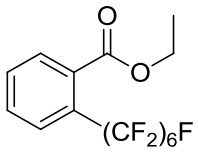


Ethyl 2-(perfluoropropyl)benzoate (Entry 3, Table 2.1.)

Inside the glovebox an oven-dried 10 ml Schlenk flask equipped with a magnetic stir bar was charged with TMP_2Zn (259 mg, 0.75 mmol) and DMPU (0.30 mL). The Schlenk flask was capped with septum and the empty balloon was connected to flask through the septum by 21G syringe needle. The flask and balloon were taken out of the glovebox and

placed in the oil bath. The $CF_3CF_2CF_2H$ was added by the needle via flask septum from the tank, inflating the attached balloon to approximately 100 ml volume. The temperature of the bath was increased to 77 °C (from RT) and the reaction mixture was allowed to stir at this temperature for 6 h. During this time the volume of the balloon decreased indicating the consumption of the $CF_3CF_2CF_2H$. After the pre-generation was complete the reaction mixture was allowed to cool to RT and the balloon was detached. The reaction mixture was placed inside the glovebox. The residue from the Schlenk flask was suspended in the additional DMPU (0.20 mL) and transferred via syringe to a 1-dram vial equipped with magnetic stirrer. Ethyl 2-iodobenzoate (138 mg, 0.50 mmol) was added to the suspension, followed by phenanthroline (18 mg, 0.10 mmol), and CuCl (5.0 mg, 0.05 mmol) in the stated order. The sealed vial was taken out of the glovebox and was placed in the oil bath at RT. The temperature of the bath was increased to 90 °C and reaction mixture was stirred for 13 h. Reaction mixture was quenched with 1M HCl (20 mL), extracted with AcOEt (3x30 mL), washed with brine, dried over anhydrous $MgSO_4$, filtered, and dry-absorbed on silica gel. After column chromatography (gradient 25%-40% CH_2Cl_2 in hexanes), 133 mg (83%) of colorless oil was obtained. R_f=0.36 (SiO_2, CH_2Cl_2/hexanes 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.36 (t, *J*=7.2 Hz, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 7.56-7.67 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.9- -124.8 (m, 2F), -106.6- -106.4 (m, 2F), -81.1 (t, *J*=10.4 Hz, 3F). FT-IR (neat, cm^{-1}) υ 2993, 1739, 1370, 1298, 1229, 1202, 1118, 1059. Anal calcd for $C_{12}H_9F_7O_2$ (318.19 g/mol): C, 45.30; H, 2.85; Found. C, 45.85; H, 2.94.

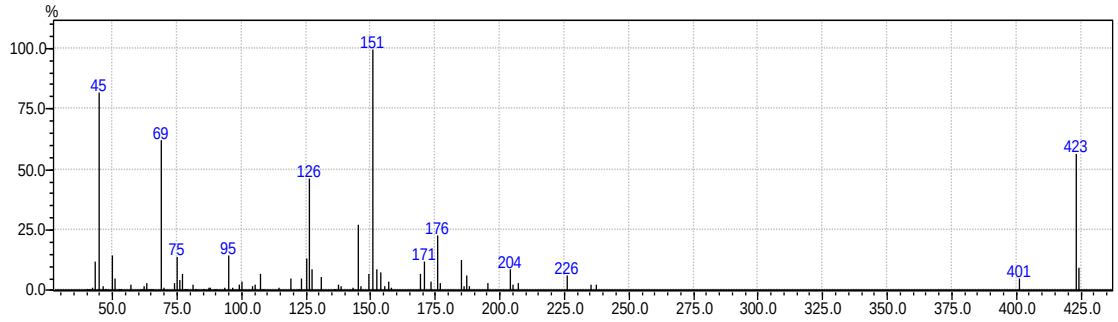


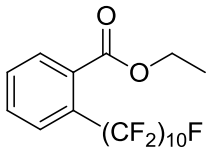


Ethyl 2-(perfluorohexyl)benzoate (Entry 4, Table 2.1.)

General procedure **A** was followed:

1-H Perfluorohexane (480 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation for 1 h at 45 °C, then 14 h at 90 °C. After column chromatography (gradient 15%-30% CH_2Cl_2 in hexanes) 204 mg (87%) of colorless oil was obtained. R_f=0.36 (SiO_2, CH_2Cl_2/hexanes 1/3). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 7.56-7.66 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -127.2- -127.0 (m, 2F), -123.8- -123.6 (m, 2F), -122.8- -122.6 (m, 2F), -120.4- -120.2 (m, 2F), -106.0- -105.8 (m, 2F), -81.8- -81.7 (m, 3F). FT-IR (neat, cm^{-1}) υ 1742, 1365, 1299, 1278, 1239, 1204, 1146. Anal calcd for $C_{15}H_9F_{13}O_2$ (468.21g/mol): C, 38.48; H, 1.94; Found. C, 38.35; H, 1.91.

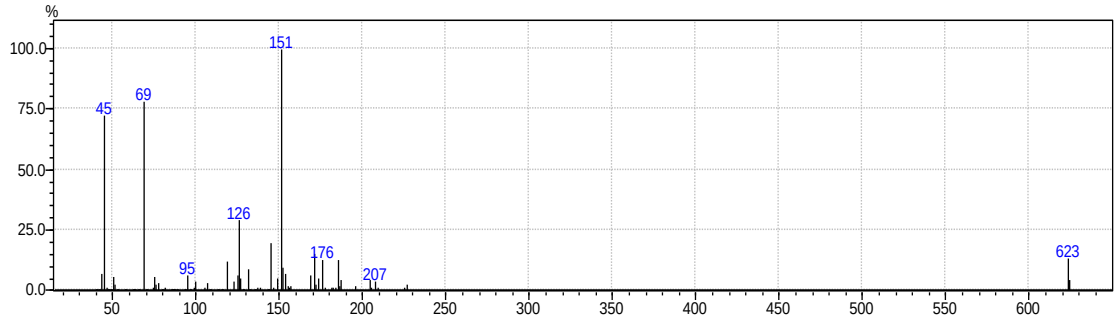


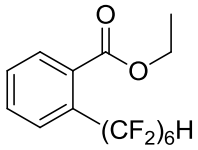


Ethyl 2-(perfluorodecyl)benzoate (Entry 5, Table 2.1.)

General procedure **A** was followed:

$H(CF_2)_9CF_3$ (780 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.40 ml), pre-generation for 2.5 h at 45 °C, then 3 h at 90 °C. After column chromatography (gradient 15%-25% CH_2Cl_2 in hexanes), 272 mg (81%) of white solid was obtained. R_f=0.36 (SiO_2, hexanes/CH_2Cl_2 3/1). Analytical sample was recrystallized from hexanes, mp 44.5-46.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 7.56-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -127.3- -126.0 (m, 2F), -123.9- -123.6 (m, 2F), -123.1- -122.3 (m, 10F), -120.3- -120.1 (m, 2F), -106.0- -105.7 (m, 2F), -82.0- -81.7 (m, 3F). FT-IR (neat, cm^{-1}) υ 1731, 1296, 1282, 1242, 1207, 1149, 1128, 1112, 1082, 1053, 1020. Anal calcd for $C_{19}H_9F_{21}O_2$ (668.24 g/mol): C, 34.15; H, 1.36; Found. C, 34.04; H, 1.30.

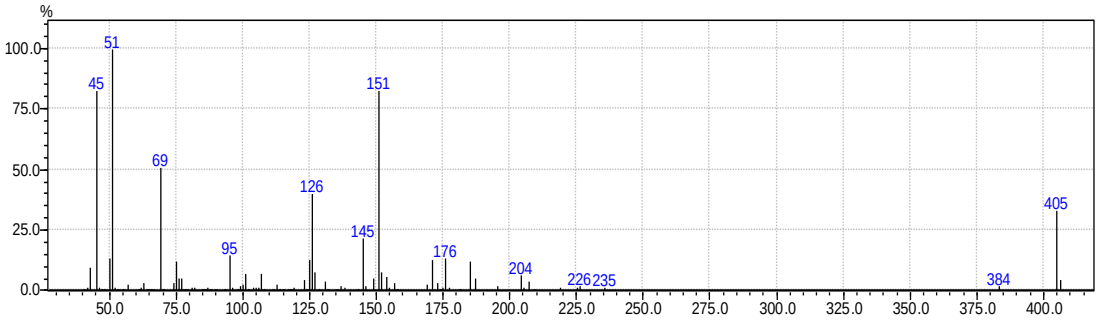


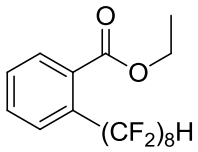


Ethyl 2-(1,1,2,2,3,3,4,4,5,5,6,6-dodecafluorohexyl)benzoate (Entry 6, Table 2.1.)

General procedure **B** was followed:

$H(CF_2)_6H$ (453 mg, 1.5 mmol), TMP_2Zn (173 mg, 0.50 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 ml), 20 min at 60 °C, then 5 h at 90 °C. After column chromatography (gradient 15%-45% CH_2Cl_2 in hexanes), 178 mg (79%) of colorless oil was obtained. R_f=0.32 (SiO_2, hexanes/CH_2Cl_2 3/1). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 6.07 (tt, *J*=5.3 and 52.0 Hz, 1H), 7.55-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -138.2- -138.0 (m, 2F), -130.7- -130.5 (m, 2F), -124.6- -124.4 (m, 2F), -122.9- -122.6 (m, 2F), -120.4- -120.2 (m, 2F), -106.0- -105.8 (m, 2F) . FT-IR (neat, cm^{-1}) υ 2983, 1738, 1305, 1279, 1198, 1140, 1105. Anal calcd for $C_{15}H_{10}F_{12}O_2$ (450.22g/mol): C, 40.02; H, 2.24; Found. C, 40.25; H, 2.13.



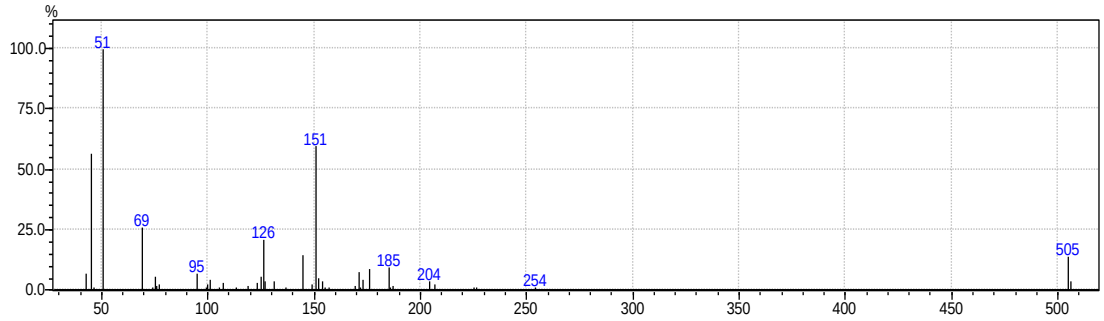


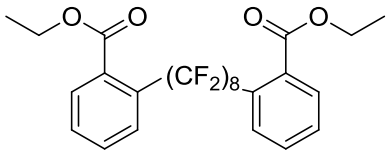
Ethyl 2-(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8-hexadecafluorooctyl)benzoate (Entry 7, Table 2.1.)

General procedure **A** was followed:

$H(CF_2)_8H$ (603 mg, 1.5 mmol), TMP_2Zn (173 mg, 0.50 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 2.5 h at 45 °C, then 3 h at 90 °C. After column chromatography (gradient 25%-50% CH_2Cl_2 in hexanes), 232 mg (84%) of the colorless oil was obtained. R_f=0.34 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 3H), 4.37 (q, *J*=7.2 Hz, 2H), 6.05 (tt, *J*=5.3 and 51.8 Hz, 1H), 7.55-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -138.2- -137.9 (m, 2F), -130.5- -130.3 (m, 2F), -124.4- -124.2 (m, 2F), -123.1- -122.7 (m, 4F), -122.6- -122.4 (m, 2F), -120.3- -120.1 (m, 2F), -105.9- -105.7 (m, 2F). FT-IR (neat, cm^{-1}) υ 1739, 1308, 1276,

1208, 1147. Anal calcd for $C_{17}H_{10}F_{16}O_2$ (550.23 g/mol): C, 37.11; H, 1.83; Found. C, 37.45; H, 1.79.



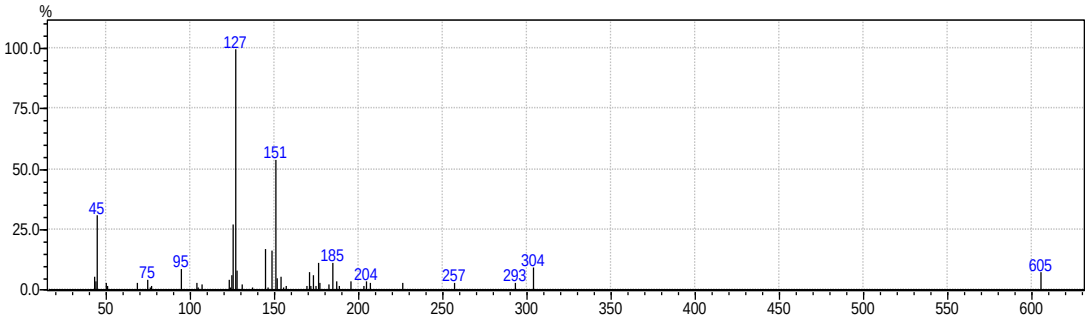


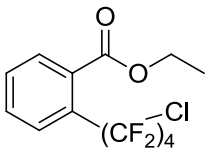
Diethyl 2,2'-(perfluorooctane-1,8-diyl)dibenzoate (Entry 8, Table 2.1.)

General procedure **A** was followed:

$H(CF_2)_8H$ (201 mg, 0.50 mmol), TMP_2Zn (345 mg, 1.0 mmol), ethyl 2-iodobenzoate (1104 mg, 4.0 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (10 mg, 0.10 mmol), DMPU (0.30 mL), pre-generation 2.5 h at 45 °C, then 3 h at 90 °C. After column chromatography (gradient 40%-80% CH_2Cl_2 in hexanes), 221 mg (63%) of yellow solid was obtained. R_f=0.39 (SiO_2, hexanes/AcOEt 3/1). Analytical sample was recrystallized from hexanes, mp 76.0-77.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 6H), 4.37 (q, *J*=7.2 Hz, 4H), 7.53-7.65 (m, 8H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -122.7 (s, 4F), -122.4 (s, 4F), -120.2 (s, 4F), -105.9 (t, *J*=14.3 Hz, 4F). FT-IR (neat, cm^{-1})

υ 1717, 1301, 1223, 1207, 1141, 1110, 1100, 1054. Anal calcd for $C_{26}H_{18}F_{16}O_4$ (698.34 g/mol): C, 44.71; H, 2.60; Found. C, 44.65; H, 2.53.

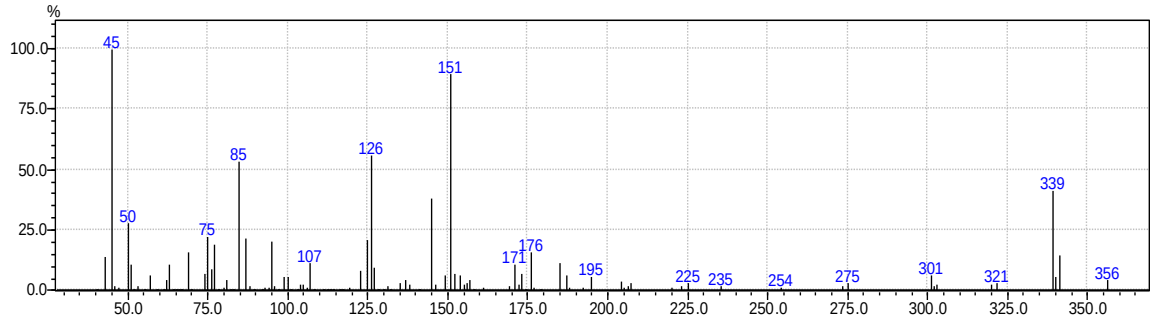


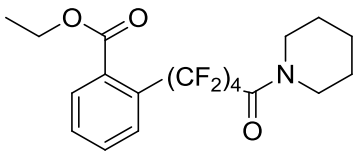


Ethyl 2-(4-chloro-1,1,2,2,3,3,4,4-octafluorobutyl)benzoate (Entry 9, Table 2.1.)

General procedure **A** was followed:

$H(CF_2)_4Cl$ (355 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), ethyl 2-iodobenzoate (138 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 1.5 h at 45 °C, then 11 h at 90 °C. After column chromatography (gradient 15%-25% CH_2Cl_2 in hexanes), 181 mg (94%) of colorless oil was obtained. R_f=0.36 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.36 (t, *J*=7.2 Hz, 3H), 4.38 (q, *J*=7.2 Hz, 2H), 7.55-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -120.9- -120.7 (m, 2F), -119.7- -119.5 (m, 2F), -106.1- -105.8 (m, 2F), -68.9- -68.8 (m, 2F). FT-IR (neat, cm^{-1}) υ 2986, 1740, 1302, 1270, 1191, 1136. Anal calcd for $C_{13}H_9ClF_8O_2$ (366.84 g/mol): C, 40.59; H, 2.36; Found. C, 40.80; H, 2.31.



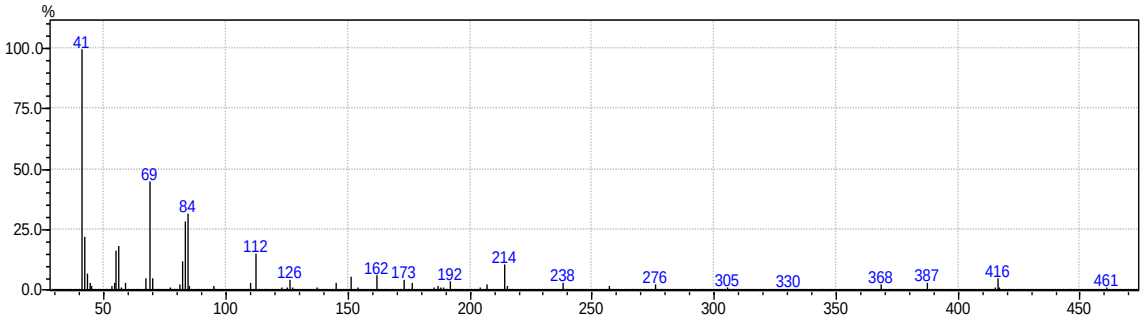


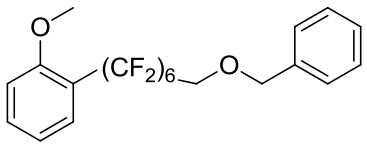
Ethyl 2-(1,1,2,2,3,3,4,4-octafluoro-5-oxo-5-(piperidin-1-yl)pentyl)benzoate (Entry 10, Table 2.1.)

General procedure **B** was followed:

2,2,3,3,4,4,5,5-Octafluoro-1-(piperidin-1-yl)pentan-1-one (157 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), ethyl 2-iodobenzoate (414 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), 20 min at 60 °C, then 5 h at 90 °C. After column chromatography (100% CH_2Cl_2) and preparative TLC (5% AcOEt in hexanes), 162 mg (62%) of thick colorless oil was obtained. R_f=0.32 (SiO_2, AcOEt/hexanes 1/3). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.2 Hz, 3H), 1.61-1.73 (m, 6H), 3.59-3.67 (m, 4H), 4.37 (q, *J*=7.2 Hz, 2H), 7.53-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -122.1- -121.9 (m, 2F), -119.5- -119.3 (m, 2F), -111.8 (t, *J*=13.6 Hz, 2F), -106.0 (t, *J*=15.0 Hz, 2F). FT-IR (neat, cm^{-1}) υ 2945, 1739, 1681, 1447,

1370, 1299, 1182, 1130, 1115, 1063. Anal calcd for $C_{19}H_{19}F_8NO_3$ (461.35 g/mol): C, 49.46; H, 4.15; N, 3.04; Found. C, 49.41; H, 4.09; N, 3.07.



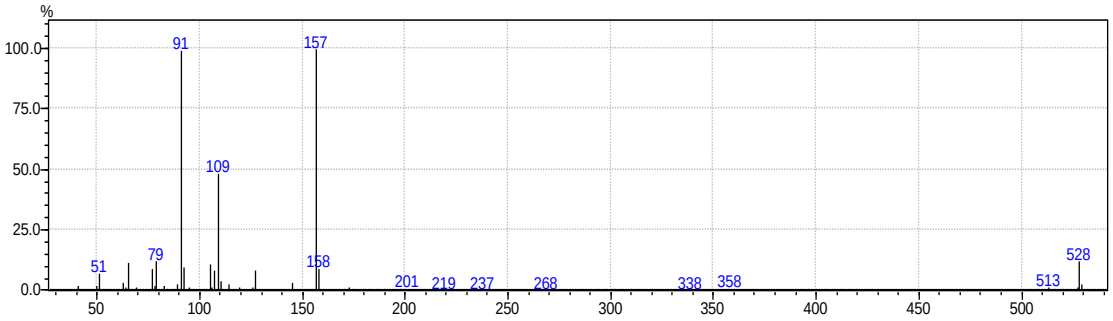


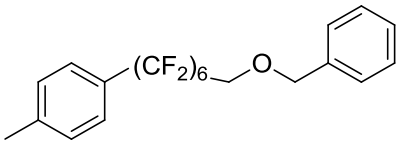
1-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-2-methoxybenzene (Entry 1, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 2-iodoanisole (351 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 2.5 h at 50 °C, reaction 13 h at 90 °C . After column chromatography (gradient 15%-25% CH_2Cl_2 in hexanes), 136 mg (51%) of colorless oil was obtained. R_f=0.44 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.86 (s, 3H), 3.89-3.97 (m, 2H), 4.68 (s, 2H), 6.99-7.06 (m, 2H), 7.30-7.39 (m, 5H), 7.47-7.53 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -124.6- -124.4 (m, 2F), -123.1- -122.8 (m, 4F), -122.4- -122.2 (m, 2F), -120.6- -120.4 (m, 2F), -108.8- -108.6 (m, 2F). FT-

IR (neat, cm^{-1}) υ 1496, 1298, 1264, 1197, 1141. Anal calcd for $C_{21}H_{16}F_{12}O_2$ (528.33 g/mol): C, 47.74; H, 3.05; Found. C, 47.65; H, 2.92.



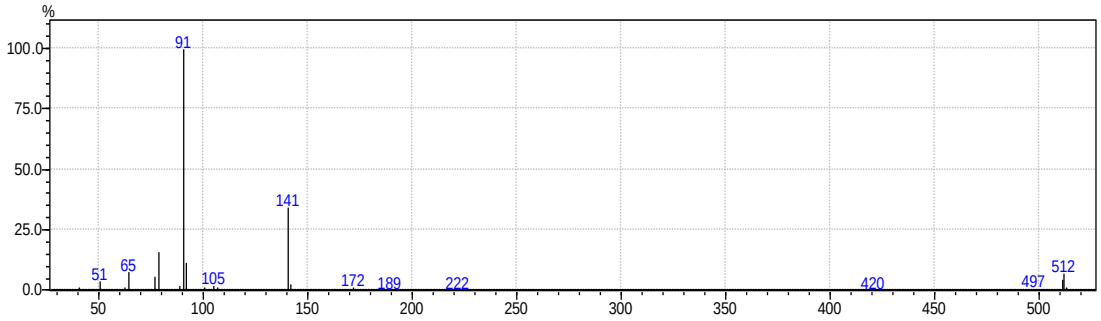


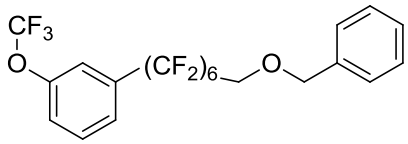
1-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-4-methylbenzene (Entry 2, Table 2.2)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 4-iodotoluene (327 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.35 mL), pre-generation 10 h at 45 °C, reaction 24 h at 90 °C. After column chromatography (gradient 5%-10% AcOEt in hexanes) and subsequent preparative HPLC (2% AcOEt in hexanes), 131 mg (51%) of colorless oil was obtained. R_f=0.52 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.41 (s, 3H), 3.93 (t, *J*=14.0 Hz, 2H), 4.67 (s, 2H), 7.27-7.40 (m, 7H), 7.44-7.49 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -124.5- -124.3 (m, 2F), -123.3- -122.9 (m, 4F), -122.5- -122.3 (m, 2F), -

120.6- -120.4 (m, 2F), -111.4 (t, *J*=14.4 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1283, 1198, 1144. Anal calcd for $C_{21}H_{16}F_{12}O$ (512.33 g/mol): C, 49.23; H, 3.15; Found. C, 49.27; H, 3.10.



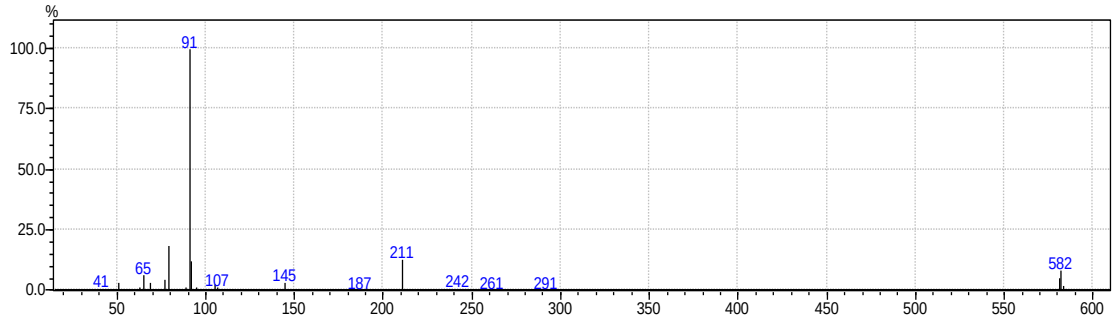


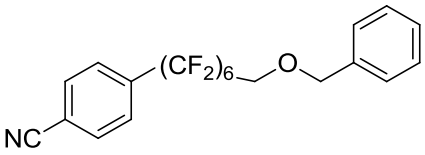
1-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-3-trifluoromethoxy)benzene (Entry 3, Table 2.2.)

General procedure **B** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 3-(trifluoromethoxy)iodobenzene (432 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), 15 min at 60 °C, then 13 h at 90 °C. After column chromatography (gradient 6%-20% CH_2Cl_2 in hexanes), 160 mg (55%) of a colorless oil was obtained. R_f=0.41 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.93 (t, *J*=14.0 Hz, 2H), 4.67 (s, 2H), 7.29-7.40 (m, 5H), 7.42-7.47 (m, 2H), 7.53-7.57 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -124.4- -124.3 (m, 2F), -123.2- -123.0 (m, 2F), -122.9- -122.8 (m, 2F), -122.4- -122.2 (m, 2F), -120.5- -120.3 (m,

2F), -111.8 (t, *J*=14.4 Hz, 2F), -59.1 (s, 3F). FT-IR (neat, cm^{-1}) υ 1446, 1265, 1199, 1143. Anal calcd for $C_{21}H_{13}F_{15}O_2$ (582.30 g/mol): C, 43.32; H, 2.25; Found. C, 43.27; H, 2.06.



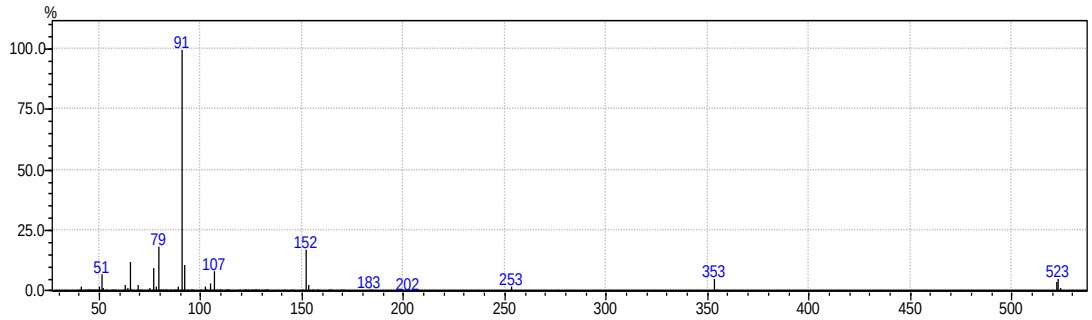


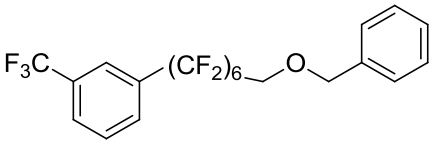
4-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)benzonitrile (Entry 4, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (633 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), 4-iodobenzonitrile (114.5 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 1 h at 60 °C, reaction 13 h at 90 °C. After column chromatography (gradient 10%-35% CH_2Cl_2 in hexanes), 217 mg (83%) of white solid was obtained. R_f=0.56 (SiO_2, hexanes/CH_2Cl_2 1/1). Analytical sample was recrystallized from hexanes, mp 76.0-77.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.88-3.98 (m, 2H), 4.67 (s, 2H), 7.29-7.40 (m, 5H), 7.72 (d, *J*=8.3 Hz, 2H), 7.81 (d, *J*=8.3 Hz, 2H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.4- -124.2 (m, 2F), -123.2- -123.0 (m, 2F), -122.9- -

122.7 (m, 2F), -122.4- -122.1 (m, 2F), -120.5- -120.3 (m, 2F), -112.6 (t, *J*=15.0 Hz, 2F). FT-IR (neat, cm^{-1}) υ 2237, 1206, 1131. Anal calcd for $C_{21}H_{13}F_{12}NO$ (523.31 g/mol): C, 48.20; H, 2.50; N, 2.68; Found. C, 48.09; H, 2.44; N, 2.78.



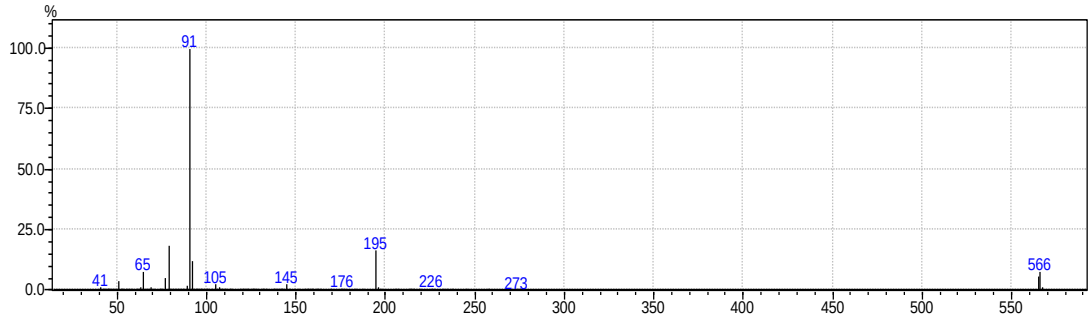


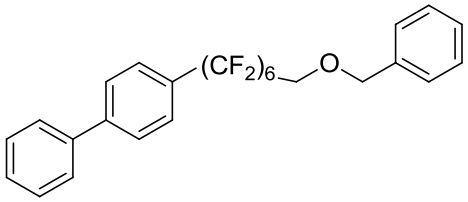
1-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-3-(trifluoromethyl)benzene (Entry 5, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 3-iodotrifluomethyl benzene (408 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 2 h at 50 °C, then 13 h at 90 °C. After column chromatography (gradient 5%-10% CH_2Cl_2 in hexanes) and subsequent preparative HPLC (2% AcOEt in hexanes), 173 mg (61%) of colorless oil was obtained. R_f=0.52 (SiO_2, hexanes/CH_2Cl_2 3/1). ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 3.88-3.98 (m, 2H), 4.68 (s, 2H), 7.29-7.42 (m, 5H), 7.63-7.69 (m, 1H), 7.77-7.82 (m,

1H), 7.83-7.87 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -124.4- -124.2 (m, 2F), -123.2- -123.0 (m, 2F), -122.8- -122.6 (m, 2F), -122.4- -122.2 (m, 2F), -120.5- -120.3 (m, 2F), -112.1- -111.9 (m, 2F), -63.9 (s, 3F). FT-IR (neat, cm^{-1}) υ 1454, 1340, 1270, 1200, 1138, 1077. Anal calcd for $C_{21}H_{13}F_{15}O$ (566.30 g/mol): C, 44.54; H, 2.31; Found. C, 44.49; H, 2.28.



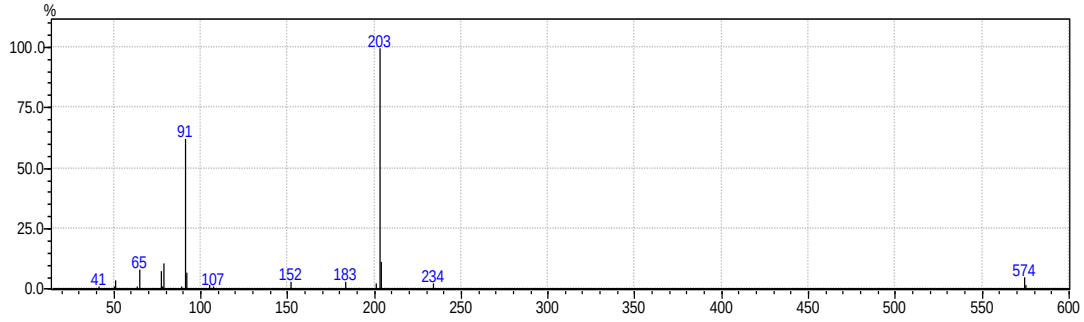


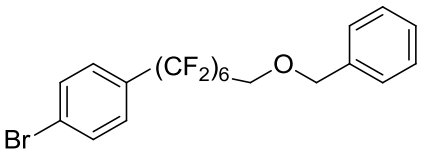
4-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)biphenyl (Entry 6, Table 2.2)

General procedure **B** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 4-iodobiphenyl (420 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.40 mL), 20 min at 60 °C, then 6 h at 90 °C . After column chromatography (gradient 5%-25% CH_2Cl_2 in hexanes), 178 mg (62%) of white solid was obtained.

R_f=0.48 (SiO_2, hexanes/CH_2Cl_2 3/1). Analytical sample was recrystallized from hexanes, mp 41.0-42.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.89-3.97 (m, 2H), 4.67 (s, 2H), 7.29-7.42 (m, 6H), 7.44-7.49 (m, 2H), 7.58-7.62 (m, 2H), 7.63-7.67 (m, 2H), 7.68-7.71 (m, 2H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.5- -124.3 (m, 2F), -123.2- -123.0 (m, 2F), -122.9- -122.7 (m, 2F), -122.4- -122.2 (m, 2F), -120.5- -120.3 (m, 2F), -111.5 (t, *J*=14.6 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1192, 1160, 1144, 1116. Anal calcd for $C_{26}H_{18}F_{12}O$ (574.40 g/mol): C, 54.37; H, 3.16; Found. C, 54.11; H, 3.07.



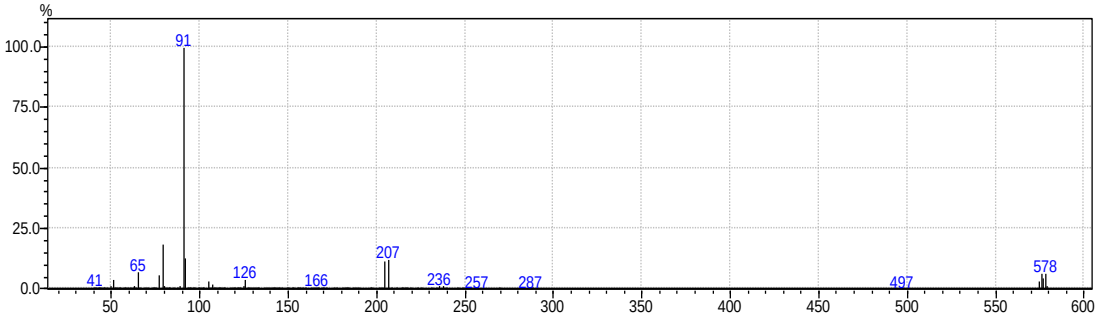


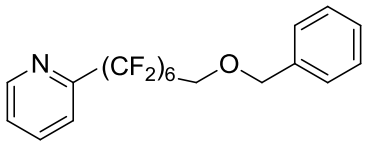
1-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-4-bromobenzene (Entry 7, Table 2.2)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 4-iodo-1-bromobenzene (425 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 2 h at 50 °C, more DMPU added (0.1

mL), reaction 13 h at 90 °C . After column chromatography (gradient 5%-20% CH_2Cl_2 in hexanes) and subsequent preparative HPLC (2% AcOEt in hexanes), 153 mg (53%) of colorless oil was obtained. R_f=0.52 (SiO_2, hexanes/CH_2Cl_2 3/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.93 (t, *J*=14.1 Hz, 2H), 4.67 (s, 2H), 7.29-7.42 (m, 5H), 7.42-7.48 (m, 2H), 7.61-7.66 (m, 2H). ^{19}F NMR (376.17 MHz, $CDCl_3$, ppm) δ -124.5- -124.3 (m, 2F), -123.3- -122.9 (m, 4F), -122.5- -122.2 (m, 2F), -120.5- -120.3 (m, 2F), -111.9 (t, J=14.1 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1280, 1198, 1144. Anal calcd for $C_{20}H_{13}BrF_{12}O$ (577.20 g/mol): C, 41.62; H, 2.27; Found. C, 41.52; H, 2.16.



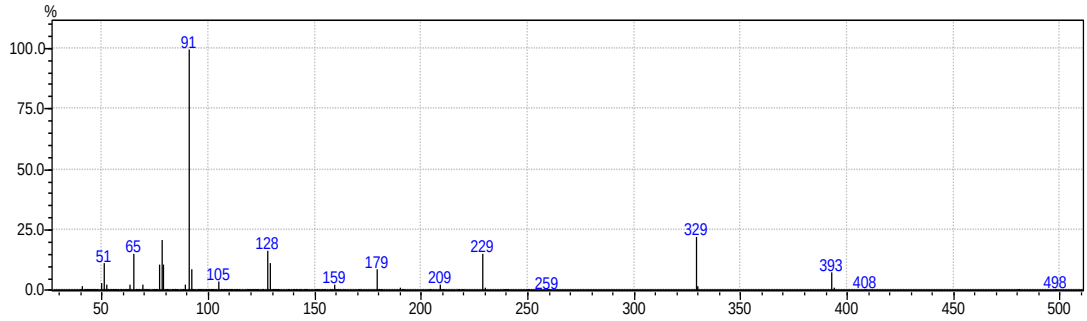


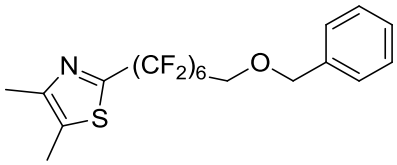
2-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)pyridine (Entry 8, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (211 mg, 0.50 mmol), TMP_2Zn (173 mg, 0.50 mmol), 2-iodopyridine (308 mg, 1.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol),

DMPU (0.30 mL), pre-generation 1 h at 60 °C, then 13 h at 90 °C . After column chromatography (gradient 25%-60% CH_2Cl_2 in hexanes), 212 mg (85%) of yellow oil was obtained. R_f=0.41 (SiO_2, hexanes/AcOEt 3/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 3.88-3.98 (m, 2H), 4.67 (s, 2H), 7.29-7.40 (m, 5H), 7.47-7.52 (m, 1H), 7.67-7.71 (m, 1H), 7.85-7.91 (m, 1H), 8.76-8.80 (m, 1H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.5- -124.2 (m, 2F), -123.2- -122.8 (m, 4F), -122.6- -122.3 (m, 2F), -120.5- -120.3 (m, 2F), -115.1 (t, *J*=14.2 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1198, 1143. Anal calcd for $C_{19}H_{13}F_{12}NO$ (499.29g/mol): C, 45.71; H, 2.62; N, 2.81; Found. C, 45.57; H, 2.48; N, 2.76.

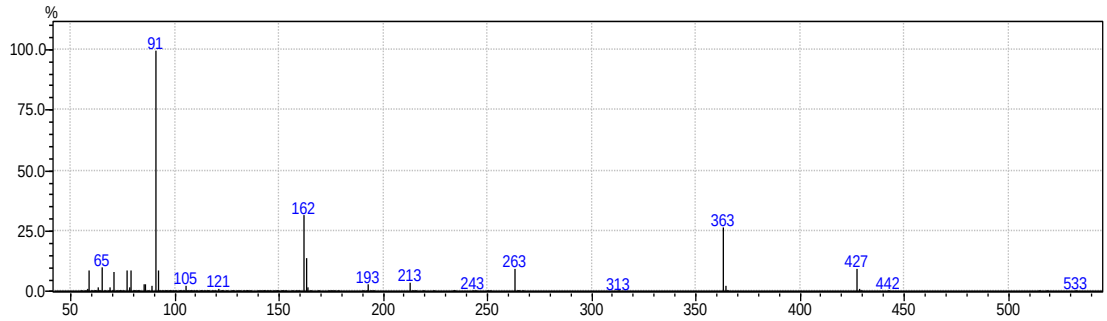


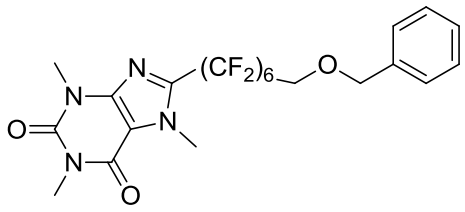


2-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-4,5-dimethylthiazole (Entry 9, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (633 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), 2-iodo-4,5-dimethylthiazole (120 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 1 h at 50 °C, more DMPU added (0.25 mL), then 12 h at 90 °C. After column chromatography (gradient 2%-10% AcOEt in hexanes), 168 mg (63%) of yellow oil was obtained. R_f=0.39 (SiO_2, hexanes/AcOEt 9/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 2.39 (s, 3H), 2.43 (s, 3H), 3.93 (t, *J*=14.1 Hz, 2H), 4.67 (s, 2H), 7.29-7.42 (m, 5H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.5- -124.3 (m, 2F), -123.2- -123.0 (m, 2F), -122.6- -122.3 (m, 4F), -120.5- -120.3 (m, 2F), -106.6 (t, *J*=14.3 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1455, 1199, 1144. Anal calcd for $C_{19}H_{15}F_{12}NOS$ (533.37g/mol): C, 42.78; H, 2.83; N, 2.63; Found. C, 42.87; H, 2.85; N, 2.67.

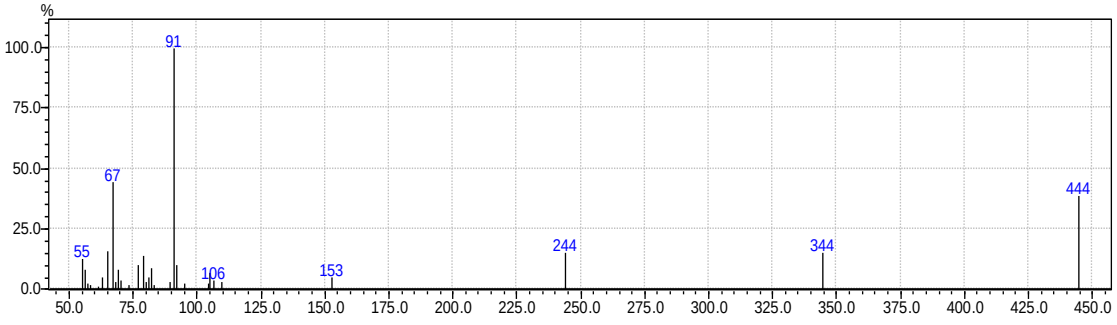


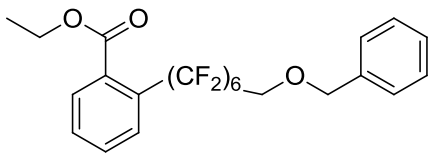


8-(7-(Benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (Entry 10, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (633 mg, 1.5 mmol), TMP_2Zn (259 mg, 0.75 mmol), iodocaffeine (160 mg, 0.50 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 1 h at 50 °C, more DMPU added (0.25 mL), then 12 h at 90 °C. After column chromatography (gradient 5%-40% AcOEt in hexanes), 290 mg (94%) of white solid was obtained. R_f=0.22 (SiO_2, hexanes/AcOEt 3/1). Analytical sample was recrystallized from hexanes/CH_2Cl_2, mp 58.5-60.0 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.42 (s, 3H), 3.59 (s, 3H), 3.95 (t, *J*=14.1 Hz, 2H), 4.19 (s, 3H), 4.68 (s, 2H), 7.30-7.40 (m, 5H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.3- -124.1 (m, 2F), -123.1- -122.9 (m, 2F), -122.5- -122.3 (m, 2F), -122.2- -122.0 (m, 2F), -120.4- -120.2 (m, 2F), -110.1 (t, *J*=13.6 Hz, 2F). FT-IR (neat, cm^{-1}) υ 1711, 1665, 1552, 1208, 1143. Anal calcd for $C_{22}H_{18}F_{12}N_4O_3$ (614.38 g/mol): C, 43.01; H, 2.95; N, 9.12; Found. C, 42.93; H, 2.88; N, 9.09.

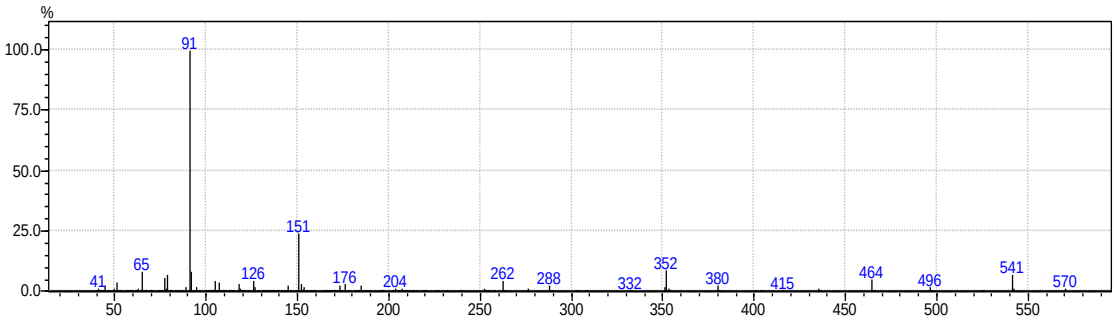




Ethyl 2-(7-(benzyloxy)-1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoroheptyl)benzoate (Entry 11, Table 2.2.)

General procedure **A** was followed:

$H(CF_2)_6CH_2OBn$ (422 mg, 1.00 mmol), TMP_2Zn (269 mg, 0.75 mmol), ethyl 2-iodobenzoate (138 mg, 0.5 mmol), phenanthroline (18 mg, 0.10 mmol), CuCl (5.0 mg, 0.05 mmol), DMPU (0.30 mL), pre-generation 3.0 h at 50 °C, reaction 18 h at 90 °C. After column chromatography (gradient 0-10 % EtOAc in pentane), 262 mg (92%) of colorless oil was obtained. R_f=0.36 (SiO_2, hexanes/EtOAc 9/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 1.35 (t, *J*=7.5 Hz, 3H), 3.94 (t, *J*=14.2 Hz, 2H), 4.36 (q, *J*=7.5 Hz, 2H), 4.68 (s, 2H), 7.30-7.40 (m, 5H), 7.55-7.65 (m, 4H). ^{19}F NMR (470.56 MHz, $CDCl_3$, ppm) δ -124.5- -124.3 (m, 2F), -123.2- -123.0 (m, 2F), -122.8- -122.5 (m, 2F), -120.5- -120.2 (m, 4F), -106.0- -105.8 (m, 2F). Anal calcd for $C_{23}H_{18}F_{12}O_3$ (570.37 g/mol): C, 48.43; H, 3.22; Found. C, 48.54; H, 3.22.



Preparation of $(C_2F_5)_2Zn(DMPU)_2$ (A)

Inside the glovebox an oven-dried 50 mL Schlenk flask equipped with a magnetic stir bar was charged with TMP_2Zn (1.73 g, 5.0 mmol) and DMPU (6.0 mL). The Schlenk flask was capped with septum and the empty balloon was connected to flask through the septum by 19G syringe needle. The flask and balloon were taken out of the glovebox and placed in the oil bath. The C_2F_5H was added by the needle via flask septum from the tank, inflating the attached balloon to approximately 400 ml volume (ca. 1.8 equiv of CF_3CF_2H). The temperature of the bath was increased to 80 °C (from RT) and the reaction mixture was allowed to stir at this temperature for 24 h. During this time the volume of the balloon decreased, indicating the consumption of the CF_3CF_2H. The reaction mixture was allowed to cool to RT and the installed balloon was detached. The reaction mixture was evacuated and placed inside the glovebox. The content of the Schlenk flask was diluted with Et_2O (20 mL) and placed inside the glovebox freezer at -35 °C. After 24 h, the precipitate was filtered while cold and washed with cold (-35 °C) Et_2O, affording 1.65 g (59 %) of an off-white solid. Single crystals suitable for X-ray diffraction studies were obtained by slow diffusion of the Et_2O in concentrated solution of THF/DMPU.

^{1}H NMR (500 MHz, DMF-D7, ppm) δ 1.91 (quintet, *J*=6.0 Hz, 4H), 2.80 (s, 12H), 3.22 (t, *J*=6.0 Hz, 8H). ^{19}F NMR (470.56 MHz, DMF-D7, ppm) δ -127.2 (s, 4F), -86.1 (s, 6F). Anal calcd for $C_{16}H_{24}F_{10}N_4O_2Zn$ (559.75 g/mol): C, 34.33; H, 4.32; N, 10.01; Found. C, 34.46; H, 4.36; N, 10.06.

Preparation of [($DMPU_3K$)($ClCuC_2F_5$)] (E)

Inside the glovebox oven dried 50 mL Schlenk flask equipped with a magnetic stir bar was charged with CuCl (2.97 g, 30 mmol), anhydrous KF (1.45 g, 25 mmol), followed by anhydrous THF (10 mL), DMPU (6 mL), and TMS-CF_3 (6.3 g, 45 mmol). The flask was capped with septum and removed from the glovebox. The reaction mixture was warmed to 60 °C and stirred for 4h under the positive pressure of argon (**Caution!** gas evolution). The reaction mixture was diluted with THF (10 mL), filtered through the plug of flame-dried Celite, the filter was washed with additional THF (30 mL), and the combined filtrate was evaporated under reduced pressure. The flask was evacuated and placed inside the glovebox. Residue was diluted with THF (10 mL) and filtered through 0.2 micron PTFE syringe filter. THF/DMPU solution was layered with Et_2O (30 mL) and placed inside the glovebox freezer at -35 °C. After several days a white solid was filtered on cold (-35 °C) filter, washed with small amount of cold (-35 °C) Et_2O, and dried inside the glovebox by passing dry nitrogen through the filter with crystals at room temperature for 5 min, affording 1.2 g (14 %) of colorless solid. Single crystals suitable for X-ray analysis were obtained by slow diffusion of Et_2O vapors in the concentrated solution of the title compound in THF/DMPU at -35 °C.

Title compound is extremely air, temperature, and moisture sensitive; it slowly decomposes at RT under argon atmosphere inside the glovebox over the course of several hours, but is stable for at least 4 weeks at -35 °C under inert atmosphere. ^1H NMR (500

MHz, DMF-D7, ppm) δ 1.91 (quintet, *J*=6.3 Hz, 6H), 2.80 (s, 18H), 3.32 (t, *J*=6.3 Hz, 12H). ^{19}F NMR (470.56 MHz, DMF-D7, ppm) δ -113.8 (s, 2F), -85.2 (s, 3F).

Mechanistic studies

^{19}F NMR experiments were performed in protio-DMPU as a solvent, using a sealed capillary filled with benzene-D_6 or acetone-D_6 for a signal lock. ^{19}F NMR spectra were collected at different temperatures and time intervals, providing qualitative estimation of the relative rates of studied reactions. Perfluoroalkyl species were assigned based on the ^{19}F NMR chemical shifts of isolated intermediates as well as literature precedent.[3,4] A short description of the results is provided below. Phenanthroline was omitted from the experiments below, since reactions with most aryl iodides give the same conversions in the presence and absence of phenanthroline.

Experiment 1.

Mixing CuCl (2.3 mg, 0.023 mmol) and excess $(CF_3CF_2)_2$Znx2DMPU (43.0 mg, 0.076 mmol) in DMPU (0.6 mL) at room temperature provides almost no observable transmetalation reaction. Increasing reaction temperature to 45 °C only marginally accelerates reaction; further increasing temperature to 70 °C and to 90 °C considerably accelerates the reaction and provides mixture of $[ClCuCF_2CF_3]^-$ (δ -113.6 ppm) and $[Cu(C_2F_5)_2]^-$ (δ -118.3) and new Zn containing species assigned as $[XZn(DMPU)_2CF_2CF_3]$ (δ -125.8 ppm). **Conclusion**: transmetalation step is slow at temperatures below 45 °C.

Experiment 2.

A preformed mixture of $[ClCuCF_2CF_3]^-$ and $[Cu(C_2F_5)_2]^-$ (made from CuCl (6.6 mg, 0.066 mmol) and excess of $(CF_3CF_2)_2$Znx2DMPU (77 mg, 0.14 mmol) in DMPU (0.6 mL) at 90 °C for 30 min) was subjected to reaction with ethyl-2-iodobenzoate (63 mg, 22.8 mmol) at room temperature. After 1 minute build up of the perfluoroalkylation product and decrease of the intensity of both $[ClCuCF_2CF_3]^-$ and $[Cu(C_2F_5)_2]^-$ species were observed.[3,4] A further increase in the temperature to 40 °C leads to a further consumption of cuprate species and build-up of perfluoroalkylation product, without consumption of the remaining zinc reagents. A further increase of the temperature to 60 °C causes a decrease in the concentration of Cu species and $(CF_3CF_2)_2$Znx2DMPU, and an increase in the amount of **5** and $[XZn(DMPU)_2CF_2CF_3]$. Even further increasing the temperature to 90 °C leads to the consumption of all of ArI and reappearance of Cu species. **Conclusion:** both perfluoroethyl copper species present in the solution are reactive towards ArI, even at room temperature and under conditions described – transmetalation from Zn to Cu appears to be rate limiting step in the reaction.

Crystal Data and Structure Refinement for Bis(perfluoroethyl)zinc DMPU Complex

Empirical formula	$C_{16}H_{24}F_{10}N_4O_2Zn$
Formula weight	559.76
Temperature	223(2) K

Wavelength	0.71073 A
Crystal system, space group	Orthorhombic, Fdd2
Unit cell dimensions	a = 17.5092(10) A alpha = 90 deg.
	b = 29.7286(18) A beta = 90 deg.
	c = 8.5863(5) A gamma = 90 deg.
Volume	4469.4(5) A^3
Z, Calculated density	8, 1.664 Mg/m^3
Absorption coefficient	1.202 mm^-1
F(000)	2272
Crystal color and shape	Colorless prismatic block
Crystal size	0.50 x 0.30 x 0.25 mm
Theta range for data collection	2.70 to 25.04 deg.
Limiting indices	0<=h<=20, 0<=k<=35, -10<=l<=10
Reflections collected / unique	5639 / 2040 [R(int) = 0.0240]
Completeness to theta = 25.04	99.9 %
Absorption correction	Empirical

Max. and min. transmission	0.9953 and 0.8311
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1855 / 5 / 128
Goodness-of-fit on F^2	1.052
Final R indices [I>4sigma(I)]	R1 = 0.0384, wR2 = 0.1020
R indices (all data)	R1 = 0.0395, wR2 = 0.1031
Flack parameter	0.44(2), racemic twin
Largest diff. peak and hole	0.375 and -0.561 e.A^-3

Crystal Data and Structure Refinement for $(C_2F_5)CuCl\ K(DMPU)_3$ Complex

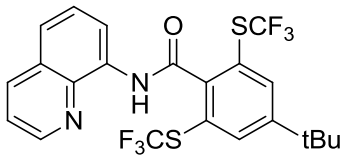
Empirical formula	$C_{20}H_{36}ClCuF_5KN_6O_3$
Formula weight	641.64
Temperature	223.15 K
Wavelength	0.71073 A
Crystal system, space group	Trigonal, R -3
Unit cell dimensions	a = 26.038(4) A alpha = 90 deg.

	b = 26.038(4) A beta = 90 deg.
	c = 21.702(4) A gamma = 120 deg.
Volume	12742(4) A^3
Z, Calculated density	18, 1.505 Mg/m^3
Absorption coefficient	1.078 mm^-1
F(000)	5976
Crystal color and shape	Colorless hexagonal column
Crystal size	0.45 x 0.20 x 0.20 mm
Theta range for data collection	1.56 to 25.04 deg.
Limiting indices	-30<=h<=0, -26<=k<=26, -18<=l<=25
Reflections collected / unique	9105 / 4994 [R(int) = 0.0823]
Completeness to theta = 25.04	99.8 %
Absorption correction	Empirical
Max. and min. transmission	0.9956 and 0.6580
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4279 / 0 / 341

Goodness-of-fit on F^2	1.022
Final R indices [I>4sigma(I)]	R1 = 0.0508, wR2 = 0.1306
R indices (all data)	R1 = 0.0597, wR2 = 0.1362
Largest diff. peak and hole	1.335 and -0.532 e.A^-3

TRIFLUOROMETHYLSULFENYLATION OF QUINOLINE AMIDES

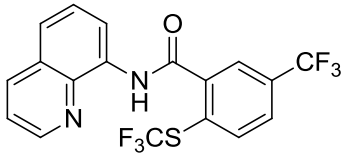
General procedure: To a 10 mL Kontes flask equipped with a stir bar was added amide (1 equiv), $Cu(OAc)_2$ (0.5 equiv), followed by bis(trifluoromethyl) disulfide (2-2.5 equiv) and DMSO via syringe. The resulting mixture was stirred at 90 °C – 110 °C for the indicated time. After completion, the mixture was cooled down to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of cellite®, and solid phase was washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography provided the desired product.



***N*-(2,6-Di(trifluoromethylthio)-4-*t*-butylbenzoyl)-8-aminoquinoline (Entry 1, Table 2.5.)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (76 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl)disulfide (66 μL, 0.50 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. After work up following the general procedure, purification by column chromatography using CH_2Cl_2/hexanes (gradient 20% to 70% CH_2Cl_2) as an eluent afforded 96 mg of the desired product (76% yield). R_f =0.69 (SiO_2, hexanes/EtOAc, 3:1), mp 115-116 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.1 (*s*, 1H) 8.94 (*dd*, *J* = 6.3 Hz, *J* = 2.3 Hz, 1H) 8.73 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.19

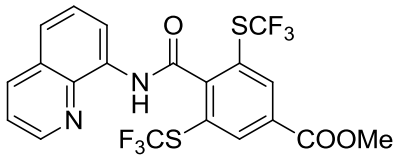
(*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.94 (*s*, 2H) 7.59–7.66 (*m*, 2H) 7.45 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 1.41 (*s*, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 164.1, 154.9, 148.7, 147.4, 138.8, 137.9, 136.6, 134.2, 129.4 (*quartet*, J_{C-F} = 309.4 Hz) 128.3, 127.6, 123.5, 122.9, 122.1, 117.4, 35.5, 31.2. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -41.6 (*s*). FT-IR (neat, cm^{-1}) υ 3346,1682, 1529, 1488, 1106. HRMS (ESI+): Calculated for $C_{22}H_{19}F_6N_2OS_2$ $[M+H]^+$ 505.08375, Found 505.08378.

A large scale (5 mmol) synthesis: The reaction was performed in a 120 ml pressure flask according to the general procedure by increasing the amount of the reagents and solvent by a factor of 20. Column chromatography on silica gel afforded 1.54 g (61%) of the product.



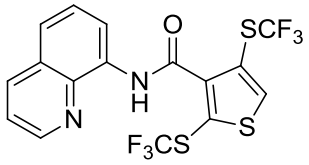
***N*-(5-(Trifluoromethyl) 2-(trifluoromethylthio) benzoyl)-8-aminoquinoline (Entry 2, Table 2.5.)** To a 10 mL Kontes flask equipped with a stir bar was added *N*-(3-trifluoromethylbenzoyl)-8-aminoquinoline (79 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.07 mL, 0.53 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. Reaction mixture was dry absorbed on the silica gel and purified by column chromatography using CH_2Cl_2/hexanes (gradient 20% to 40% CH_2Cl_2) as an eluent. Evaporation of the fractions containing the product afforded 56 mg (53 %) of a white solid, R_f = 0.58 (SiO_2,

hexanes/CH_2Cl_2, 1:1), mp 93-96 °C . ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.5 (*br s*, 1H) 8.91–8.87 (*m*, 1H) 8.82–8.80 (*m*, 1H) 8.23–8.19 (*m*, 1H) 8.10–8.08 (*m*, 1H) 7.99–7.95 (*m*, 1H) 7.83–7.80 (*m*, 1H) 7.64–7.60 (*m*, 2H) 7.52–7.48 (*m*, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 164.5, 148.9, 141.1, 138.8, 136.8, 135.4, 134.1, 132.5, 130.2, 129.5 (*quartet*, $J_{C\text{-}F}$ = 309.1 Hz), 128.3, 128.2–127.9 (*m*), 127.6, 125.8–125.5 (*m*), 123.5 (*quartet*, $J_{C\text{-}F}$ = 272.7 Hz), 123.1, 122.3, 117.4. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -40.7 (*s*), -62.8 (*s*). FT-IR (neat, cm^{-1}) υ 3337, 1668, 1532, 1340, 1165, 1150, 1128, 1114, 1092.



Methyl 2,3-di(trifluoromethylthio)-4-(quinolin-8-ylcarbamoyl)benzoate (Entry 3, Table 2.5.) To a 10 mL Kontes flask equipped with a stir bar was added methyl 4-(quinolin-8-ylcarbamoyl)benzoate (77 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (100 mg, 0.50 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. The reaction mixture was dry absorbed on the silica gel and purified by column chromatography using CH_2Cl_2/hexanes (gradient 50% to 90% CH_2Cl_2) as an eluent. Evaporation of the fractions containing the product afforded 91 mg (72 %) of a white solid, mp 135-137 °C ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.16 (*br s*, 1H), 8.95 – 8.89 (*m*, 1H), 8.75 – 8.71 (*m*, 1H), 8.59 (*s*, 2H), 8.22 – 8.17 (*m*, 1H), 7.67 – 7.60 (*m*, 2H), 7.49 – 7.45 (*m*, 1H), 4.03 (*s*, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.4, 163.0, 153.2, 148.8, 141.0, 138.7, 136.6, 133.8, 133.0, 129.0 (*quartet*, J_{C-F} = 309.6 Hz), 128.2, 127.6, 124.9, 123.2, 122.2, 117.5, 53.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -41.2 (s, 6F). FT-IR (neat, cm^{-1}) υ 3313, 1733, 1673, 1536, 1489, 1288, 1266, 1147, 1102. HRMS (ESI+): Calculated for $C_{20}H_{13}F_6N_2O_3S_2$ $[M+H]^+$ 507.02663, Found 507.02694.



<u>*N*-(3-(2,4-di(Trifluoromethyl)thienyl)-8-aminoquinoline (Entry 4, Table 2.5.)</u> To a 10 mL Kontes flask equipped with a stir bar was added *N*-(3-thienyl)-8-aminoquinoline (64 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followd by bis(trifluoromethyl) disulfide (100 mg, 0.50 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. Reaction mixture was dry absorbed on the silica gel and purified by column chromatography using CH_2Cl_2/hexanes (gradient 20% to 60% CH_2Cl_2) as an eluent. Evaporation of the fractions containing the product afforded 64 mg (56 %) of a white solid, mp 113-115 °C . ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.53 (*br s*, 1H), 8.94 – 8.89 (*m*, 1H), 8.81 – 8.77 (*m*, 1H), 8.21-8.17 (*m*, 1H) 8.05 (*s*, 1H), 7.60 (*d*, *J* = 4.6 Hz, 2H), 7.49 – 7.45 (*m*, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 156.0, 148.7, 148.4, 140.9, 138.8, 136.5, 134.1, 128.5 (*quartet*, J_{C-F} = 311.9 Hz), 129.0 (*quartet*, J_{C-F} = 309.5 Hz), 128.2, 127.5, 123.5, 122.9, 122.1, 121.5, 117.4. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -42.6 (s, 3F), -43.1 (s, 3F). FT-IR (neat, cm^{-1}) υ 3322, 1668, 1534, 1482, 1138,

1100. HRMS (ESI+): Calculated for $C_{16}H_9F_6N_2OS_3[M+H]^+$ 454.97757, Found 454.97798.

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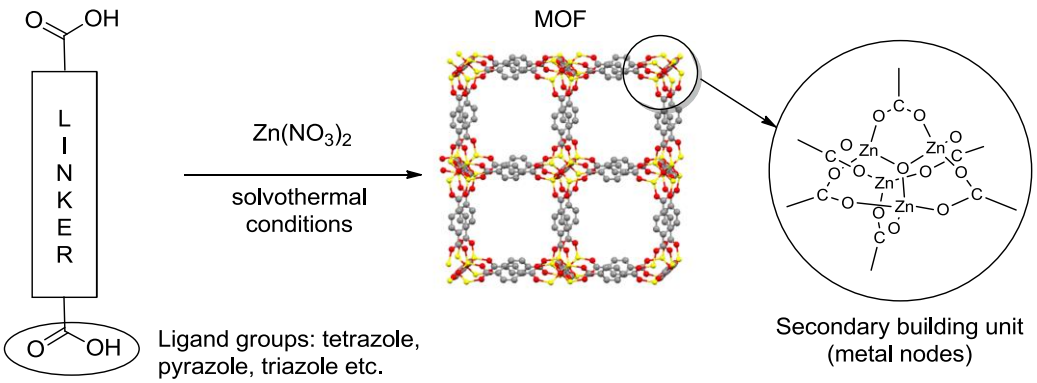
CHAPTER 3 MOF SYNTHESIS

I. Introduction

Recently, much attention has been devoted towards studies of modularly synthesized metal-organic frameworks (MOFs). These are salts that are built from organic ligands with particular spatial arrangements.[1] Most often polycarboxylic acids or azolates and metal ions are used as building blocks of MOFs. By building a three-dimensional structure, these salts create unoccupied space within the crystal, which can lead to permanent porosity.[2] These crystalline sponges can be used in gas sorption, separation, and catalysis.[3] The ability to select the organic linkers and metal ions suggests that in principle tailor made frameworks for particular applications can be prepared (Scheme 3.1.)

Scheme 3.1. Structure of MOF

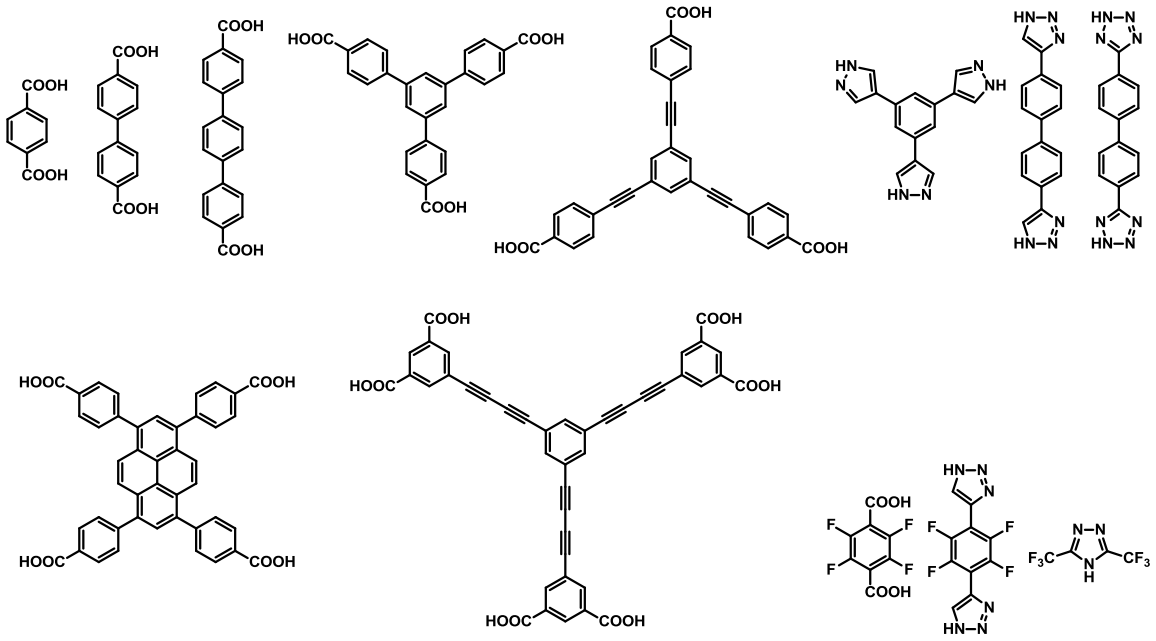


Despite the progress in the understanding of structure-properties relationships and large number of materials prepared, it is still very challenging to predict the properties of the bulk MOFs based on the topology of the network and the properties of corresponding

constituents. Therefore to fully realize great potential of these modular functional materials, organic synthesis has to be employed to prepare organic linkers.

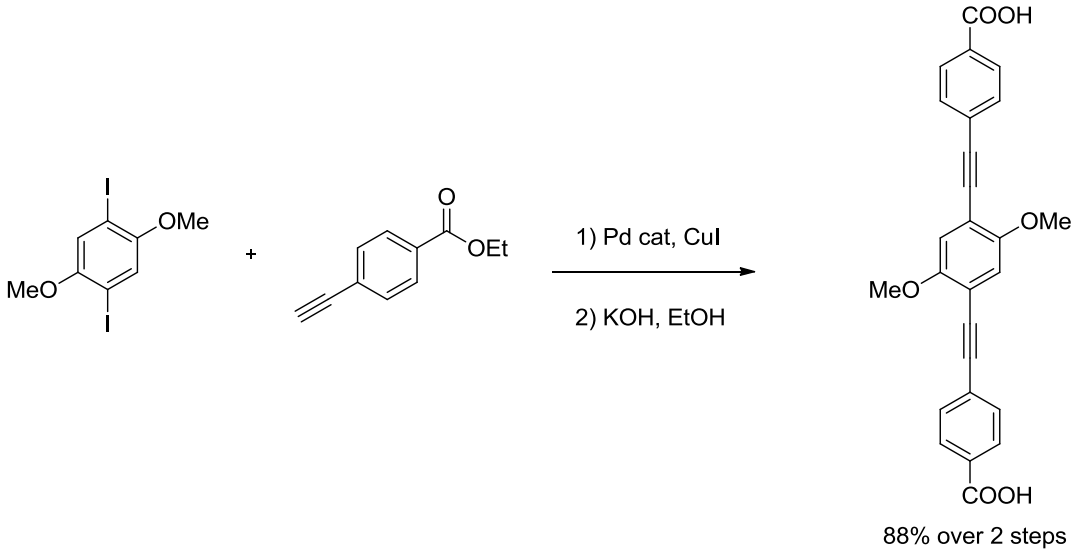
One of the particular attributes of MOFs is the ability to translate functional features of the organic linkers into a specific property of the bulk material. Therefore, synthesis of the diversely substituted organic linkers is of paramount importance (Scheme 3.2).[4]

Scheme 3.2. Different geometrically defined linkers for MOF



For example, introduction of hydrophilic functional groups on the ligand backbone can result in the increased hydrophilic character of the resulting MOF compared to the parent framework.[5] Linkers for these remarkable MOFs were prepared using multiple Sonogashira coupling procedures (Scheme 3.3).[5]

Scheme 3.3. Organic linker prepared for hydrophilic MOF

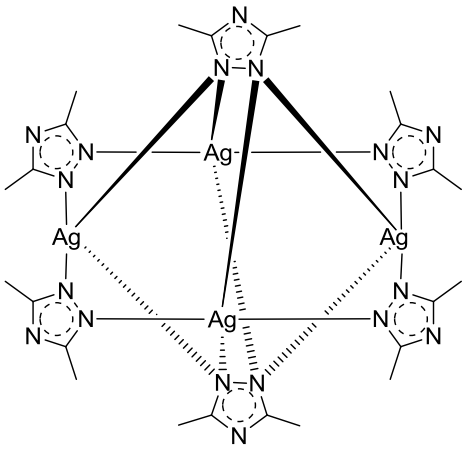


Most of polycarboxylic acids and azoles organic linkers are either commercially available or can be accessed in a straightforward manner using conventional methods. On contrary, only very small number of polyfluorinated linkers has been employed in the synthesis of MOFs. Primarily this is due to the lack of general and reliable methods of their synthesis.

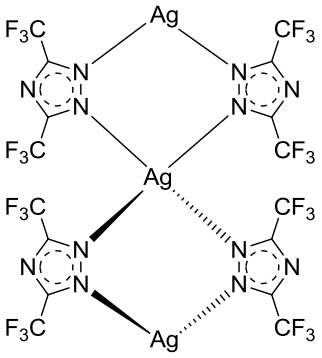
In 2004 Kobayashi and coworkers prepared 2D and 3D materials based on tetrafluoroterephthalic acid.[6] Authors described synthesis and were able crystallographically characterize obtained materials. Subsequently Long and coworkers disclosed synthesis of copper-based MOF using 2,3,5,6-tetrafluoroditriazole as an organic linker.[7] This material possesses properties and dimensions similar to its nonfluorinated counterpart.

Omary and coworkers disclosed preparation of perfluorinated MOF (FMOF-1 and FMOF-2) based on 3,5-di(trifluoromethyl)triazole as an organic linker and silver as a metal ion and studied their adsorption properties. The material has desirable properties such as high stability and superhydrophobic character. Moreover, a number of hydrocarbons can be adsorbed in the pores of this remarkable MOF and it can be used as a sorbent in the case of oil spills (Scheme 3.4).

Scheme 3.4. Building blocks of FMOF-1 and FMOF-2



FMOF-1



FMOF-2

II. Conclusions

Metal-organic frameworks are promising materials for many applications in catalysis and separation. Even greater structural and functional diversity of these materials, combined with ease of access, can be envisioned by applying plethora of C-H functionalization methodologies, especially in the context of inaccessible polyfluorinated substrates. We envision that such innovative approaches will provide increased access to

diverse structural functionality and complexity of organic linkers, and therefore open a new venue in the research on possible potential applications of such materials.

III. References

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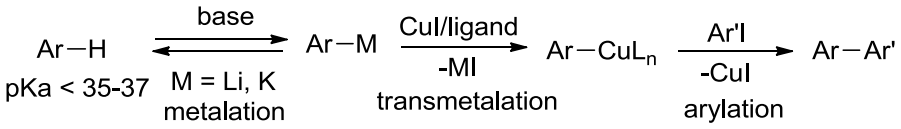
CHAPTER 4 COPPER-PROMOTED, PALLADIUM-CATALYZED SYNTHESIS OF POLYFLUORINATED ARYL CARBOXYLATES AND AZOLATES AS PRECURSORS FOR HOF AND MOF SYNTHESIS

I. Introduction

Our initial studies were focused on the development on the deprotonative cross-coupling of relatively acidic C-H bonds of polyfluorobenzenes. General methods for the deprotonative functionalizations of acidic arenes and heteroarenes have been extensively studied by our group.[1] The general reaction mechanism is provided in the Scheme 4.1.

Scheme 4.1. Deprotonative cross-coupling of acidic C-H bonds



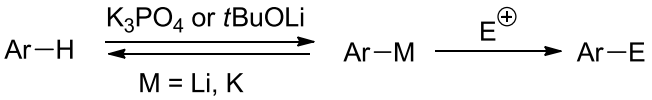
Polyfluoroarenes containing C-H bonds can be employed in the cross-coupling reaction with aryl iodides under copper catalysis. As can be seen above, the first step in the reaction is the deprotonation of acidic C-H bond and formation of the aryl-lithium or aryl-potassium intermediates. Subsequent trapping with copper halide affords aryl copper species. Mechanistically this sequence of elementary reactions can be formally considered as functionalization of an acidic sp^2 C-H bond with an electrophile.

Copper species are more stable than corresponding aryl lithium and potassium intermediates from which they are derived. Quantitative generation of such copper species using appropriate copper base would be beneficial. Essentially, aryl copper intermediates can function as a more stable aryl anion equivalent with added benefits. Copper has higher affinity for iodide than palladium. Consequently, aryl transfer between aryl copper and palladium iodide species should be facile and irreversible.

Copper-catalyzed reactions can be compared with palladium-catalyzed processes. The latter are generally performed under milder conditions and as a consequence are more functional group tolerant. For example, Sonogashira[2] and Castro-Stevens[3] reactions both utilize copper acetylides in the reaction with aryl iodides. However, palladium-catalyzed process can be performed under ambient conditions whereas copper-mediated process requires forcing conditions.

As mentioned above, because deprotonation and subsequent transmetalation step from aryl-lithium and aryl-potassium, intermediates with copper halide can formally be viewed as C-H functionalization of arene with electrophile. In addition to developing copper-promoted palladium-catalyzed cross-coupling, we sought to expand this approach to other electrophiles (Scheme 4.2.). This reaction is an extremely useful one-step deprotonative functionalization of relatively acidic arene C-H bonds with a variety of halogen, carbon and sulfur-based electrophiles.

Scheme 4.2. Deprotonative functionalization of acidic C-H bonds



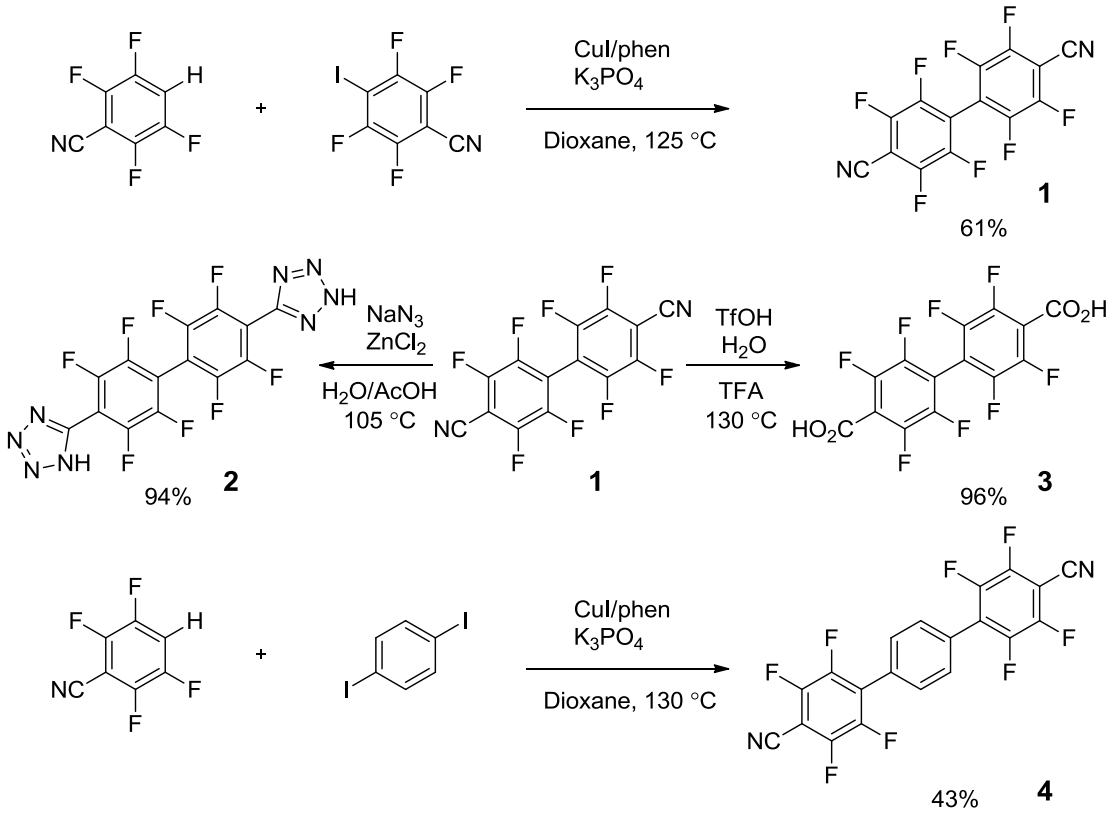
II. Results and Discussion

II.1 Copper-promoted palladium-catalyzed cross-coupling

We turned our attention towards copper catalysis in order to prepare geometrically diverse fluorinated building blocks that are potentially useful in the preparation of mesoporous and microporous materials. As previously described, state-of-the-art materials are made predominantly from polycarboxylic acids or azoles possessing geometrically and spatially defined backbone structures. Usually rigid linear, trigonal, or tetragonal arrangement is used.[4] Therefore, in order to increase the utility of the method, diversifying element should be introduced in the synthetic strategy. Nitrile functional group can act as a surrogate for both carboxylate and tetrazole moiety. Gratifyingly, after careful study of the pool of commercially available starting materials, 2,3,5,6-tetrafluorocyanobenzene was identified as a suitable candidate. Thus, reaction between tetrafluorocyanobenzene and iodo tetrafluorocyanobenzene in dioxane solvent under copper catalysis afforded linear dicyanooctofluorobephenyl, which was further elaborated using hydrolysis and cycloaddition reactions.[1] Nitrile functionality could be conveniently converted to carboxylic acid under strongly acidic conditions specifically developed for perfluorinated nitriles. Alternatively, acetic acid and zinc dichloride-promoted reaction between sodium azide and dinitrile gave rise to perfluoroaryl ditetrazole.[5] Additionally,

1,4-diiodobenzene can be cross-coupled with tetrafluorocyanobenzene to provide the product in synthetically useful yield (Scheme 4.3.).

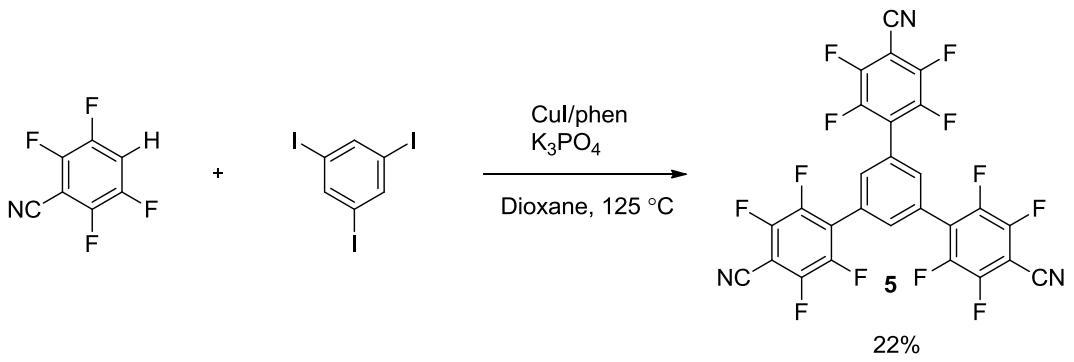
Scheme 4.3. Cross-coupling and elaboration of linear struts



Unfortunately, direct introduction of tetrafluorobenzoic acid esters under copper catalysis proved to be very challenging, and only trace amounts of the product were observed in the reaction mixture. Cross-coupling between tetrafluorocyanobenzene and 1,3,5-triiodobenzene provided product in low yield under optimized reaction conditions. Additionally, to scale up of the reaction from 1 mmol to 3 mmol proved to be extremely challenging, and the product was isolated in very low yield. We attribute this to the

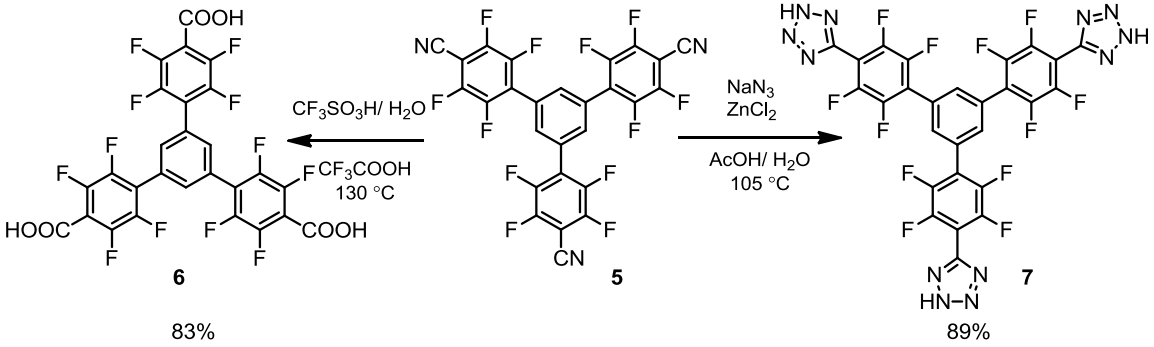
inadequate mass transfer under reaction conditions, since the reaction mixture contains heterogeneous base and requires very efficient stirring (Scheme 4.4.).

Scheme 4.4. Cross-coupling of tetrafluorocyanobenzene and triiodobenzene



Nonetheless, obtained amount of the trinitrile was sufficient to elaborate it. Using our protocol, trinitrile was converted to triacid and tritetrazole in high yield (Scheme 4.5.).

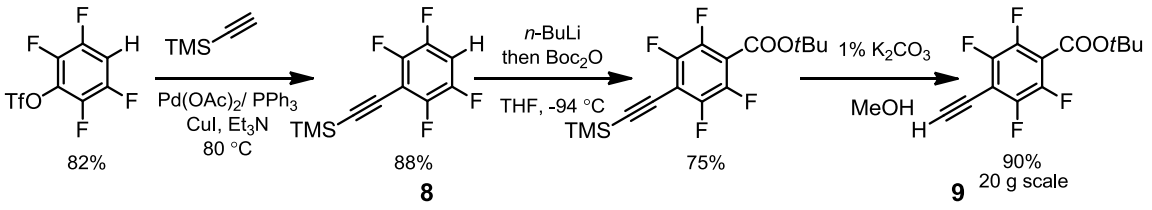
Scheme 4.5. Elaboration of trinitrile



In order to address synthesis of extended trigonal and linear struts we had to identify appropriate starting material. Towards this end, alkyne substituted tetrafluorobenzoic acid ester was chosen and synthesized (Scheme 4.6.). Sonogashira

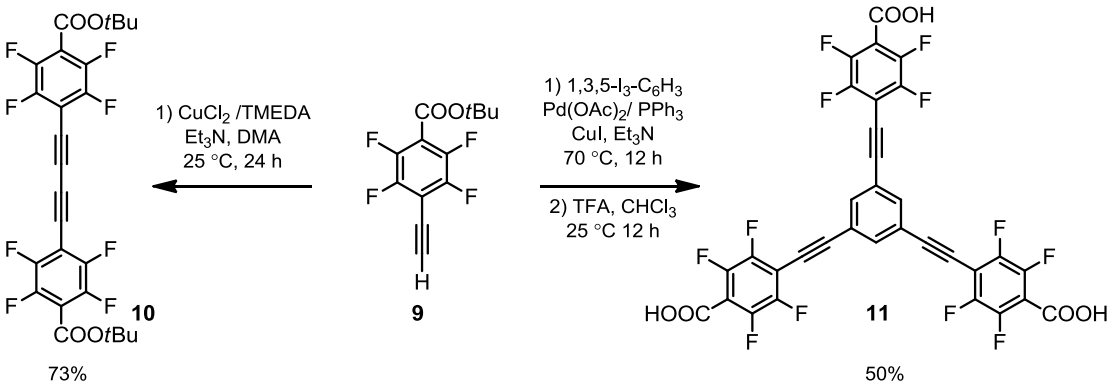
reaction of readily accessible tetrafluorophenyl triflate with TMS-acetylene afforded substituted tetrafluorobenzene. Deprotonation of the most acidic C-H bond and quenching with dicarbonate, followed by deprotection of acetylene moiety, afforded target alkyne substituted tetrafluorobenzoic acid *tert*-butyl ester.

Scheme 4.6. Synthesis of alkyne starting material



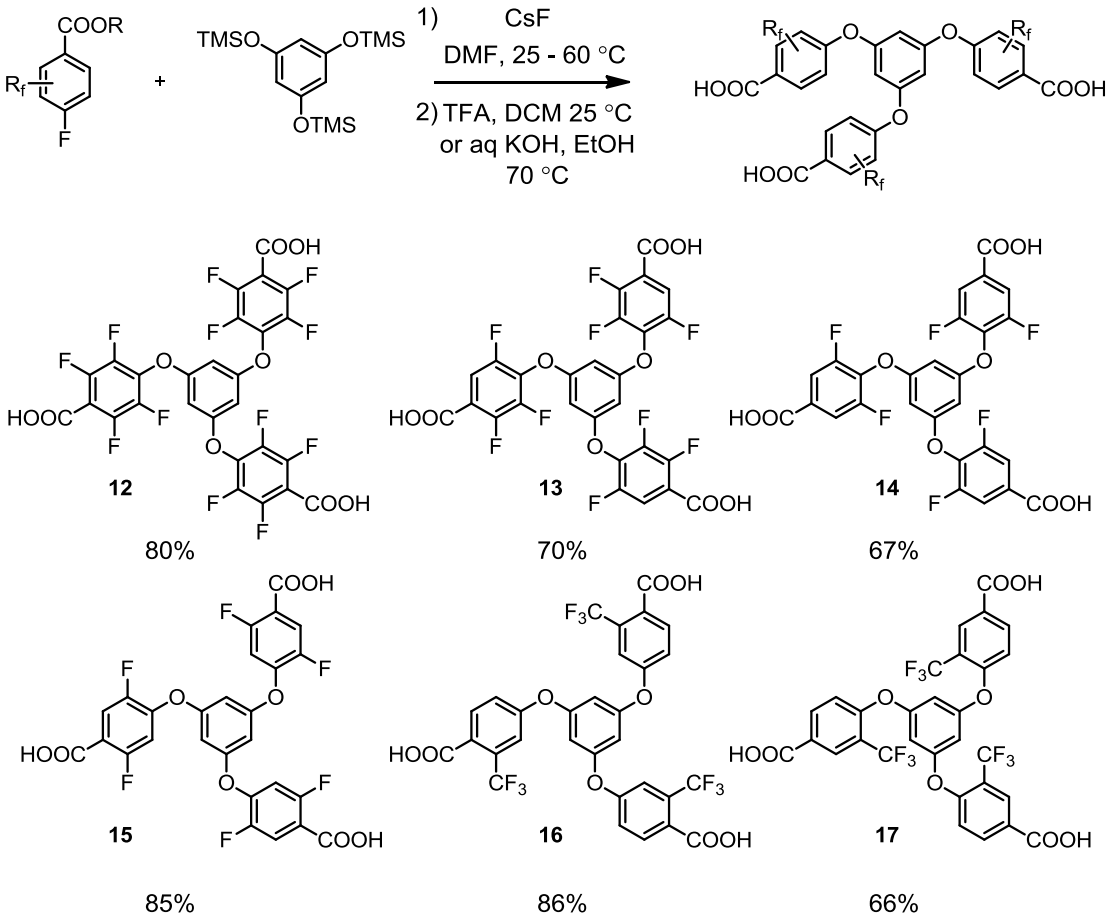
Using alkyne starting material **9** and performing Glaser-Hay or Sonogashira reaction followed by deprotection of carboxylate for the latter, afforded extended polyfluorinated dicarboxylic ester and tricarboxylic acid respectively (Scheme 4.7.). Reactions were performed under very mild conditions and polycarboxylic acid product **11** was isolated in good overall yield.

Scheme 4.7. Synthesis of extended linear and trigonal struts



Next, we have turned our attention towards developing novel synthetic route towards synthesis of polyfluorinated carboxylic acids based on trigonal geometry with oxygen bridge. Exploiting well-established reactivity of perfluorinated arenes towards strong nucleophiles via nucleophilic aromatic substitution mechanism, reaction between number of fluorinated carboxylates and latent trianion of phloroglucinol provided straightforward access to trigonal carboxylates (Scheme 4.8.).[6] Subsequent ester cleavage, either using trifluoroacetic acid or basic hydrolysis, afforded corresponding carboxylic acids in high yields. Diverse substitution patterns and the different number of fluorines on the aromatic ring open possibility to establish structure-activity relationship in the synthesized micro or mesoporous metal organic frameworks.

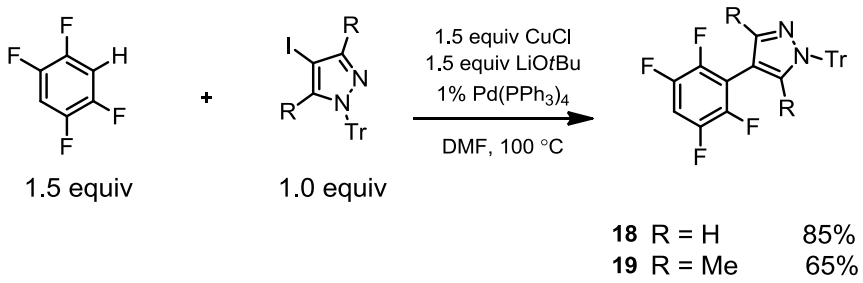
Scheme 4.8. Synthesis of trigonal struts via S_NAr mechanism



It is a well established fact that pyrazole-based MOFs are more stable than corresponding isostructural tetrazole-based materials.[7] Therefore, highly modular synthesis of polypyrazole-based struts is of high importance. Typically, arylpyrazole ligands useful for MOF preparation are made in multistep synthesis from corresponding carboxylic acids. Our approach is a direct installation of pyrazole moiety onto an aromatic ring using deprotonative carbon-hydrogen bond functionalization.

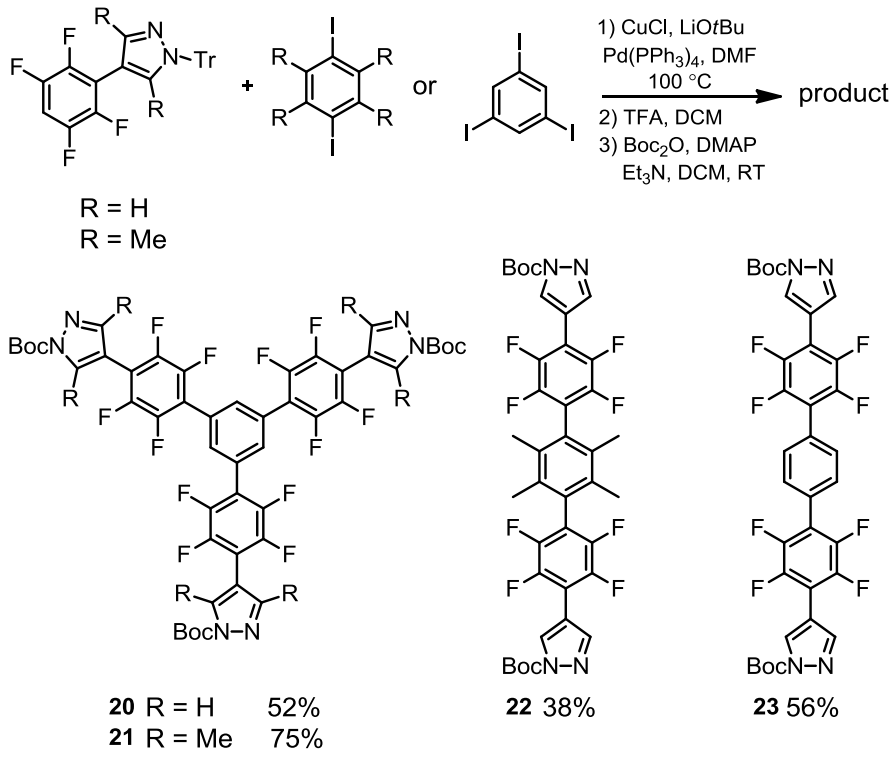
Initial attempts to use well established copper-catalyzed process provided intractable mixture of products. Optimization of the reaction conditions led to the discovery that catalytic amounts of palladium salt in the presence of stoichiometric copper *tert*-butoxide, led to complete conversion to the desired product. Application of this protocol to coupling between N-protected pyrazoles and tetrafluorobenzene provided initial building blocks for the geometrically defined polypyrazoles (Scheme 4.9.).

Scheme 4.9. Synthesis of pyrazole building blocks



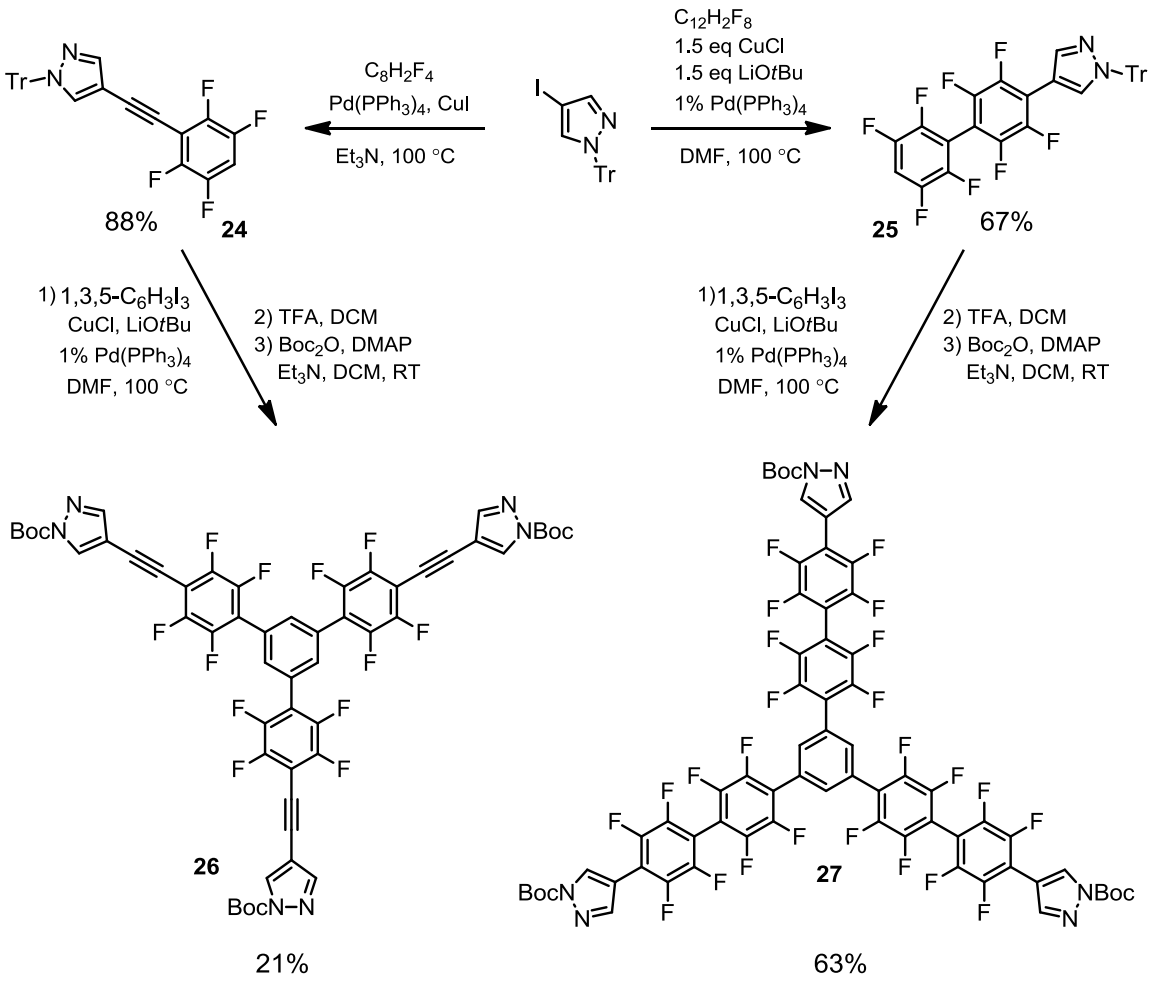
Tetrafluorophenyl substituted pyrazoles were subsequently coupled with several aryl iodides to provide linear and trigonal di- and tripyrazole advanced building blocks. Subsequent cleavage of trityl protecting group and introduction of *tert*-butyloxycarbonyl substituent onto nitrogen provided MOF and HOF precursors in good overall yields (Scheme 4.10.).

Scheme 4.10. Synthesis of pyrazole-based MOF and HOF precursors



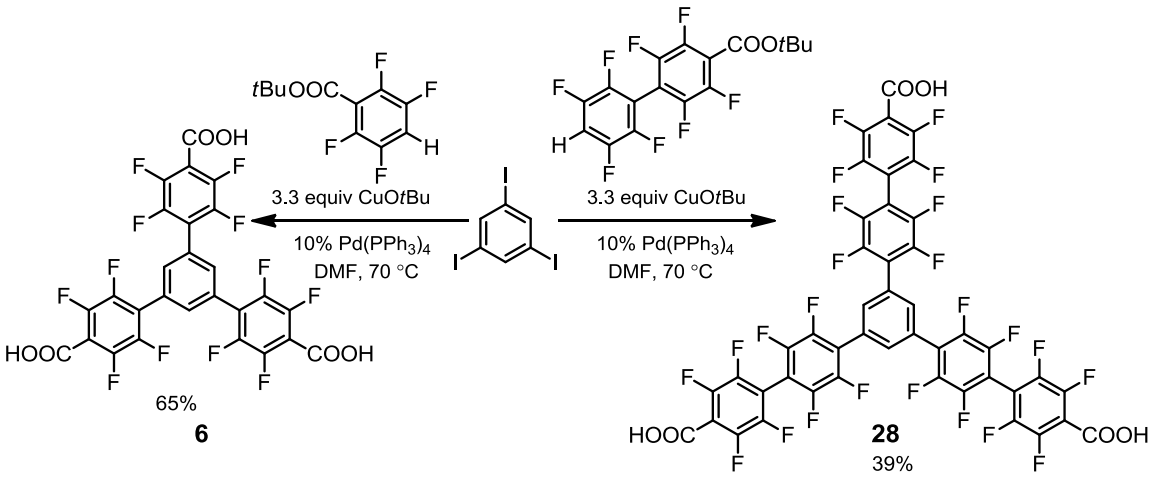
Additionally, extended trigonal polypyrazolate linkers were synthesized using our approach. Both alkyne and extra *para*-tetrafluorophenylene substituents were used to create longer tripyrazole linkers. Tetrafluorophenyl acetylene and 4,4'-octafluorobipenyl were cross-coupled with N-trityl 4-iodopyrazole to afford extended pyrazole building blocks. Subsequent cross-coupling under previously employed palladium-catalyzed conditions and substituent swap on pyrazole nitrogen atom afforded extended tripyrazoles (Scheme 4.11.).

Scheme 4.11. Synthesis of extended tripyrazoles



Encouraged by functional group tolerance of the palladium method, we sought to revisit direct introduction of tetrafluorocarboxylic acid derivatives onto aromatic ring. Gratifyingly, by lowering reaction temperature tetrafluorobenzoic acid *tert*-butyl ester could be efficiently cross-coupled with 1,3,5-triiodobenzene. Moreover, octafluorobiphenic acid appeared to be suitable substrate as well, providing after deprotection extended polyfluorinated tricarboxylic acid in synthetically useful yield (Scheme 4.12.).

Scheme 4.12. Cross-coupling of polyflouro *tert*-butyl arylcarboxylates



In conclusion, we have developed a general strategy for incorporation of fluorous carboxylic acid, tetrazole, and pyrazole-containing moieties onto aromatic rings. These structures are of interest for materials science application. Additionally, this new synthetic strategy of direct introduction of pyrazoles through cross-coupling, as well as copper-promoted, palladium-catalyzed deprotonative arylation methodology, should further contribute to synthesis of structures useful for materials science application. Mild reaction conditions and high functional group tolerance of the employed methods attest to their generality and robustness of the selected strategy.

II.2. Synthesis of macrocyclic tricarboxylate

As discussed above, pores in metal organic frameworks are typically created due to inability of building blocks to efficiently pack in the crystalline phase. This is mostly due to constraints imposed by linker and metal node geometry. Thus, porosity of the MOFs mainly is created in between the linkers in the solid state. We were interested on

introducing additional pores *via* linker design, i.e. creating macrocyclic linkers with appropriate arrangement of functional groups typically used in MOF syntheses. As a proof of concept, we have selected phenylene ethynylene macrocycles used by Moore and others as a template.[8] Thus, employing method pioneered by Moore we were able to prepare macrocyclic tricarboxylate **41**, which can be viewed as both extended mesitic acid or cyclic ethynylphenyl tricarboxylic acid (Figure 4.1.).

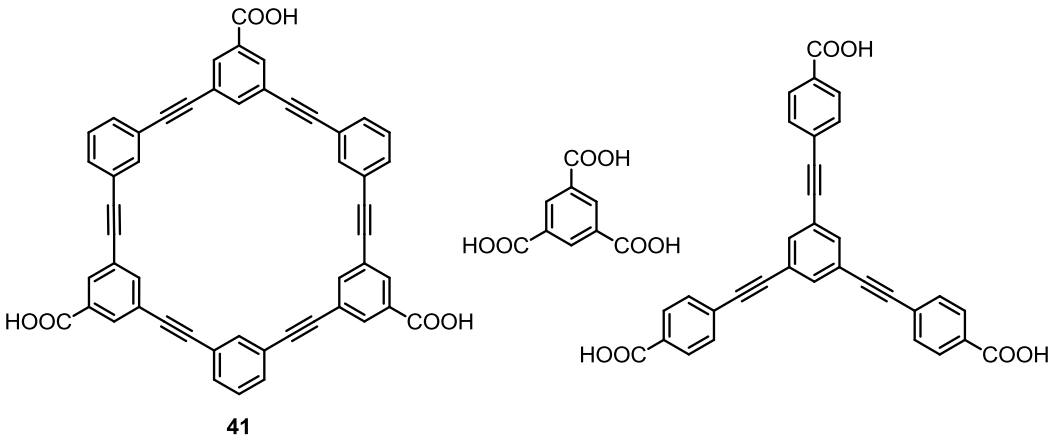
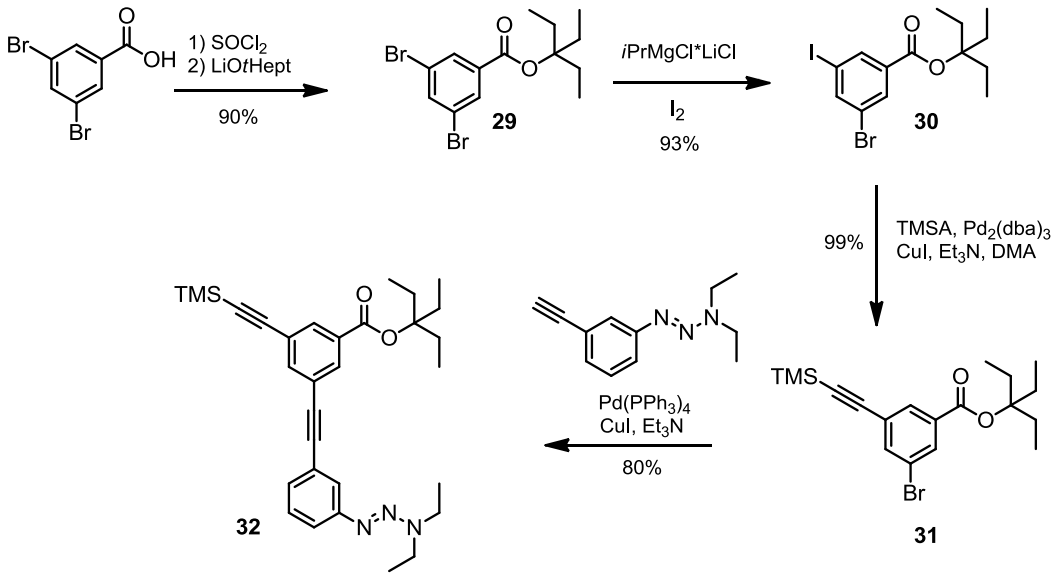


Figure 4.1. Macrocyclic tricarboxylate and other tricarboxylic acids

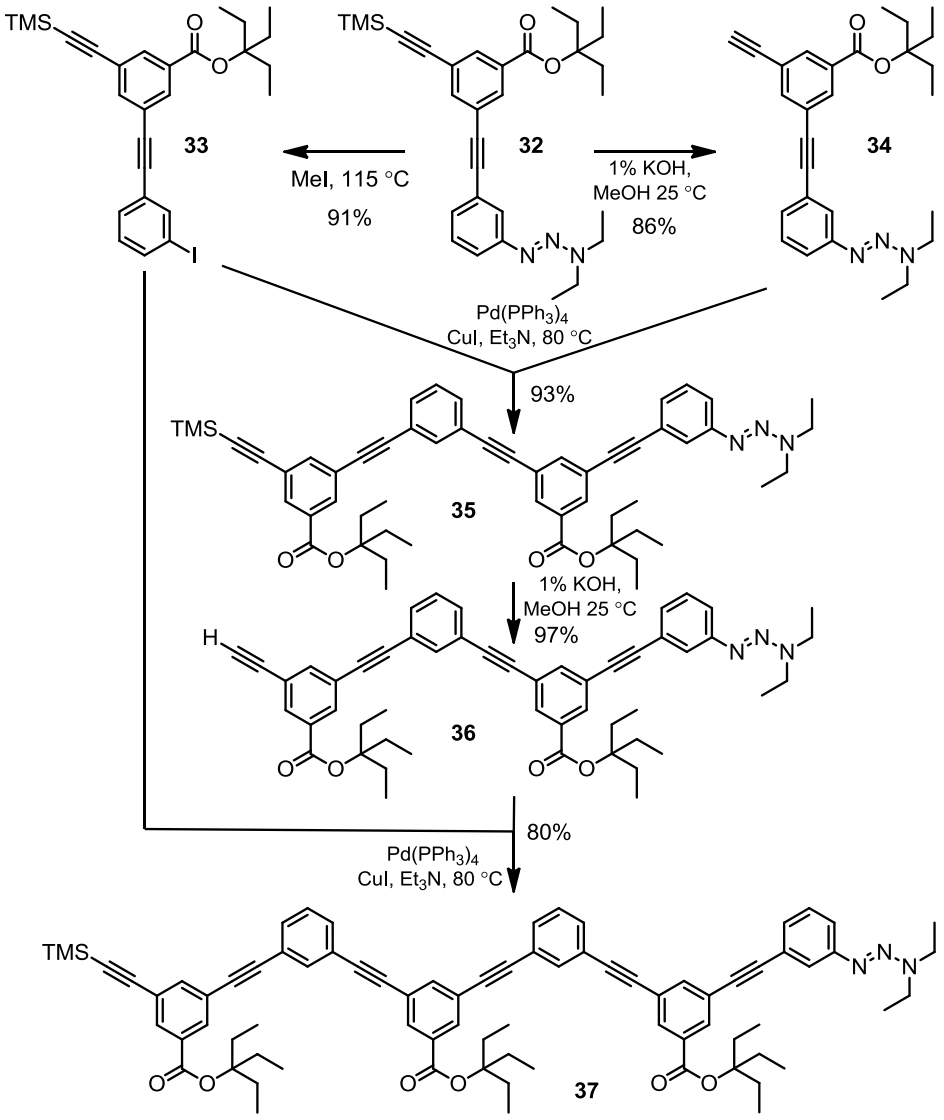
Synthesis of this tricarboxylate linker is accomplished in 13 steps in a longest linear sequence from 3,5-dibromobenzoic acid. Esterification, followed by two sets of magnesium/halogen exchanges and Sonogashira coupling provides advanced intermediate **32** containing orthogonally protected terminal acetylene functionality and latent aryl iodide as a diethyltriazene moiety (Scheme 4.13.).

Scheme 4.13. Synthesis of advanced intermediate **32**



Two-thirds of the advanced intermediate **32** was converted to aryl iodide **33** by reaction with excess amount of MeI. The remaining amount of intermediate **32** was converted to the terminal alkyne **34**, after which Sonogashira coupling was performed in equimolar ratio of iodide and alkyne to provide **35**. Subsequently, novel intermediate **35** containing orthogonally protected reactive groups was converted to terminal alkyne **36** and cross-coupled with the remaining amount of aryl iodide **33** to provide all six benzene rings and orthogonally protected aryl iodide and terminal alkyne **37** (Scheme 4.14.).

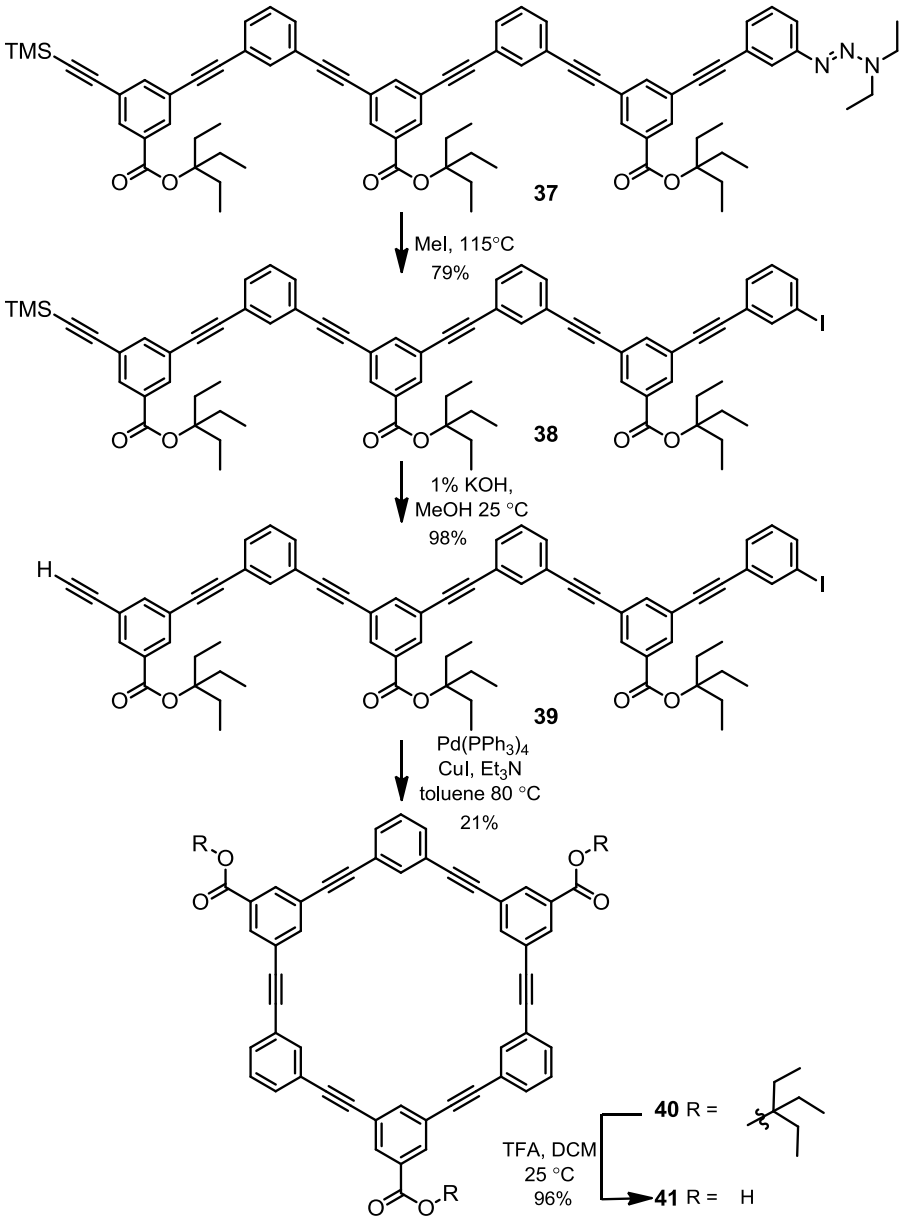
Scheme 4.14. Synthesis of complete linear sequence of macrocyclic ester



The last steps of the sequence included complete deprotection of **37** to obtain intermediate **39**, which after kinetic cyclization under pseudo high dilution conditions, using slow addition of compound **39** to the solution of the catalyst using syringe pump over 100 hours, afforded corresponding macrocyclic triester intermediate **40** in modest

yield. Acid mediated cleavage of ester group completes synthesis of macrocyclic tricarboxylic acid **41** (Scheme 4.15.).

Scheme 4.15. Final cyclization/deprotection sequence



Remarkably, we have discovered that the corresponding macrocyclic ester **40** cocrystallizes with a variety of the polyfluorinated benzenes. Obtained inclusion complexes were crystallographically characterized by using single crystal X-ray diffraction studies. One of the representative examples is shown in the Figure 4.2.

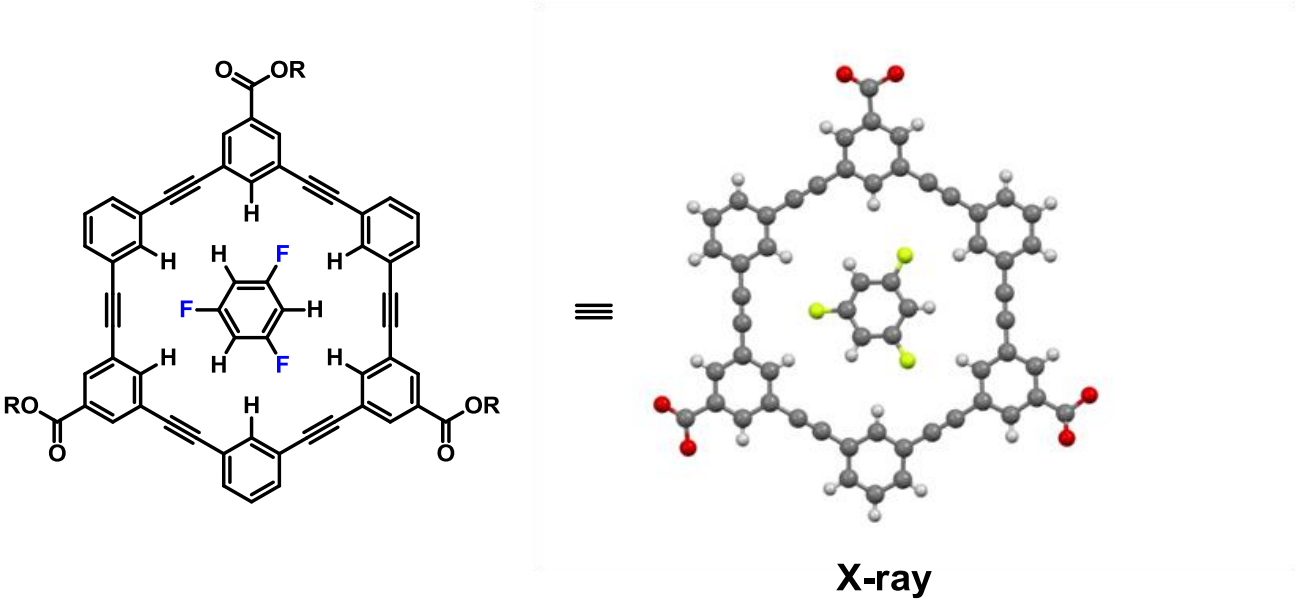


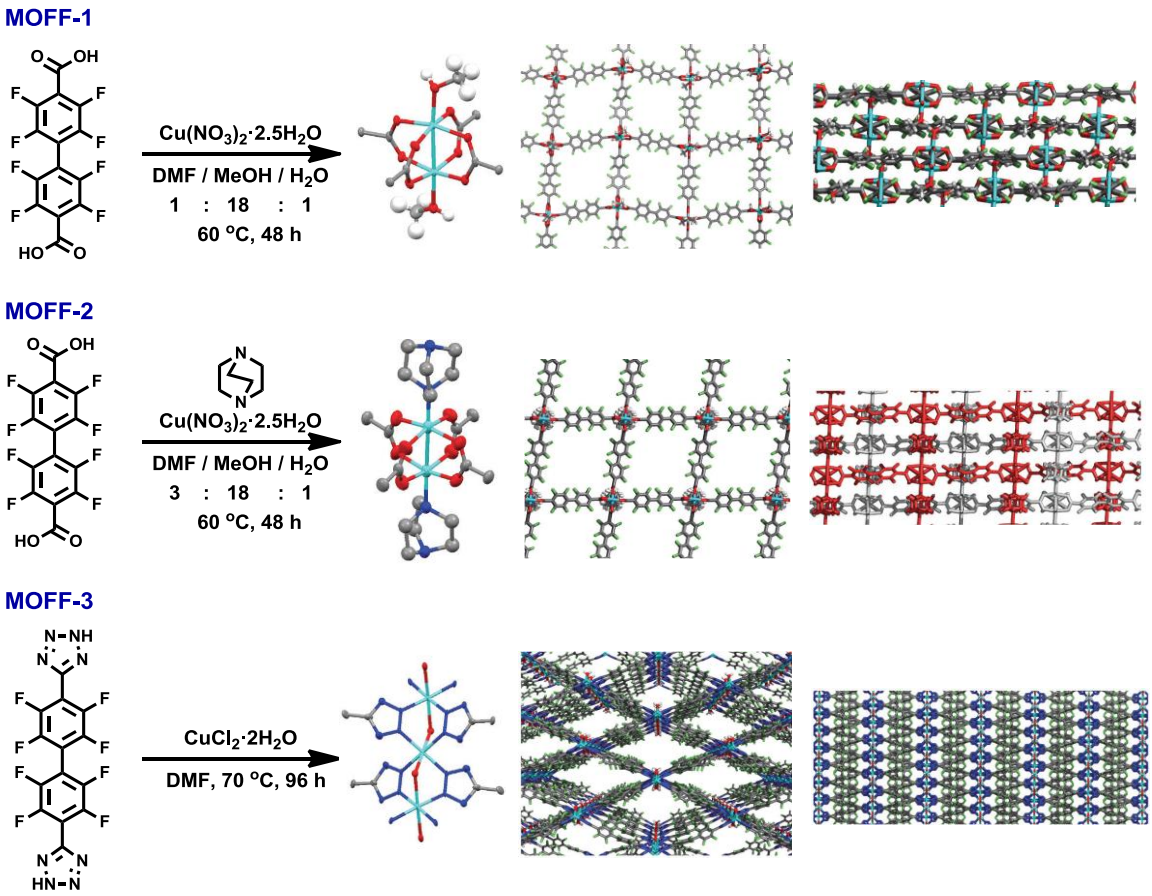
Figure 4.2. Structural view of inclusion complex, ester groups are omitted for clarity

In conclusion, we have synthesized macrocyclic tricarboxylate as a precursor for MOF. Additionally, we have also discovered unprecedented host-guest behavior of the corresponding macrocyclic ester with polyfluorinated benzenes in the solid state. We applied conceptually distinct approach towards the synthesis of organic building blocks for MOF precursors. We believe this approach will stimulate further studies and discoveries in the materials science relevant to metal organic frameworks and their applications.

II.3. Synthesis of MOFF and their properties

Our collaborators, Professor Ognjen Š. Miljanić and Teng-Hao Chen, prepared series of extensively fluorinated MOFs (called MOFFs) using our linkers as precursors.[9] Synthesis and structural features of these materials presented in Scheme 4.16.

Scheme 4.16. Synthesis of MOFFs and their structures



Materials that we designate MOFF-1 and MOFF-2 are structural analogues to ones reported by Kobayashi and coworkers.[10] Similarly, MOFF-3 has a structure similar

to that reported by Long and coworkers.[11] MOFF-3 is an interesting compound because its structure is flexible and it exhibits a so-called breathing effect.

Next, water contact angle measurements were performed, which reveal hydrophobic nature of MOFF-3 and even superhydrophobicity in case of MOFF-2. Hydrophobicity is an important MOF property for use as possible adsorbents for oil spill mitigation (Table 4.1.).

Table 4.1. Water contact angle measurements

Framework	MOFF-1	MOFF-2	MOFF-3
Contact angle	~0 [b]	151 ± 1° [c]	134 ± 1° [c]
	108 ± 2° [c]		135 ± 2° [d]

a Average of three measurements. b Air-dried. c Dried in a vacuum oven (120 °C, 24 h). d Dried with supercritical CO_2

Additionally, gas adsorption experiments were carried out. These revealed that MOFF-3 with its flexible structure has unusual selectivity profile and it can selectively absorb N_2, O_2 whereas CO_2 and H_2O are almost not absorbed (Figure 4.3.). Hysteresis loop observed for oxygen gas is indicative of mechanism change for adsorption and desorption processes.

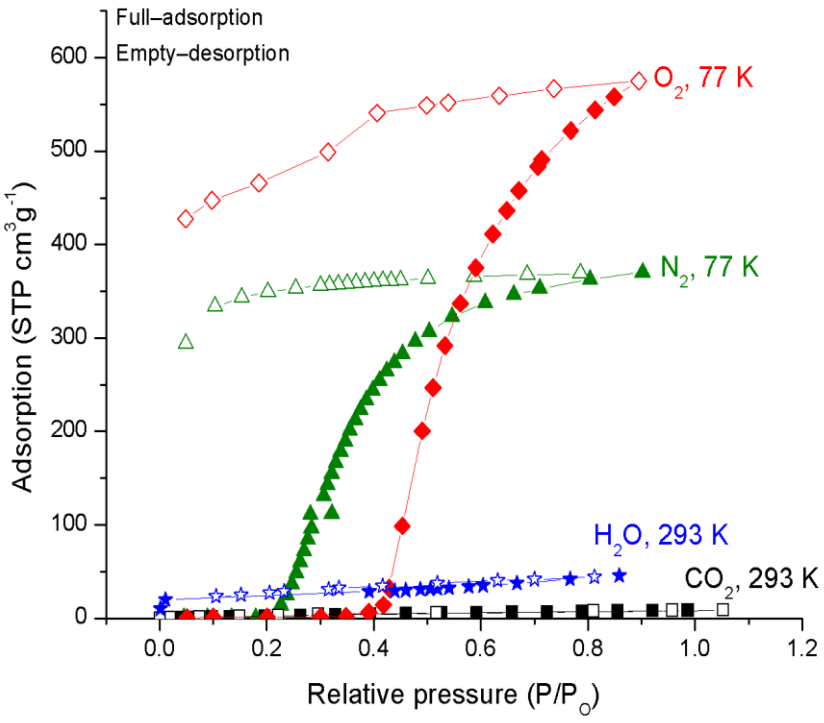


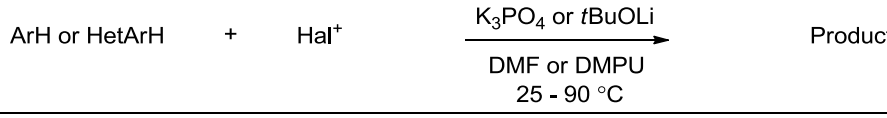
Figure 4.3. Hysteresis in gas adsorption

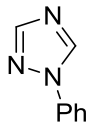
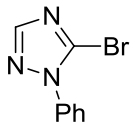
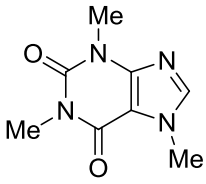
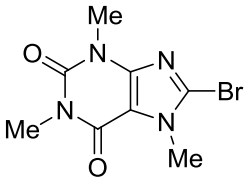
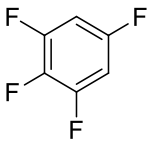
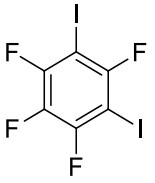
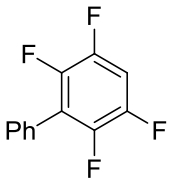
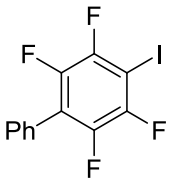
In summary, we have utilized C-H functionalization to access novel perfluorinated aromatic linkers, which were reticulated into highly hydrophobic, extensively fluorinated metal-organic frameworks (MOFFs) by our collaborators. The preparative route to ligands presented here is simple and general, and other extensively fluorinated ligands (and the derived MOFs) could be generated through straightforward adaptation of our protocol. As the extended aromatic ligands shown here open up pathways to highly porous fluorinated MOFs, it should be possible to explore and capitalize upon unique adsorption and binding properties anticipated for these materials.

II.4. Functionalization of acidic arene C-H bonds with simple electrophiles

As has been pointed out earlier in the introduction, deprotonative functionalization of acidic C-H bonds with simple electrophiles is an attractive concept, especially in the context of simple base-mediated reactions. We were able to show that polyfluorinated benzene derivatives as well as select heteroarenes can be efficiently halogenated in the presence of simple base and formal halonium donor. Partial reaction scope is presented in Table 4.2.

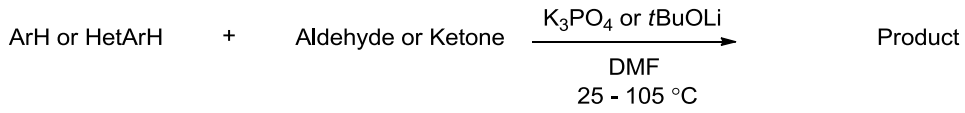
Table 4.2. Halogenation of acidic aryl and heteroaryl C-H bonds

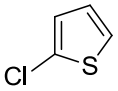
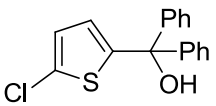
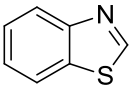
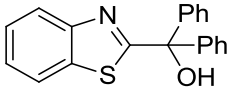
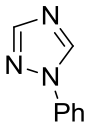
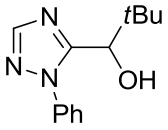
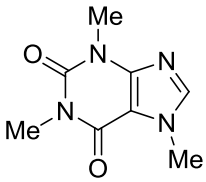
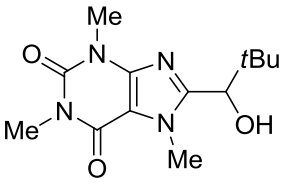
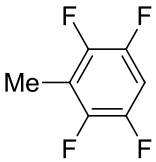
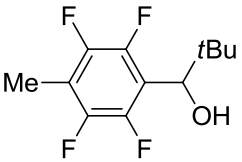


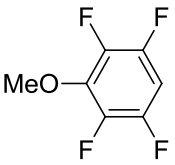
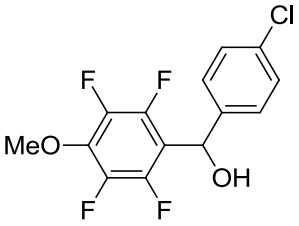
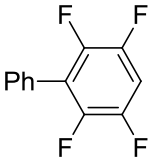
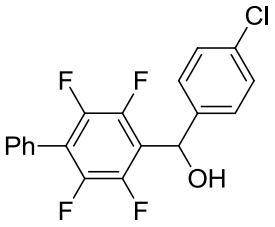
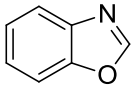
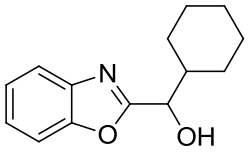
Entry	Arene	Reagent/Base	Product	Yield (%)
1		$(BrCF_2)_2$ *t*BuOLi		77
2		$(BrCF_2)_2$ *t*BuOLi		65
3		I_2 *t*BuOLi		95
4		I_2 *t*BuOLi		97

Additionally, intermediate aryl lithium or aryl potassium generated can be trapped with carbonyl electrophiles. Ketone, tertiary, or secondary aldehydes are reactive with a variety of fluorinated arenes and heteroarenes (Table 4.3.)

Table 4.3. Deprotonative alkylation with aldehydes and ketones

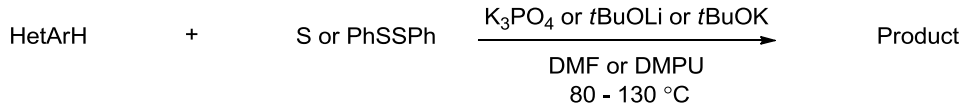


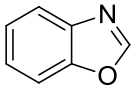
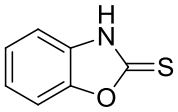
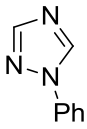
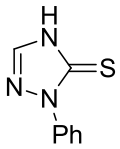
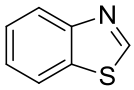
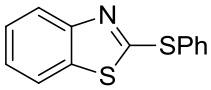
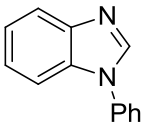
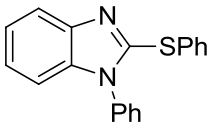
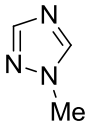
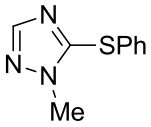
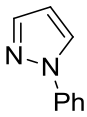
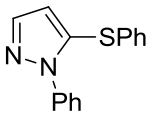
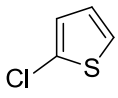
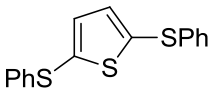
Entry	Arene	Reagent/Base	Product	Yield (%)
1		Ph_2CO *t*BuOLi		41
2		Ph_2CO *t*BuOLi		77
3		*t*BuCHO *t*BuOLi		66
4		*t*BuCHO *t*BuOLi		91
5		*t*BuCHO *t*BuOLi		68

6		p- Chlorobenzaldehyde *t*BuOLi		93
7		p- Chlorobenzaldehyde *t*BuOLi		85
8		$C_6H_{13}CHO$ K_3PO_4		50

Similarly, a number of sulfur electrophiles reacted with heteroarenes to provide sulfenylated products under our reaction conditions. Both elemental sulfur and diphenyl disulfide afforded products in good to excellent yields. Reaction scope is summarized in the Table 4.4.

Table 4.4. Deprotonative sulfenylation with disulfide or elemental sulfur



Entry	Arene	Reagent/Base	Product	Yield (%)
1		S *t*BuOLi		90
2		S *t*BuOLi		74
3		PhSSPh K_3PO_4		85
4		PhSSPh *t*BuOLi		84
5		PhSSPh *t*BuOLi		55
6		PhSSPh *t*BuOK		81
7		PhSSPh *t*BuOLi		82

In conclusion, we have developed general method for selective functionalization of relatively acidic arene carbon-hydrogen bonds using non-cryogenic conditions, simple base and number of electrophiles. Highly diverse substrate scope, good functional group tolerance, and mild reaction conditions combined with good yields are attributes of the developed protocol.

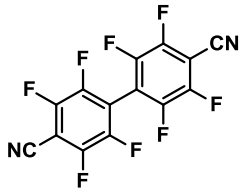
III. Conclusions

We have developed a novel strategy for the synthesis of polyfluorinated aryl carboxylic acids and azoles based on carbon-hydrogen bond functionalization. Simple, readily available starting materials, as well as simple, scalable protocol, afford both unprecedented scope and generality of the approach. Linear as well as trigonal linkers for MOFs have been prepared having geometrically and functionally diverse structures. In addition, synthesis of macrocyclic tricarboxylic acid allows *de novo* design of the MOF linkers. Unprecedented host-guest chemistry of the macrocyclic triester with polyfluorobenzenes in the solid state has been established using single crystal X-ray crystallographic studies. Additionally, we have developed simple and user friendly method for functionalization of simple acidic arenes with halogen-, carbon-, and sulfur-based nucleophiles.

IV. Experimental section

General Considerations. Schlenk flasks or vials with PTFE/Liner caps were used as the reaction vessels for the synthesis of precursors, while standard scintillation vials were used as vessels for the synthesis of MOFFs. Solvents THF, Et_2O, and pentane were dried over activated alumina in Braun solvent purification system. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m×0.25 mm I.D.). The ^{1}H and ^{19}F NMR spectra were recorded on JEOL ECA-500 or ECX-400P spectrometers using the peaks of TMS or residual solvent as standards. Melting points were measured in a Barnstead International Mel-TEMP® apparatus, and are uncorrected. Trifluorotoluene ($PhCF_3$, $\delta = -63.72$ ppm) was used as the internal standard in ^{19}F NMR spectra. Analytical thin layer chromatography was performed on Fluka silica gel/TLC plates with a fluorescent indicator emitting when irradiated at 254 nm. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer using Pike MIRacle Micrometer pressure clamp. Microanalyses were conducted by Intertek USA, Inc. Thermogravimetric analyses (TGA) was carried out on a TA Instruments TGA 2050 thermogravimetric analyzer at a temperature ramping rate of 2 °C/min under the flow of N_2 gas. Powder X-ray diffraction (PXRD) data were collected at 25 °C on a Phillips X'pert Pro diffractometer. Simulated PXRD patterns were calculated with the Material Studio software package employing the structure model from the obtained single crystal data.

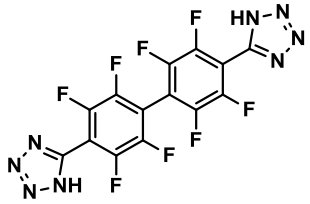
Materials. The following starting materials were obtained from the respective commercial sources and used without further purification: 1,4-diiodobenzene, Boc_2O, and $ZnCl_2$ (Alfa Aesar); dioxane, K_3PO_4, CuI, and phenanthroline (Acros); 2,3,5,6-tetrafluorobenzonitrile and NaN_3 (TCI America); 2,3,5,6-tetrafluorophenol, triflic anhydride, and triflic acid (SynQuest Labs); trimethylsilylacetylene and TMEDA (Matrix Scientific); triphenylphosphine and $CuCl_2$ (Aldrich); $Pd(OAc)_2$ (Pressure Chemical); $Cu(NO_3)_2 \cdot 2.5H_2O$ and $CuCl_2 \cdot 2H_2O$ (JT Baker). Compound 2,3,5,6-tetrafluoro-4-iodo-benzonitrile was prepared from 2,3,5,6-tetrafluorobenzonitrile by reaction with *t*-BuOLi and iodine. All the solvents for synthesizing MOFFs were obtained from commercial sources and used without further purification.



2,2',3,3',5,5',6,6'-Octafluorobiphenyl-4,4'-dicarbonitrile (1)

A 40 mL scintillation vial was equipped with a magnetic stirbar and charged with 2,3,5,6-tetrafluorobenzonitrile (2.27 g, 13.0 mmol) and 2,3,5,6-tetrafluoro-4-iodo-benzonitrile (3.01 g, 10.0 mmol). Vial was purged with N_2 and placed inside a nitrogen-filled glovebox. Phenanthroline (0.90 g, 5.00 mmol) and CuI (0.95 g, 5.00 mmol) were added, followed by K_3PO_4 (6.40 g, 30.0 mmol) and dioxane (12 mL). Vial was capped and taken out of the glovebox. Reaction mixture was stirred for 2 min at 25 °C and then placed inside aluminum reaction block preheated to 125 °C and stirred vigorously for 12 h.

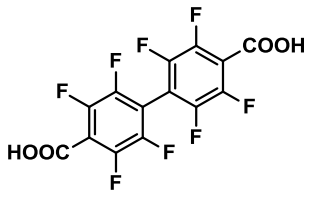
Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (50 mL), and filtered through the plug of Celite to remove the inorganic salts. Filter cake was washed with additional CH_2Cl_2 (3×25 mL). Resulting organic phases were combined and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2/ hexanes (gradient 10 % to 50% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white crystalline solid (2.30 g, 66 %). R_f=0.27 (SiO_2, hexanes/EtOAc 19/1), mp 124–127 °C (hexanes/CH_2Cl_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5–148.2 and 146.4–146.1 (m, 4C), 145.0–144.8 and 143.1–142.8 (m, 4C), 111.9–111.5 (m, 2C), 106.6–106.4 (m, 2C), 97.3–97.1 (m, 2C) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –134.4 to –134.7 (m, 4F), –138.0 to –138.2 (m, 4F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 2249, 1729, 1484, 1289, 1267, 1005, 991, 975. ESI MS m/z: 348 (100 %), 279 (24 %), 349 (16 %), 174 (15 %), 248 (7 %).



5,5'-(Perfluorobiphenyl-4,4'-diyl)bis(1*H*-tetrazole) (2)

A 120 mL glass pressure vessel was equipped with a magnetic stirbar and charged with $ZnCl_2$ (6.00 g, 44 mmol) and NaN_3 followed by deionized water (7 mL). Mixture was stirred until all inorganic salts dissolved. Glacial acetic acid (35 mL) was added followed by dinitrile **2** (1.40 g, 4.00 mmol) and additional acetic acid (7 mL). Pressure vessel was capped and placed in an oil bath preheated to 105 °C. Reaction mixture was vigorously

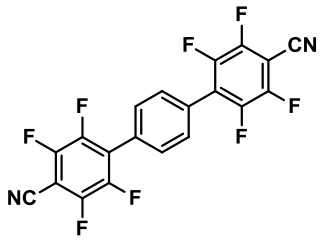
stirred at that temperature for 24 h. After completion, reaction mixture was cooled to 25 °C and poured into a 1N aqueous solution of HCl (200 mL), causing the precipitation of the product. White solid was filtered and washed with additional 1N HCl (2×50 mL) followed by H_2O (20 mL). Solid was dried under high vacuum for 24 h over P_2O_5, affording the title compound (1.74 g, 94 %) as a white solid, mp 260–263 °C (dec). ^{13}C NMR (125 MHz, DMSO-d_6) δ 147.8 (s, 2C), 145.3–144.7 (m, 4C), 143.3–142.8 (m, 4C), 109.4–109.0 (m, 2C), 108.2–107.6 (m, 2C) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ −137.1 to −137.3 (m, 4F), −137.3 to −137.4 (m, 4F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 3459, 1571, 1500, 1475, 1372, 1303, 1242, 1122, 1053, 999, 973.



2,2',3,3',5,5',6,6'-Octafluorobiphenyl-4,4'-dicarboxylic acid (3)

A 120 mL glass pressure vessel was equipped with a magnetic stirbar and charged with dinitrile **2** (3.56 g, 10.0 mmol) followed by trifluoroacetic acid (15 mL) and triflic acid (13.2 g, 88.0 mmol). Reaction mixture was stirred until all solids completely dissolved. Deionized H_2O (7 mL) was carefully added, causing a **highly exothermic reaction (CAUTION!)**. This glass vessel was capped and placed inside an oil bath preheated to 130 °C, and the reaction mixture was vigorously stirred at this temperature for 48 h. After completion, reaction mixture was cooled to 25 °C and diluted with 1N HCl (100 mL) causing the precipitation of the reaction product. White solid was filtered off and washed

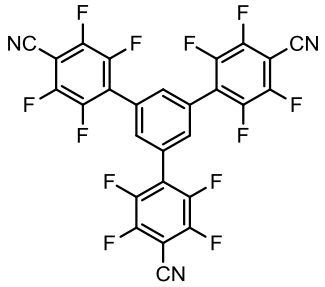
with additional 1N HCl (2×50 mL) followed by H_2O (20 mL). Solid was dried under high vacuum for 24 h over P_2O_5 affording the title compound (3.70 g, 96 %) as a white solid, mp 310–312 °C (dec). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.5 (br s, 2H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ −136.7 to −137.9 (m, 4F), −140.4 to −140.6 (m, 4F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 1719, 1477, 1418, 1307 1262, 1231, 1004, 981.



1,4-Bis(2',3',5',6'-tetrafluoro-4'-cyanophenyl)benzene (4)

An 8 mL scintillation vial was equipped with a magnetic stirbar and charged with 2,3,5,6-tetrafluorobenzonitrile (0.70 g, 4.00 mmol) and 1,4-diiodobenzene (0.30 g, 1.00 mmol). Vial was purged with N_2 and placed inside a nitrogen-filled glovebox, where CuI (0.19 g, 1.00 mmol) and phenanthroline (0.18 g, 1.00 mmol) were added, followed by K_3PO_4 (0.85 g, 4.00 mmol) and dioxane (1.5 mL). Vial was capped and taken out of the glovebox. Reaction mixture was stirred for 2 min at 25 °C and then placed inside aluminum reaction block preheated to 130 °C and stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (30 mL) and filtered through the plug of Celite to remove the inorganic salts. Filter cake was washed with additional CH_2Cl_2 (3×20 mL). Resulting organic phases were combined and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 and hexanes (gradient 10 % to 50 % of CH_2Cl_2) as eluent, and evaporation of the fractions containing

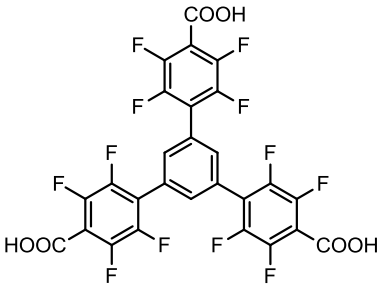
product, title compound (182 mg, 43 %) was obtained as a white crystalline solid. R_f=0.56 (SiO_2, hexanes/CH_2Cl_2 1/1), mp 199–201 °C (hexanes/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 4H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −131.5 to −131.6 (m, 4F), −139.5 to −139.6 (m, 4F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 2923, 2864, 2242, 1648, 1487, 1407, 1320, 1282, 1196, 987. EI MS m/z: 424 (100 %), 212 (41 %), 425 (21 %), 355 (10 %), 162 (9%), 199 (9 %), 225 (6%), 404 (6 %), 177 (5 %), 373 (5 %), 167 (5 %), 405 (4 %).



1,3,5-Tris(2',3',5',6'-tetrafluoro-4'-cyanophenyl)benzene (5)

A 36 mL scintillation vial was equipped with a magnetic stirring bar and charged with 2,3,5,6-tetrafluorobenzonitrile (2.89 g, 16.5 mmol) and 1,3,5-triiodobenzene (1.58 g, 3.50 mmol). Vial was purged with N_2 and placed inside a nitrogen-filled glovebox, where CuI (0.570 g, 3.50 mmol) and phenanthroline (0.540 g, 3.00 mmol) were added, followed by K_3PO_4 (3.50 g, 16.5 mmol) and dioxane (5.25 mL). Vial was capped and taken out of the glovebox. Reaction mixture was vigoruosly stirred for 2 min at 25 °C and then placed inside aluminum reaction block preheated to 130 °C and stirred vigorously for 24 h. After completion, reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (100 mL) and filtered through the plug of Celite® to remove the inorganic salts. Filter cake was washed

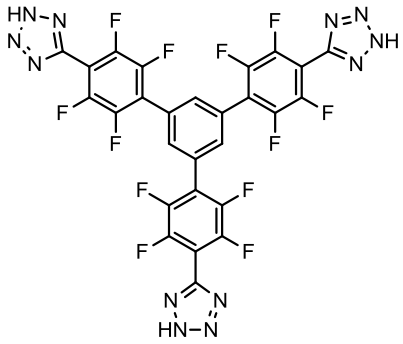
with additional CH_2Cl_2 (3×30 mL). Resulting organic phases were combined and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 and hexanes (gradient 30 % to 75 % of CH_2Cl_2) as eluent, and evaporation of the fractions containing product, title compound (0.46 g, 22 %) was obtained as a white crystalline solid. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.78 (s, 3H) ppm. ^{19}F NMR (470 MHz, CD_2Cl_2) δ −132.0 to −132.1 (m, 6F), −140.2 to −140.4 (m, 6F) ppm. HRMS (CI + mode): Calculated for $[C_{27}H_3F_{12}N_3]^+$ 597.0135, Found 597.0142.



4,4',4''-(benzene-1,3,5-tris(2,3,5,6-tetrafluorobenzoic acid) (6)

A 40 mL glass pressure vessel was equipped with a magnetic stirring bar and charged with trinitrile **5** (0.597 g, 1.0 mmol) followed by trifluoroacetic acid (10 mL) and triflic acid (2.7 g, 10.0 mmol). Reaction mixture was stirred until all solids completely dissolved. Deionized H_2O (0.5 mL) was carefully added, causing a **highly exothermic reaction (CAUTION!)**. This glass vessel was capped and placed inside an oil bath preheated to 130 °C, and the reaction mixture was vigorously stirred at this temperature for 48 h. After completion, reaction mixture was cooled to 25 °C and diluted with 4M HCl (100 mL), causing the precipitation of the reaction product. White solid was filtered off and washed with additional 1M HCl (2×50 mL) followed by H_2O (20 mL). Solid was

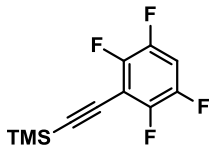
dried under high vacuum for 24 h over P_2O_5 affording the title compound (0.54 g, 83 %) as a beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.0 to 13.0 (br s, 3H), 7.95 (s, 3H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −140.9 to −141.1 (m, 6F), −142.4 to −142.6 (m, 6F) ppm. HRMS (CI + mode): Calculated for $[C_{27}H_6O_6F_{12}]^+$ 653.9973, Found 653.9990.



4,4',4''-(benzene-1,3,5-tris(2,3,5,6-tetrafluorophenyl 1*H*-tetrazole) (7)

A 120 mL glass pressure vessel was equipped with a magnetic stirbar and charged with $ZnCl_2$ (5.45 g, 40 mmol) and NaN_3 (2.34 g, 36 mmol), followed by deionized water (6 mL). Mixture was stirred until all inorganic salts dissolved. Glacial acetic acid (35 mL) was added followed by trinitrile **5** (1.86 g, 3.10 mmol) and additional acetic acid (5 mL). Pressure vessel was capped and placed in an oil bath preheated to 105 °C. Reaction mixture was vigorously stirred at that temperature for 24 h, during which time cloudy, white suspension gradually turned into clear solution. After completion, reaction mixture was cooled to 25 °C and poured into a 1N aqueous solution of HCl (200 mL), causing the precipitation of the product. White solid was filtered and washed with additional 1N HCl (2×50 mL) followed by H_2O (20 mL). Solid was dried under high vacuum for 24 h over P_2O_5, affording the title compound (2.0 g, 89 %) as a grey solid. ^{1}H NMR (500 MHz,

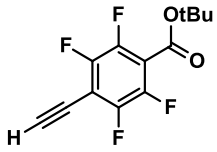
DMSO-d_6) δ 8.11 (s, 3H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −138.7 to −139.0 (m, 6F), −142.2 to −142.6 (m, 6F) ppm. HRMS (ESI + mode): Calculated for $[C_{27}H_6F_{12}N_{12} + H]^+$ 727.07200, Found 727.07000.



Trimethyl((2,3,5,6-tetrafluorophenyl)ethynyl)silane (8)

2,3,5,6-Tetrafluorophenol (25.0 g, 150 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and the resulting solution was cooled to 0 °C. Triethylamine (24.0 mL, 170 mmol) was added at once followed by a slow addition of triflic anhydride (45.2 g, 160 mmol) via a syringe, over 20 min. Reaction mixture was allowed to warm up to 25 °C and stirred for 1 h. Reaction mixture was dry-absorbed on silica gel. Purification by column chromatography eluting with CH_2Cl_2/hexanes (20% CH_2Cl_2) and evaporation of the solvent afforded the triflate product (37 g, 82 % yield) as a colorless oil. A 500 mL Schlenk flask was charged with $Pd(OAc)_2$ (224 mg, 1.00 mmol), PPh_3 (524 mg, 2.00 mmol), and CuI (190 mg, 1.00 mmol), followed by the addition of 2,3,5,6-tetrafluorophenyltriflate (37.0 g, 124 mmol). The flask was capped with a septum and was evacuated and backfilled with nitrogen 3 times. Degassed Et_3N (150 mL) was transferred into the flask under nitrogen via a canula, followed by the addition of anhydrous degassed DMA (20 mL). Trimethylsilyl acetylene (17.2 g, 175 mmol) was added in one portion through the septum and the reaction mixture was allowed to stir at room temperature for 5 min. Temperature of the oil bath was gradually increased to 90 °C

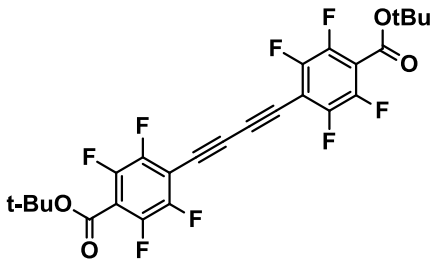
and the reaction mixture was stirred at this temperature for 48 h. Reaction mixture was then cooled to 25 °C and the excess of Et_3N was evaporated under reduced pressure. The residue was diluted with hexanes (200 mL) and treated with 1N HCl (200 mL). Organic layer was separated and the aqueous layer was extracted with another portion of hexanes (100 mL). Combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification by column chromatography on silica gel eluting with CH_2Cl_2/ hexanes (gradient 0 % to 10 % of CH_2Cl_2) afforded the product (24.5 g, 80 %) as a dark oil. R_f=0.76 (SiO_2, hexanes/EtOAc 19/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08–7.00 (m, 1H), 0.30 (s, 9H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −136.3 to −136.5 (m, 2F), −138.9 to −139.0 (m, 2F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 3082, 2965, 2903, 2173, 2068, 1643, 1610, 1497, 1464, 1397, 1279, 1253, 1178, 1035, 938. EI MS m/z: 231 (100 %), 232 (15 %), 164 (15 %), 115 (13 %), 81 (13 %), 101 (12 %), 165 (8 %), 75 (7 %), 246 (6 %), 145 (5 %).



<u>*tert*-Butyl 4-ethynyl-2,3,5,6-tetrafluorobenzoate (9)</u>

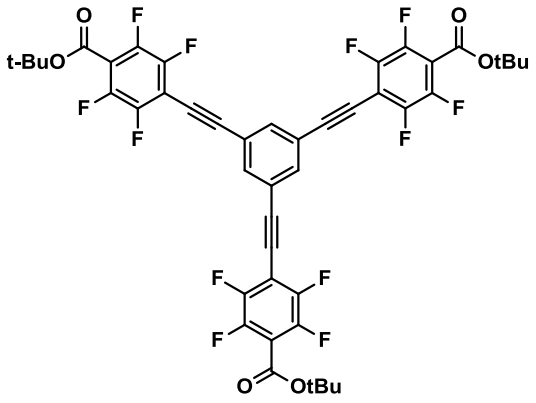
Compound **8** (8.00 g, 32.5 mmol) was dissolved in anhydrous THF (120 mL) under nitrogen. The solution was cooled to −94 °C using acetone/liquid nitrogen bath. To this mixture, a 2.5M solution of BuLi in hexanes (14.0 mL, 35.0 mmol) was added dropwise over 30 min via a syringe. Reaction mixture was then stirred for 5 min at −94 °C and the solution of Boc_2O (7.86 g, 36.0 mmol) in anhydrous THF (10 mL) was added in one

portion. Reaction mixture was warmed to −20 °C and quenched by the addition of 10 % aqueous solution of citric acid (100 mL). Ethyl acetate (100 mL) was added to the mixture and the organic layer was separated. Water layer was extracted with additional EtOAc (2×50 mL). Combined organic extracts were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and evaporated. Purification by column chromatography on silica gel, eluting with a CH_2Cl_2/ hexanes (gradient 5 % to 25 % of CH_2Cl_2) and evaporation of solvent afforded *t*-butyl 2,3,5,6-tetrafluoro-4-((trimethyl)ethynyl)benzoate as a tan solid (8.1 g, 73 % yield). Obtained benzoate (7.30 g, 21.0 mmol) was dissolved in THF (30 mL) and MeOH (100 mL) was added, followed by 2 drops of 50 % aqueous KOH. Reaction mixture was stirred for 24 h at 25 °C. Organic solvents were evaporated under vacuum and the resulting residue was purified by column chromatography on silica gel eluting with CH_2Cl_2/ hexanes (gradient 0% to 25% of CH_2Cl_2). Evaporation of the fractions containing the product afforded title compound (5.20 g, 90 % yield) as a dark brown oil. R_f=0.48 (SiO_2, hexanes/EtOAc 19/1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.71 (m, 1H), 1.60 (s, 9H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −135.3 to −135.5 (m, 2F), −140.7 to −140.9 (m, 2F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 3307, 2985, 2128, 1732, 1647, 1482, 1372, 1326, 1245, 1156, 1058, 990. ESI MS m/z: 201 (100 %), 56 (97 %), 57 (97 %), 123 (20 %), 218 (18 %), 173 (17 %), 202 (10 %), 259 (8 %), 219 (5 %), 274 (1 %).



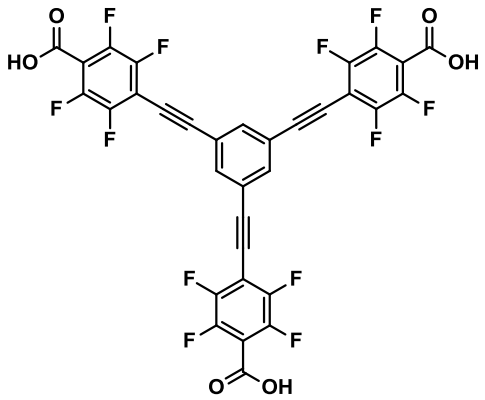
tert-Butyl 4,4'-(buta-1,3-diyne-1,4-diyl)bis(2,3,5,6-tetrafluorobenzoate) (10)

A round bottom flask was charged with acetylene **9** (1.10 g, 4.00 mmol), $CuCl_2$ (1.40 g, 10.0 mmol), TMEDA (0.60 g, 5.00 mmol), Et_3N (3 mL), and DMA (3 mL). Reaction mixture was stirred at 25 °C under O_2 atmosphere for 24 h. Excess of Et_3N was evaporated under the reduced pressure and the resulting residue was quenched with 10 % aqueous citric acid (50 mL) and extracted with EtOAc (100 mL). Organic layer was separated, dried over anhydrous $MgSO_4$, filtered and solvent was evaporated under vacuum. Product was purified by column chromatography eluting with CH_2Cl_2/ hexanes (gradient 0 % to 100 % of CH_2Cl_2). Evaporation of the fractions containing the product afforded the title compound (814 mg, 74 %) as a light yellow solid. R_f=0.46 (SiO_2, hexanes/EtOAc 19/1), mp 193–195 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (s, 18H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −133.4 to −133.6 (m, 4F), −139.9 to −140.1 (m, 4F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 2985, 1738, 1653, 1484, 1372, 1326, 1248, 1154, 1061, 988.



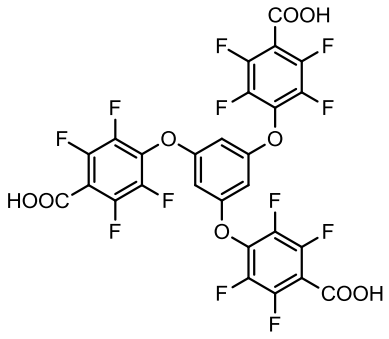
tert-Butyl 4,4',4''-(benzene-1,3,5-triyltris(ethyne-2,1-diyl))tris(2,3,5,6-tetrafluorobenzoate) (9a)

A 100 mL Schlenk flask was charged with 1,3,5-triiodobenzene (2.3 g, 5.0 mmol), $Pd(OAc)_2$ (112 mg, 0.50 mmol), PPh_3 (524 mg, 2.0 mmol), and CuI (190 mg, 1.0 mmol). Flask was capped with a septum and then evacuated and backfilled with nitrogen 3 times. Degassed Et_3N (70 mL) was transferred into the flask under nitrogen via a canula, followed by the addition of acetylene **9** (4.90 g, 17.8 mmol) in one portion. Reaction mixture was placed into the oil bath preheated to 50 °C and stirred for 48 h. Reaction mixture was then cooled to 25 °C and excess of triethylamine was evaporated under vacuum. Obtained precipitate was dissolved in $CHCl_3$ (50 mL) and filtered through a plug of silica gel. Evaporation of the solvent and subsequent recrystallization from $CHCl_3$ afforded the title compound (2.95 g, 66 %) as a light tan powder. R_f=0.34 (SiO_2, hexanes/EtOAc 19/1), mp 194–196 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 3H), 1.61 (s, 27H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ −135.0 to −135.2 (m, 6F), −140.5 to −140.7 (m, 6F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 2980, 2938, 2762, 2682, 2230, 1740, 1732, 1651, 1587, 1484, 1372, 1332, 1309, 1258, 1238, 1153, 991.



4,4',4''-(Benzene-1,3,5-triyltris(ethyne-2,1-diyl))tris(2,3,5,6-tetrafluorobenzoic acid) (11)

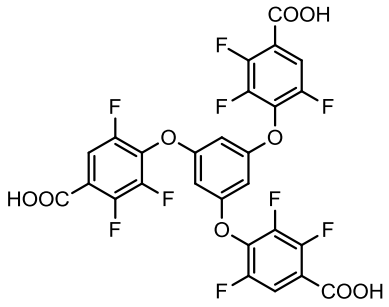
Triester **9a** (1.0 g, 1.1 mmol) was dissolved in $CHCl_3$ (3 mL) and TFA (2 mL) was added. Reaction mixture was stirred at 25 °C overnight. Precipitate was filtered off and washed with CH_2Cl_2 (3×20 mL). After overnight drying in high vacuum, the title product (0.61 g, 76 %) was obtained as a light tan solid, mp 272–274 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.96 (s, 3H) ppm.^{19}F NMR (376 MHz, DMSO-d_6) δ −134.6 to −134.9 (m, 6F), −139.4 to −139.6 (m, 6F) ppm. FT-IR (neat, cm^{-1}) $\tilde{\nu}$ 3501, 2927, 2229, 1720, 1647, 1586, 1478, 1427, 1325, 1252, 1080, 990.



4,4',4''-(Benzene-1,3,5-triyltris(oxy))tris(2,3,5,6-tetrafluorobenzoic acid) (12)

A 50 mL round-bottom flask with magnetic stirring bar was charged with *tert*-Bu-pentafluorobenzoate (9.38 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (25 mL) was added, followed by CsF (1.52 g, 10.0 mmol). Reaction mixture was capped with septum, taken out of the glovebox and stirred at 25 °C for 24 hours. After completion, reaction mixture was diluted with water (150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL) dried over anhydrous $MgSO_4$ filtered and dry absorbed

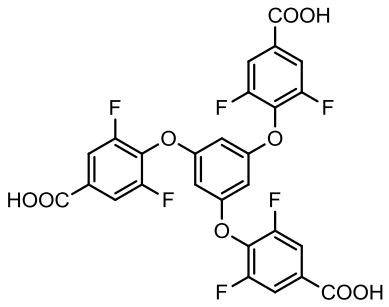
on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 80% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded 7.66 g of triester intermediate. Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (7.5 g), Et_3SiH (2.33 g, 20 mmol) and CH_2Cl_2 (45 mL). Resulting clear solution was treated with trifluoroacetic acid (5 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Resulting triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). Obtained white solid was dried in vacuum for 2 hours to provide the product (5.68 g, 80 % over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.0 to 13.0 (br s, 3H), 7.00 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ –140.3 to –140.5 (m, 6F), –154.1 to –154.3 (m, 6F) ppm. HRMS (CI - mode): calculated for $C_{27}H_6O_9F_{12}$ 701.9820 found 701.9822.



4,4',4''-(benzene-1,3,5-triyltris(oxy))tris(2,3,5-trifluorobenzoic acid) (13)

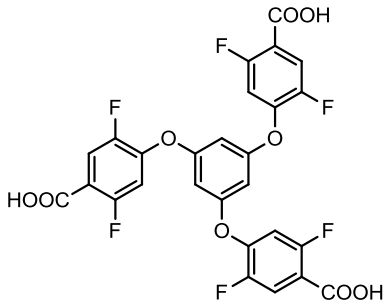
A 50 mL round-bottom flask with magnetic stirring bar was charged with *tert*-Bu-tetrafluorobenzoate (8.75 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (25 mL) was added, followed by CsF (1.52 g, 10.0 mmol).

Reaction mixture was capped with septum, taken out of the glovebox and stirred at 25 °C for 24 hours. After completion, reaction mixture was diluted with water (150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL), and dried over anhydrous $MgSO_4$, filtered and dry absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 80% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (7.66 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (7.6 g), Et_3SiH (2.33 g, 20 mmol) and CH_2Cl_2 (45 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). White solid was dried in vacuum for 2 hours to provide the product (4.53 g, 70 % over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 15.0 to 13.0 (br s, 3H), 7.70–7.60 (m, 3H), 6.78 (s, 3H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ –130.8 to –130.9 (m, 3F), –136.6 to –136.8 (m, 3F), –147.5 to –147.6 (m, 3F) ppm. HRMS (CI + mode): calculated for $C_{27}H_9O_9F_9$ 648.0103 found 648.0097.



4,4',4''-(benzene-1,3,5-triyltris(oxy))tris(3,5-difluorobenzoic acid) (14)

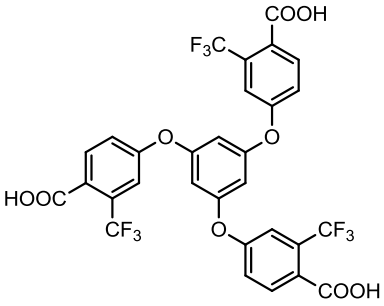
A 50 mL round-bottom flask with magnetic stirring bar was charged with *tert*-butrifluorobenzoate (8.13 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (20 mL) was added, followed by CsF (1.52 g, 10.0 mmol). Reaction vessel was capped with septum, taken out of the glovebox, and stirred at 25 °C for 24 hours. After completion, reaction mixture was diluted with water (150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and dry absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 80% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (5.37 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (5.2 g), Et_3SiH (3.50 g, 30 mmol) and CH_2Cl_2 (40 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). White solid was dried in vacuum for 2 hours to provide the product (4.0 g, 67 % over two steps).). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.0 to 13.0 (br s, 3H), 7.73–7.68 (m, 6H), 6.50 (s, 3H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ –125.4 to –125.5 (m, 6F), ppm. HRMS (CI + mode): calculated for $C_{27}H_{12}O_9F_6$ 594.0386 found 594.0398.



4,4',4''-(Benzene-1,3,5-triyltris(oxy))tris(2,5-difluorobenzoic acid) (15)

A 50 mL round-bottom flask with magnetic stirring bar was charged with *tert*-butrifluorobenzoate (8.13 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (20 mL) was added, followed by CsF (1.52 g, 10.0 mmol). Reaction mixture was capped with septum, taken out of the glovebox, and stirred at 25 °C for 24 hours. After completion, reaction mixture was diluted with water (150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and dry absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 80% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (6.74 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (6.3 g), Et_3SiH (3.50 g, 30 mmol) and CH_2Cl_2 (40 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). White

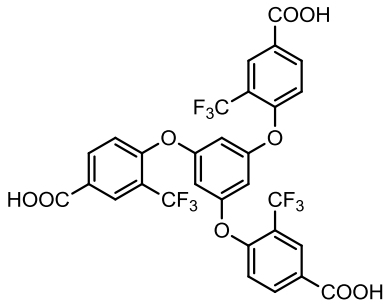
solid was dried in vacuum for 2 hours to provide the product (5.10 g, 85 % over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.0 to 13.0 (br s, 3H), 7.79–7.73 (m, 3H), 7.30–7.24 (m, 3H), 6.95 (s, 3H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ –110.8 to –110.9 (m, 3F), –136.5 to –136.6 (m, 3F) ppm. HRMS (CI + mode): calculated for $C_{27}H_{12}O_9F_6$ 594.0386 found 594.0398.



4,4',4''-(Benzene-1,3,5-triyltris(oxy))tris(2-(trifluoromethyl)benzoic acid) (16)

A 50 mL round-bottom flask with magnetic stirring bar was charged with *tert*-butyl-4-fluoro-2-trifluoromethylbenzoate (9.24 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (20 mL) was added, followed by CsF (1.52 g, 10.0 mmol). Reaction mixture was capped with septum, taken out of the glovebox and stirred at 60 °C for 24 hours. After completion, reaction mixture was diluted with water (150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and dry absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester

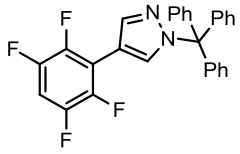
intermediate (5.85 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (5.73 g), Et_3SiH (2.32g, 20 mmol) and CH_2Cl_2 (40 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). White solid was dried in vacuum for 2 hours to provide the product (4.6 g, 66 % over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.8 to 13.0 (br s, 3H), 7.85 (d, J = 8.6 Hz, 3H), 7.46 (d, J = 2.9 Hz, 3H), 7.39 (dd, J = 8.6 Hz and 2.9 Hz) 6.87 (s, 3H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ –58.24 (s, 3F) ppm. HRMS (CI + mode): calculated for $C_{30}H_{15}O_9F_9$ 690.0572 found 690.0591.



4,4',4''-(Benzene-1,3,5-triyltris(oxy))tris(3-(trifluoromethyl)benzoic acid) (17)

A 50 mL round-bottom flask equipped with magnetic stirring bar was charged with *n*-butyl-4-fluoro-3-trifluoromethylbenzoate (9.24 g, 35.0 mmol) followed by the addition of 1,3,5-tris-(trimethylsilyloxy)benzene (3.43 g, 10.0 mmol). Reaction flask was evacuated and placed inside the glovebox. Dry DMF (20 mL) was added, followed by CsF (1.52 g, 10.0 mmol). Reaction mixture was capped with septum, taken out of the glovebox, and stirred at 60 °C for 24 hours. After completion, reaction mixture was diluted with water

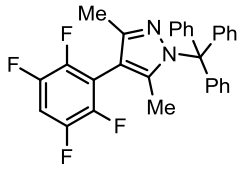
(150 mL) and extracted with diethyl ether (3 x 50 mL). Combined ethereal extracts were washed with water (5 x 50 mL), brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and dry absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/hexanes (gradient 30 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (8.2 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (6.3 g), EtOH (70 mL) followed by KOH (5.6 g, 100 mmol) dissolved in water (10 mL). Resulting reaction mixture was vigorously stirred at 70 °C for 30 hours. After completion, 4N aqueous HCl (40 mL was added) and the reaction mixture was extracted with diethyl ether (3 x 50 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Resulting triacid was suspended in CH_2Cl_2 (100 mL) and filtered. Obtained white solid was dried in vacuum for 2 hours to provide the product (5.99 g, 86 % over two steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.36 (s, 3H), 8.17–8.13 (m, 6H), 7.32–7.28 (m, 3H), 6.93 (s, 3H) ppm. ^{19}F NMR (470 MHz, DMSO-d_6) δ –60.87 (s, 3F) ppm. HRMS (CI + mode): calculated for $C_{30}H_{15}O_9F_9$ 690.0572 found 690.0573.



4-(2,3,5,6-Tetrafluorophenyl)-1-trityl-1H-pyrazole (18)

Inside a glovebox a 500 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (15.0 g, 150 mmol) and *t*BuOLi (12.0 g, 150 mmol). Dry

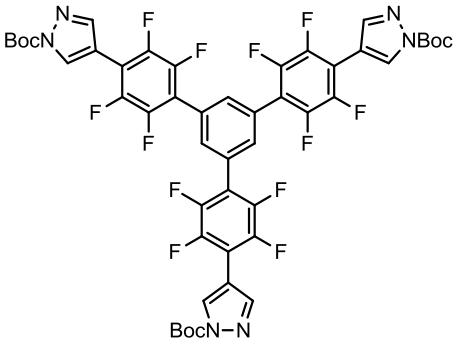
DMF (240 mL) was added, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. Tetrafluorobenzene (22.5 g , 150 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (1.15 g, 1.00 mmol) was added, followed by N-trityl-4-iodopyrazole (43.6 g, 100 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (500 mL) and 3% aqueous citric acid (400 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×50 mL). Combined organic layer was separated and washed with deionized water (5×350 mL), followed by brine (250 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 50 % to 90% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a tan oil (39.0 g, 85 %). R_f = 0.46 (SiO_2, hexanes/ CH_2Cl_2 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.98 (s, 1H), 7.40–7.30 (m, 9H), 7.22–7.15 (m, 6H), 6.96–6.84 (m, 1 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –139.7 to –139.8 (m, 2F), –141.1 to –141.3 (m, 2F) ppm. HRMS (CI + mode): calculated for $C_{28}H_{18}F_4N_2$ 458.1406 found 458.1401.



3,5-Dimethyl-4-(2,3,5,6-tetrafluorophenyl)-1-trityl-1H-pyrazole (19)

Inside a glovebox, a 500 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (13.5 g, 135 mmol) and *t*BuOLi (10.8 g, 135 mmol). Dry DMF (150 mL) was added. Subsequently reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. Tetrafluorobenzene (21.0 g , 140 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (2.3 g, 2.0 mmol) was added, followed by N-trityl-2,5-dimethyl-4-iodopyrazole (32.0 g, 68.9 mmol). Reaction mixture was sealed, taken out of the glovebox, and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 24 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (500 mL) and 3% aqueous citric acid (400 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×50 mL). Combined organic layer was separated and washed with deionized water (5×350 mL), followed by brine (250 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 30 % to 45% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title

compound was obtained as a tan oil (21.7 g, 65 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 9H), 7.21–7.17 (m, 6H), 7.07–7.00 (m, 1 H), 2.15 (s, 3H), 1.40 (s, 3H ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –139.3 to –139.5 (m, 2F), –139.6 to –139.8 (m, 2F) ppm. HRMS (CI + mode): calculated for $C_{30}H_{22}F_4N_2$ 486.1719 found 486.1712.

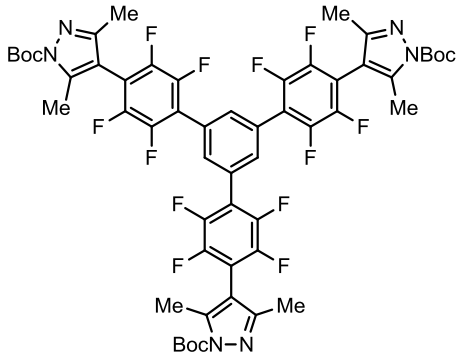


tert-Butyl 4-{4-[3,5-bis(4-{1-[(tert-butoxy)carbonyl]-1H-pyrazol-4-yl}-2,3,5,6-tetrafluorophenyl)phenyl]-2,3,5,6-tetrafluorophenyl}-1H-pyrazole-1-carboxylate (20)

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (3.35 g, 33.5 mmol) and *t*BuOLi (2.68 g, 33.5 mmol). Dry DMF (40 mL) was added. Subsequently reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. N-Trityl protected pyrazole **18** (15.6 g , 34.0 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (347 mg, 0.30 mmol) was added,

followed by 1,3,5-triiodobenzene (4.56 g, 10 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (150 mL) and 3% aqueous citric acid (100 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×25 mL). Combined organic layer was separated and washed with deionized water (5×100 mL), followed by brine (100 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 50 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded 13.46 g of trityl-protected tripyrazole intermediate. Next, a 250 mL flask equipped with magnetic stirring bar was charged with trityl-protected tripyrazole intermediate (13.3 g, 9.2 mmol) and $CHCl_3$ (140 mL). Resulting clear solution was treated with trifluoroacetic acid (12 mL) under vigorous stirring, resulting in color change from colorless to yellow. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Precipitate was filtered off and the solid was washed with fresh $CHCl_3$ (3×50 mL). Obtained light tan solid was dried in vacuum for 2 hours. A 250 mL flask equipped with magnetic stirring bar was charged with previously isolated salt and CH_2Cl_2 (100 mL) was added. Resulting suspension was treated with Et_3N (9 mL), followed by the addition of DMAP (1.22 g, 10.0 mmol). To the open flask Boc_2O (12.0 g, 55 mmol) was added via syringe over 5 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped

with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using EtOAc / CH_2Cl_2 (gradient 1 % to 8% of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (5.3 g, 52 % over three steps). R_f = 0.48 (SiO_2, EtOAc / CH_2Cl_2 5/95). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (s, 3H), 8.25 (s, 3H), 7.78 (s, 3H), 1.71 (s, 27 H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –139.8 to –140.0 (m, 6F), –143.7 to –143.9 (m, 6F) ppm. HRMS (ESI + mode): Calculated for $[C_{48}H_{36}F_{12}N_6O_6 + Na]^+$ 1043.23970, Found 1043.23810.

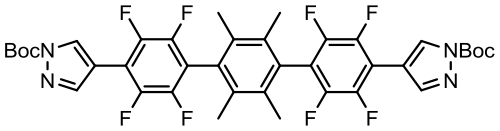


tert-Butyl 4-{4-[3,5-bis(4-{1-[(tert-butoxy)carbonyl]-3,5-dimethyl-1H-pyrazol-4-yl}-2,3,5,6-tetrafluorophenyl)phenyl]-2,3,5,6-tetrafluorophenyl}-3,5-dimethyl-1H-pyrazole-1-carboxylate (21)

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (3.35 g, 33.5 mmol) and *t*BuOLi (2.68 g, 33.5 mmol). Dry DMF (40 mL) was added. Subsequently reaction vessel was sealed, taken out of the

glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. N-Trityl protected pyrazole **19** (16.54 g, 34.0 mmol) was added in one portion. Subsequently reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (560 mg, 0.50 mmol) was added, followed by 1,3,5-triiodobenzene (4.56 g, 10 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (150 mL) and 3% aqueous citric acid (100 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×25 mL). Combined organic layer was separated and washed with deionized water (5×100 mL), followed by brine (100 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 50 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded trityl-protected tripyrazole intermediate (14.73 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with trityl-protected tripyrazole intermediate (14.7 g, 9.6 mmol) and CH_2Cl_2 (400 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring, resulting in color change from colorless to yellow. Reaction mixture was vigorously stirred at 25 °C for 20 hours. After completion, reaction was quenched with 10% aqueous K_2CO_3 solution until pH of water layer turned basic. Suspension was filtered and the solid collected was dried in

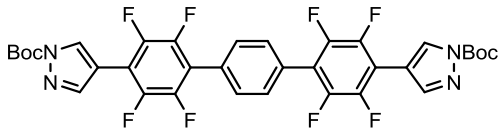
vacuum for 2 hours. Next, a 250 mL flask equipped with magnetic stirring bar was charged with previously isolated crude tripyrazole and CH_2Cl_2 (100 mL) was added. Resulting suspension was treated with Et_3N (9 mL), followed by the addition of DMAP (1.22 g, 10.0 mmol). To the open flask Boc_2O (12.0 g, 55 mmol) was added via syringe over 5 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using EtOAc / CH_2Cl_2 (gradient 5 % to 10% of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (8.3 g, 75 % over three steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (s, 3H), 2.45 (s, 9H), 2.25 (s, 9H), 1.67 (s, 27 H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –138.7 to –138.8 (m, 6F), –143.2 to –143.4 (m, 6F) ppm. HRMS (ESI + mode): Calculated for $[C_{54}H_{48}F_{12}N_6O_6 +2Na]^{2+}$ 575.16140, Found 575.16150.



tert-Butyl 4-{4-[4-(4-{1-[(tert-butoxy)carbonyl]-1H-pyrazol-4-yl}-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetramethylphenyl]-2,3,5,6-tetrafluorophenyl}-1H-pyrazole-1-carboxylate (22)

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (1.64 g, 16.5 mmol) and *t*BuOLi (1.36 g, 17 mmol). Dry DMF (40 mL) was added, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. N-Trityl protected pyrazole **18** (7.56 g, 16.5 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (347 mg, 0.30 mmol) was added, followed by 2,3,5,6-tetramethyl-1,4-diiodobenzene (2.90 g, 7.50 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 24 h. Reaction mixture was cooled to 25 °C, diluted with $CHCl_3$ (150 mL) and 3% aqueous citric acid (100 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional $CHCl_3$ (3×25 mL). Combined organic layer was separated and washed with deionized water (5×100 mL), followed by brine (100 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using $CHCl_3$/ hexanes (gradient 30 % to 100% of $CHCl_3$) as eluent and evaporation of the fractions containing the product afforded 5.90 g of trityl-protected dipyrazole intermediate. Next, a 250 mL flask equipped with magnetic stirring bar was charged with trityl-protected dipyrazole intermediate (5.9 g) and $CHCl_3$ (60 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring, resulting in color change from

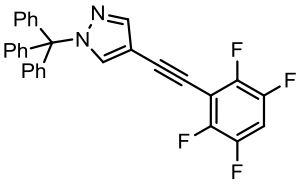
colorless to yellow. Reaction mixture was vigorously stirred at 25 °C for 20 hours. All volatiles were evaporated in vacuo and the resulting residue was treaturated with hexanes/ EtOAc mixture (1/1, 50 mL). Resulting salt that was formed was filtered off and dried in vacuum for 2 hours. Next, a 100 mL flask equipped with magnetic stirring bar was charged with previously isolated salt and CH_2Cl_2 (20 mL) was added. Resulting suspension was treated with Et_3N (3 mL), followed by the addition of DMAP (0.244 g, 2.00 mmol). To the open flask Boc_2O (2.0 g, 11 mmol) was added via syringe over 2 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using EtOAc / CH_2Cl_2 (gradient 1 % to 8% of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (2.2 g, 38 % over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 2H), 8.25 (s, 2H), 2.07 (s, 12H), 1.69 (s, 18 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –140.1 to –140.3 (m, 4F), –140.4 to –140.6 (m, 4F) ppm. HRMS (CI + mode): calculated for $C_{38}H_{34}F_8N_4O_4$ 762.2452 found 762.2456.



tert-Butyl 4-{4-[4-(4-{1-[(tert-butoxy)carbonyl]-1H-pyrazol-4-yl}-2,3,5,6-tetrafluorophenyl)phenyl]-2,3,5,6-tetrafluorophenyl}-1H-pyrazole-1-carboxylate (23)

Inside a glovebox, a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (1.35 g, 13.5 mmol) and *t*BuOLi (1.08 g, 13.5 mmol). Dry DMF (30 mL) was added. Subsequently reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. N-Trityl protected pyrazole **18** (6.33 g, 13.8 mmol) was added in one portion, reaction mixture was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (347 mg, 0.30 mmol) was added, followed by 1,4 - diiodobenzene (2.15 g, 6.50 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 2 h. Reaction mixture was cooled to 25 °C, diluted with DMF (50 mL) filtered through a glass filter. Crude product was washed with CH_2Cl_2 (40 mL) and air dried for 1 h. Next, a 250 mL flask equipped with magnetic stirring bar was charged with crude trityl-protected dipyrazole intermediate and CH_2Cl_2 (80 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring, resulting in color change from colorless to yellow. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Resulting salt that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×20 mL). Obtained light tan solid was dried in vacuum for 2 hours. Next, a 250 mL flask equipped with magnetic stirring bar was

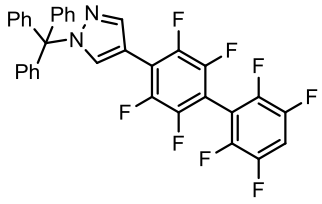
charged with previously isolated salt and CH_2Cl_2 (100 mL) was added. Resulting suspension was treated with Et_3N (9 mL), followed by the addition of DMAP (1.22 g, 10.0 mmol). To the open flask Boc_2O (12.0 g, 55 mmol) was added via syringe over 5 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using EtOAc / CH_2Cl_2 (gradient 1 % to 10 % of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (2.60 g, 56 % over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 2H), 8.24 (s, 2H), 7.66 (s, 4H), 1.71 (s, 18 H) ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ –140.3 to –140.5 (m, 4F), –143.8 to –144.0 (m, 4F) ppm. HRMS (CI + mode): calculated for $C_{34}H_{26}F_8N_4O_4$ 706.1826 found 706.1847.



4-((2,3,5,6-Tetrafluorophenyl)ethynyl)-1-trityl-1H-pyrazole (24)

Trimethyl((2,3,5,6-tetrafluorophenyl)ethynyl)silane (8.83 g, 32.8 mmol) was dissolved in THF (30 mL) and MeOH (100 mL) was added, followed by 2 drops of 50 % aqueous

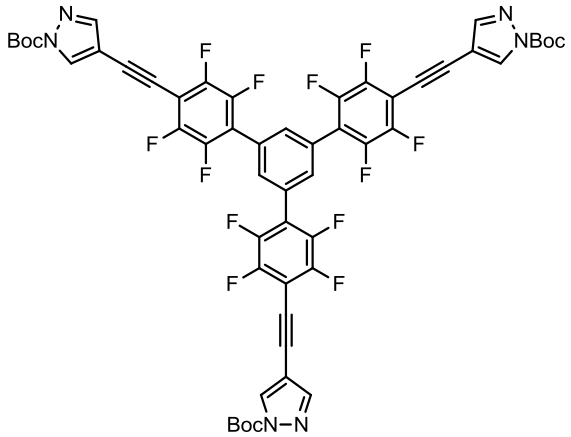
KOH. Reaction mixture was stirred for 4 h at 25 °C. Organic solvents were evaporated under vacuum and the resulting residue was used for Sonogashira coupling without further purification. Inside a glovebox a 200 mL Schlenk flask was charged with iodopyrazole (10.46 g, 24 mmol), $Pd(PPh_3)_4$ (0.40 g, 0.35 mmol), and CuCl (0.20 g, 2.0 mmol). Flask was capped with a septum degassed Et_3N (100 mL) was transferred into the flask under nitrogen via a canula. Reaction mixture was placed into the oil bath preheated to 89 °C and stirred for 24 h. After completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 30 % to 70% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a tan oil (10.2 g, 88 %). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.69 (s, 1H), 7.40–7.30 (m, 9H), 7.20–7.11 (m, 6H), 6.96–6.84 (m, 1 H) ppm. HRMS (CI + mode): calculated for $C_{30}H_{18}F_4N_2$ 482.1406 found 482.1404.



4-(2,2',3,3',5,5',6,6'-Octafluorobiphenyl-4-yl)-1-trityl-1H-pyrazole (25)

Inside a glovebox a 500 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (7.23 g, 73.0 mmol) and *t*BuOLi (5.60 g, 70 mmol). Dry DMF (150 mL) was added, after that reaction mixture was sealed, taken out of the glovebox

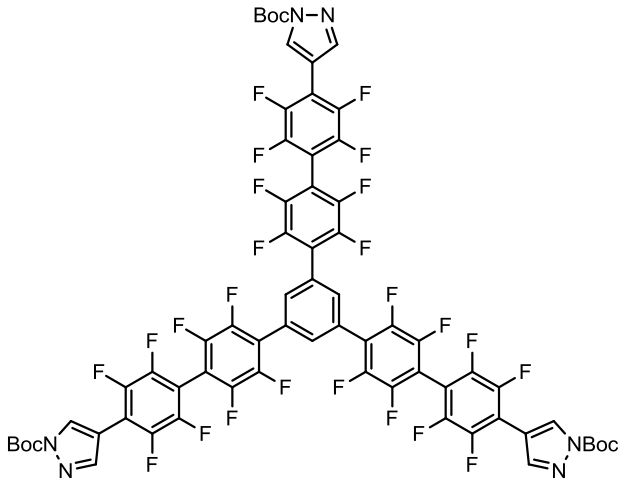
and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. 1H,1'H-Octafluorobenzene (25.0 g, 150 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (1.15 g, 1.00 mmol) was added, followed by N-trityl-4-iodopyrazole (26.2 g, 60 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 100 °C, where it was stirred vigorously for 48 h. Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (500 mL) and 3% aqueous citric acid (400 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×50 mL). Combined organic layer was separated and washed with deionized water (5×350 mL), followed by brine (250 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 10 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (24.3 g, 67 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.98 (s, 1H), 7.40–7.30 (m, 9H), 7.22–7.15 (m, 7H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –137.7 to –137.9 (m, 2F), –138.0 to –138.1 (m, 2F), –139.4 to –139.6 (m, 2F), –140.2 to –140.4 (m, 2F) ppm. HRMS (CI + mode): calculated for $C_{34}H_{18}F_8N_2$ 606.1342 found 606.1336.



tert-Butyl 4-[2-(4-{3,5-bis[4-(2-{1-[(tert-butoxy)carbonyl]-1H-pyrazol-4-yl}ethynyl)-2,3,5,6-tetrafluorophenyl]phenyl}-2,3,5,6-tetrafluorophenyl)ethynyl]-1H-pyrazole-1-carboxylate (26)

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (1.93 g, 19.5 mmol) and *t*BuOLi (1.56 g, 19.5 mmol). Dry DMF (24 mL) was added, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. Alkyne-containing N-trityl pyrazole **24** (9.65 g, 20.0 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (347 mg, 0.30 mmol) was added, followed by 1,3,5-triiodobenzene (2.74 g, 6.00 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 80 °C, where it was stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, diluted with DMF (100 mL) filtered through a glass filter. Crude product was air dried for 4 h and than dried

in high vacuo for 12 h. Next, a 250 mL flask equipped with magnetic stirring bar was charged with crude trityl-protected tripyrazole intermediate and CH_2Cl_2 (150 mL). Resulting suspension was treated with trifluoroacetic acid (10 mL), followed by TfOH (5 mL) causing salt to precipitate. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Resulting salt that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×50 mL). Obtained light tan solid was dried in vacuum for 2 hours. A 250 mL flask equipped with magnetic stirring bar was charged with previously isolated salt and CH_2Cl_2 (150 mL) was added. Resulting suspension was treated with Et_3N (12 mL), followed by the addition of DMAP (1.22 g, 10.0 mmol). To the open flask Boc_2O (12.0 g, 55 mmol) was added via syringe over 5 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using EtOAc / hexanes (gradient 0 % to 10% of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (1.4 g, 21 % over three steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 3H), 7.89 (s, 3H), 7.73 (s, 3H), 1.67 (s, 27H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –135.9 to –136.1 (m, 6F), –143.3 to –143.5 (m, 2F) ppm. HRMS (ESI + mode): Calculated for $[C_{54}H_{36}F_{12}N_6O_6 + 2Na]^{2+}$ 569.11450, Found 569.11550.

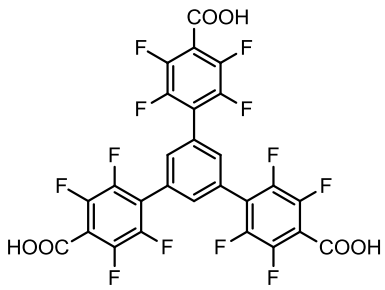


tert-Butyl 4-[4-(4-{3,5-bis[4-(4-{1-[(tert-butoxy)carbonyl]-1H-pyrazol-4-yl}-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetrafluorophenyl]phenyl}-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetrafluorophenyl]-1H-pyrazole-1-carboxylate (27)

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stir bar and charged with CuCl (2.20 g, 22.0 mmol) and *t*BuOLi (1.76 g, 22.0 mmol). Dry DMF (40 mL) was added, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. N-Trityl pyrazole **25** (13.94 g, 23.0 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox and sonicated for 5 min and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (0.560 g, 0.50 mmol) was added, followed by 1,3,5-triiodobenzene (3.19 g, 7.00 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 80 °C, where it was stirred vigorously for 24 h Reaction mixture was cooled to 25 °C, diluted with CH_2Cl_2 (150 mL) and 3% aqueous citric acid (100 mL) was added. Reaction mixture was filtered through

the plug of Celite to remove the copper iodide. Filter cake was washed with additional CH_2Cl_2 (3×25 mL). Combined organic layer was separated and washed with deionized water (5×100 mL), followed by brine (100 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. Purification of the reaction mixture by column chromatography on silica gel using CH_2Cl_2/ hexanes (gradient 50 % to 100% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded trityl-protected tripyrazole intermediate (12.2 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with trityl-protected tripyrazole intermediate (12.0 g) and $CHCl_3$ (130 mL). Resulting clear solution was treated with trifluoroacetic acid (12 mL), followed by TfOH (5 mL) causing salt to precipitate. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Resulting salt that was formed during the reaction was filtered off and the solid was washed with fresh $CHCl_3$ (3×50 mL). Obtained light tan solid was dried in vacuum for 2 hours. Next, a 250 mL flask equipped with magnetic stirring bar was charged with previously isolated salt and CH_2Cl_2 (150 mL) was added. Resulting suspension was treated with Et_3N (12 mL), followed by the addition of DMAP (1.22 g, 10.0 mmol). To the open flask Boc_2O (12.0 g, 55 mmol) was added via syringe over 5 min **CAUTION!!!** DURING THE ADDITION RAPID EVOLUTION OF CO_2 IS OBSERVED!!! After addition of Boc_2O was complete reaction flask was capped with a septum connected to a bubbler. Reaction mixture was stirred vigorously at 25 °C until the evolution of CO_2 ceased (typically 12-36 hours). Upon completion, reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using eluting first with CH_2Cl_2/ Hexanes (9/1), then pure CH_2Cl_2 and finally

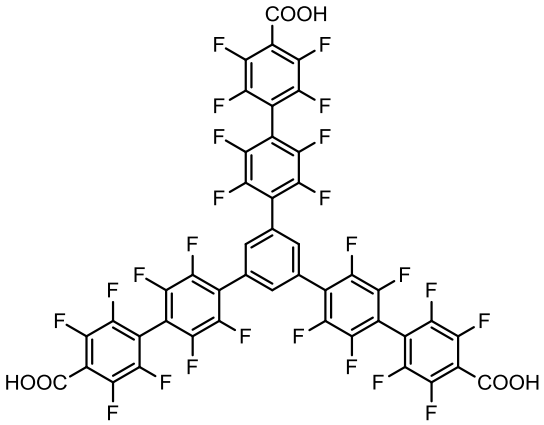
EtOAc / CH_2Cl_2 (1 % of EtOAc) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (6.5 g, 63 % over three steps).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 3H), 8.22 (s, 3H), 7.89 (s, 3H), 1.69 (s, 27H) ppm. ^{19}F NMR (470 MHz, $CDCl_3$) δ –137.2 to –137.4 (m, 6F), –138.1 to –138.3 (m, 6F), –139.3 to –139.5 (m, 6F), –142.2 to –142.4 (m, 6F) ppm. HRMS (ESI + mode): Calculated for $[C_{66}H_{36}F_{24}N_6O_6 + 2Na]^{2+}$ 755.10490, Found 755.10450.



4,4',4''-(benzene-1,3,5-tris(2,3,5,6-tetrafluorobenzoic acid) (6)

Inside a glovebox, a 250 mL screw cap pressure vessel was equipped with magnetic stirring bar and charged with CuCl (5.45 g, 55.0 mmol) and *t*-BuOLi (4.40 g, 55.0 mmol). Dry DMF (65 mL) was added, after that reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min, followed by vigorous stirring at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. *tert*-butyl 2,3,5,6-tetrafluorobenzoate (13.05 g, 52.5 mmol) was added in one portion, after that reaction vessel was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (2.31 g, 2.00 mmol) was added, followed by 1,3,5-triiodobenzene (7.30 g, 16.0 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 65 °C, where it

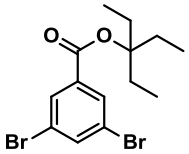
was stirred vigorously for 12 h. After completion, reaction mixture was cooled to 25 °C, diluted with diethyl ether (300 mL) and 3% aqueous citric acid (200 mL) was added. Reaction mixture was filtered through the plug of Celite to remove the copper iodide. Filter cake was washed with additional diethyl ether (2×50 mL). Combined organic layer was separated and washed with deionized water (5×150 mL), followed by brine (150 mL). Further, organic layer was dried over anhydrous $MgSO_4$, filtered and dry-absorbed on silica gel. Purification by column chromatography on silica gel using CH_2Cl_2/ hexanes (gradient 20 % to 50% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (8.40 g). Next, a 250 mL flask equipped with magnetic stirring bar was charged with triester intermediate (8.4 g) and CH_2Cl_2 (40 mL). Resulting clear solution was treated with trifluoroacetic acid (10 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). White solid was dried in vacuum for 2 hours to provide the product (6.8 g, 65 % over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.0 to 13.0 (br s, 3H), 7.95 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −140.9 to −141.1 (m, 6F), −142.4 to −142.6 (m, 6F) ppm. HRMS (CI + mode): Calculated for $[C_{27}H_6O_6F_{12}]^+$ 653.9973, Found 653.9990.



4-(4-{3,5-Bis[4-(4-carboxy-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetrafluorophenyl]phenyl}-2,3,5,6-tetrafluorophenyl)-2,3,5,6-tetrafluorobenzoic acid 28

Inside a glovebox a 100 mL screw cap pressure vessel was equipped with magnetic stirring bar and charged with CuCl (1.20 g, 12.0 mmol) and *t*-BuOLi (0.96 g, 12.0 mmol). Dry DMF (14 mL) was added, after that reaction mixture was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. *tert*-Butyl 2,2'3,3',5,5',6,6'-octafluorobiphenyl-4-carboxylate (4.90 g, 12.3 mmol) was added in one portion, after that reaction mixture was sealed, taken out of the glovebox, sonicated for 5 min, and vigorously stirred at 25 °C for 1 hour. Pressure vessel was placed back inside glovebox. $Pd(PPh_3)_4$ (0.41 g, 0.35 mmol) was added, followed by 1,3,5-triiodobenzene (1.59 g, 3.50 mmol). Reaction mixture was sealed, taken out of the glovebox and then placed inside an oil bath preheated to 70 °C, where it was stirred vigorously for 24 h. After completion, reaction mixture was cooled to 25 °C, diluted with diethyl ether (150 mL), and 3% aqueous citric acid (100 mL) was

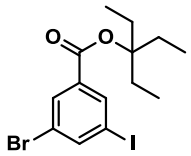
added. Reaction mixture was filtered through the plug of Celite® to remove the copper iodide. Filter cake was washed with additional diethyl ether (2×30 mL). Combined organic layer was separated and washed with deionized water (3×100 mL), followed by brine (100 mL). Organic layer was dried over anhydrous $MgSO_4$, filtered, and dry-absorbed on silica gel. Purification by column chromatography on silica gel using CH_2Cl_2/ hexanes (gradient 10 % to 50% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product afforded triester intermediate (2.1 g). Next, a 100 mL flask equipped with magnetic stirring bar was charged with triester intermediate (2.00 g) and $CHCl_3$ (25 mL). Resulting clear solution was treated with TfOH (1 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 2 hours. Triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (2×20 mL). White solid was dried in vacuum for 2 hours to provide the product (1.5 g, 39 % over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 3H) ppm. ^{19}F NMR (376 MHz, DMSO-d_6) δ −137.3 to −137.5 (m, 6F), −138.4 to −138.5 (m, 6F), −139.7 to −139.9 (m, 6F), −142.0 to −142.2 (m, 6F) ppm. HRMS (ESI - mode): Calculated for $[C_{90}H_{12}O_{12}F_{48}-2H]^{2-}$ 1096.97080, Found 1096.97430.



3-Ethylpentan-3-yl 3,5-dibromobenzoate (29)

A 250 mL round bottom flask was equipped with a magnetic stirring bar and charged with 3,5-dibromobenzoic acid (50.0 g, 178 mmol) and thionyl chloride (50.0 g, 420

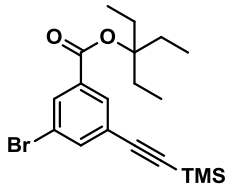
mmol) and dry toluene (60 mL), followed by the addition of few drops of dry DMF. Reaction mixture was placed in an oil bath at 70 °C and was stirred vigorously for 12 h. Reaction mixture was cooled to 25 °C, and all volatiles were removed *in vacuo*. Obtained benzoyl chloride was redissolved in dry diethyl ether (200 mL) under N_2 atmosphere. Resulting solution was cooled to -78 °C using dry ice/ acetone bath. Solution of lithium salt of 3-ethylpentan-3-ol in dry diethyl ether (200 mL) was added via canula. Reaction mixture was slowly warmed up to 25 °C, after which silica (100 g) was carefully added to the solution and all volatiles were removed *in vacuo*. After purification by column chromatography on silica gel using CH_2Cl_2 and hexanes (gradient 5 % to 15 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a colorless thick oil (60.5 g, 90 %). R_f = 0.63 (SiO_2, hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 4H) ppm. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.80 (s, 1H) 1.95 (q, J=7.3 Hz, 6H), 0.86 (t, J=7.3 Hz, 9H) ppm.



3-Ethylpentan-3-yl 3-bromo-5-iodobenzoate (30)

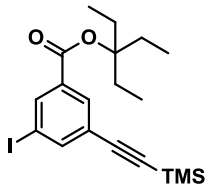
A 1000 mL round bottom flask was equipped with a magnetic stirring bar and charged with ester **1** (60.0 g, 159 mmol) and dry tetrahydrofurane (400 mL) under N_2 atmosphere. Resulting solution as cooled to -78 °C using dry ice/ acetone bath. Solution of *i*PrMgCl*LiCl 1.3M in THF (159 mL, 206 mmol) was added via canula over 15 min. After addition was finished, cooling bath was changed to ice/water bath and the reaction

mixture was stirred at 0 °C for 2 h until Br/Mg exchange was complete as can be judged by quenching reaction aliquotes with water and performing GC analyses. After full conversion to the Grignard reagent was achieved, mixture was recooled to -78 °C using dry ice/ acetone bath. Solution of I_2 (56.1 g, 220 mmol) in dry THF (100 mL) was added via canula under vigorous stirring. Upon completion, reaction was warmed to 25 °C and DI water (100 mL) was added. Most of tetrahydrofurane was evaporated using rotary evaporator. Resulting mixture was diluted with 10% aq citric acid (200 mL) and diethyl ether (400 mL). Organic layer was separated and washed with $NaHCO_3$ (100 mL), $Na_2S_2O_3$ (200 mL) and brine (200 mL). Drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent afforded crude product. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 20 % to 40 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a colorless thick oil (62.9 g, 93 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22−8.20 (m, 1H), 8.05−8.03 (m, 1H), 8.00−7.99 (m, 1H) 1.95 (q, J=7.4 Hz, 6H), 0.86 (t, J=7.4 Hz, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 143.5, 137.2, 132.0, 123.1, 94.2, 90.9, 27.0, 8.0 ppm. HRMS (CI positive mode) m/z: calculated for $[C_{14}H_{18}{}^{79}BrIO_2]^+$ 423.9535, found 423.9545.



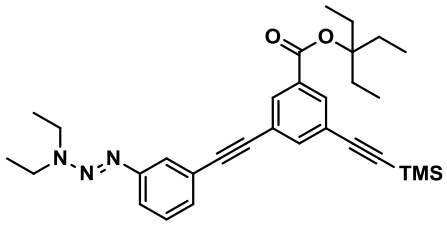
3-Ethylpentan-3-yl 3-bromo-5-((trimethylsilyl)ethynyl)benzoate (31)

A 1000 mL round bottom flask was equipped with a magnetic stirring bar and charged with ester (62.8 g, 147 mmol), $Pd(PPh_3)_4$ (1.15g, 1 mmol), CuI (0.380 g, 2 mmol). Reaction flask was evacuated and backfilled with argon 3 times. Dry degassed DMA (50 mL) was added to the reaction flask via canula. Resulting solution was cooled to 0 °C using ice/ water bath. Degassed solution of TMSA (15.2 g, 155 mmol) in degassed Et_3N (500 mL) was slowly added with vigorous stirring via canula and reaction mixture was stirred for 4 h at 0 °C temperature. Reaction mixture was warmed to 25 °C and stirred for additional 12 h until GC-MS analysis indicated complete consumption of the starting aryl iodide. Upon completion, all the volatiles were removed using rotary evaporator and the obtained residue was triturated with diethyl ether (300 mL) and 10 % aqueous citric acid (200 mL). Organic layer was separated and washed with water, brine, dried over anhydrous $MgSO_4$, filtered and evaporated. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 10 % to 40 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (58.3 g, 99%).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04−8.02 (m, 1H), 7.97−7.95 (m, 1H), 7.75−7.73 (m, 1H) 1.96 (q, J=7.4 Hz, 6H), 0.86 (t, J=7.4 Hz, 9H), 0.25 (s, 9H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 138.4, 133.9, 132.5, 131.6, 125.4, 122.2, 97.1, 92.8, 92.7, 90.6, 90.5, 27.0, 8.0, 0.0 ppm.



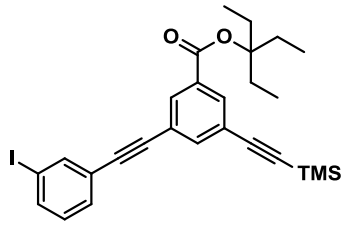
3-Ethylpentan-3-yl 3-iodo-5-((trimethylsilyl)ethynyl)benzoate

A 1000 mL round bottom flask was equipped with a magnetic stirring bar and charged with bromo ester (58.0 g, 146 mmol) and dry tetrahydrofurane (350 mL) under N_2 atmosphere. Resulting solution as cooled to -78 °C using dry ice/ acetone bath. Solution of *i*PrMgCl*LiCl 1.3M in THF (147 mL, 191 mmol) was added via canula over 15 min. After addition was finished, cooling bath was changed to ice/water bath and the reaction mixture was stirred at 0 °C for 24 h until Br/Mg exchange was complete as can be judged by quenching reaction aliquotes with water and performing GC analyses. After full conversion to the Grignard reagent was achieved, mixture was recooled to -78 °C using dry ice/ acetone bath. Solution of I_2 (51.0 g, 200 mmol) in dry THF (100 mL) was added via canula under vigorous stirring. Upon completion, reaction was warmed to 25 °C and DI water (100 mL) was added. Most of the tetrahydrofurane was evaporated using rotary evaporator. Resulting mixture was diluted with 10% aq citric acid (200 mL) and diethyl ether (400 mL). Organic layer was separated and washed with $NaHCO_3$ (100 mL), $Na_2S_2O_3$ (200 mL) and brine (200 mL). Drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent afforded crude product. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 5 % to 15 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow thick oil (48.0 g, 74 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23−8.21 (m, 1H), 7.99−7.97 (m, 1H), 7.95−7.93 (m, 1H) 1.95 (q, J=7.4 Hz, 6H), 0.86 (t, J=7.4 Hz, 9H), 0.25 (s, 9H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{19}H_{27}O_2SiI]^+$ 442.0825, found 442.0829.



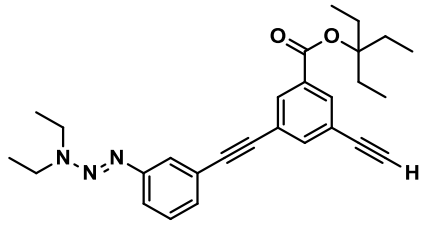
3-Ethylpentan-3-yl 3-((3-(3,3-diethyltriaz-1-enyl)phenyl)ethynyl)-5-((trimethylsilyl)ethynyl) benzoate (32)

A 500 mL round bottom flask was equipped with a magnetic stirring bar and charged with aryl iodide (10.7 g, 19.7 mmol), acetylene (14.3 g, 18.2 mmol), $Pd_2(dba)_3$ (366 mg, 0.4 mmol), PPh_3 (524 mg, 2.0 mmol), CuI (190 mg, 1.0 mmol). Reaction flask was evacuated and backfilled with argon 3 times, after which dry degassed Et_3N (350 mL) was added via canula. Reaction mixture was stirred at 95 °C for 22 h. After completion, reaction mixture was cooled to 25 °C and the amount of Et_3N was reduced to ca 50 mL. Diethyl ether (350 mL) was added and the reaction mixture was filtered through a plug of celite. Filter cake was additionally washed with ether (2 x 50 mL). Combined filtrate was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 10 % to 60 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (17.5 g, 80%). %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05−8.03 (m, 1H), 7.99−7.97 (m, 1H), 7.77−7.75 (m, 1H), 7.60−7.58 (m, 1H), 7.42−7.38 (m, 1H), 7.33−7.26 (m, 2H), 3.78 (q, J=6.9 Hz, 4H), 1.98 (q, J=7.4 Hz, 6H), 1.33−1.24 (br s, 6H), 0.88 (t, J=7.4 Hz, 9H), 0.26 (s, 9H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{31}H_{41}N_3O_2Si]^+$ 515.2968, found 515.2958.



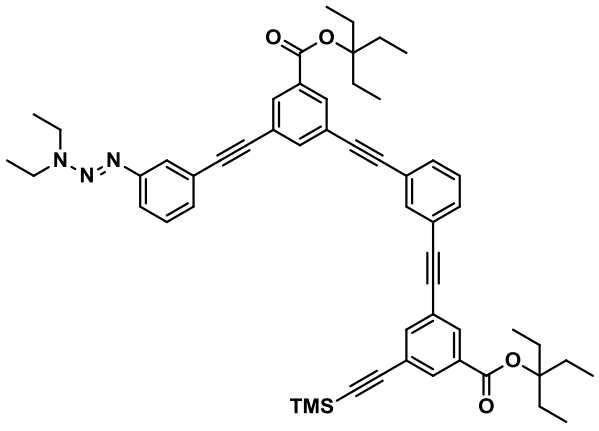
3-Ethylpentan-3-yl 3-((3-iodophenyl)ethynyl)-5-((trimethylsilyl)ethynyl)benzoate (33)

Pressure bomb equipped with magnetic stirring bar was charged with triazene starting **32** material (23.7 g, 46 mmol) and MeI (150 mL) added. Reaction mixture was thoroughly degassed by bubbling nitrogen gas, then sealed and placed in a preheated oil bath (115 °C). Reaction mixture was stirred at 115 °C for 24 hours. After completion, reaction mixture was diluted with CH_2Cl_2 (300 mL) and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 20 % to 40 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a colorless oil (22.8 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−8.01 (m, 2H), 7.90−7.88 (m, 1H), 7.77−7.75 (m, 1H), 7.70−7.66 (m, 2H), 7.50−7.46 (m, 1H), 7.11−7.06 (m, 1H), 1.98 (q, J=7.3 Hz, 6H), 0.88 (t, J=7.3 Hz, 9H), 0.27 (s, 9H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{27}H_{31}O_2SiI]^+$ 542.1138, found 542.1129.



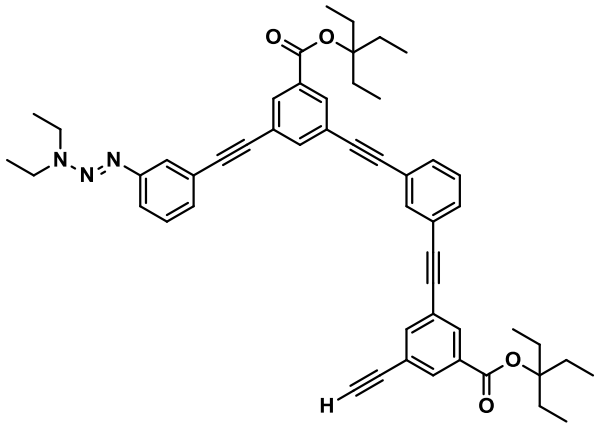
3-Ethylpentan-3-yl 3-((3-(3,3-diethyltriaz-1-enyl)phenyl)ethynyl)-5-ethynylbenzoate (34)

TMS-protected acetylene **32** (12.4 g, 24 mmol) was dissolved in CH_2Cl_2 (250 mL), followed by addition of MeOH (120 mL) and K_2CO_3 (2.0 g, 14.5 mmol). Reaction mixture was stirred at 25 °C for 2 hours. After completion, silica gel was added and reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 20 % to 70 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (9.21 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10−8.08 (m, 1H), 8.04−8.02 (m, 1H), 7.80−7.78 (m, 1H), 7.62−7.60 (m, 1H), 7.44−7.40 (m, 1H), 7.34−7.28 (m, 2H), 3.78 (q, J=6.9 Hz, 4H), 3.13 (s, 1H), 1.98 (q, J=7.3 Hz, 6H), 1.33−1.23 (br s, 6H), 0.89 (t, J=7.3 Hz, 9H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{28}H_{33}N_3O_2]^+$ 443.2573, found 443.2574.



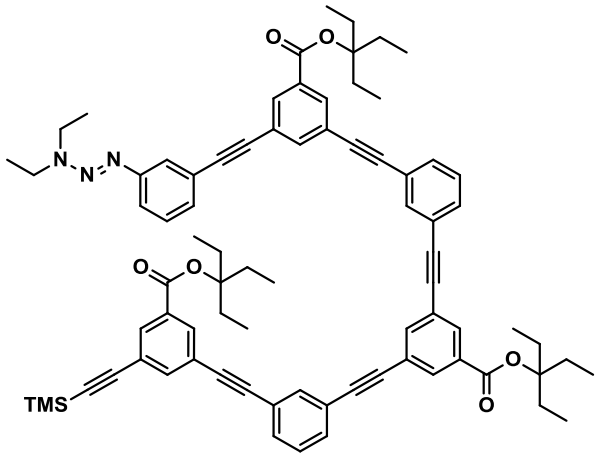
3-Ethylpentan-3-yl 3-((3-(3,3-diethyltriaz-1-enyl)phenyl)ethynyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((trimethylsilyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)benzoate (35)

A 500 mL round bottom flask was equipped with a magnetic stirring bar and charged with aryl iodide **33** (12.1 g, 22.0 mmol), acetylene **34** (9.00 g, 20.0 mmol), $Pd_2(dba)_3$ (366 mg, 0.4 mmol), PPh_3 (524 mg, 2.0 mmol), CuI (190 mg, 1.0 mmol). Reaction flask was evacuated and backfilled with argon 3 times, after which dry degassed Et_3N (350 mL) was added via canula. Reaction mixture was stirred at 95 °C for 22 h. After completion, reaction mixture was cooled to 25 °C and the amount of Et_3N was reduced to ca 50 mL. Diethyl ether (350 mL) was added and the reaction mixture was filtered through a plug of celite. Filter cake was additionally washed with ether (2 x 50 mL). Combined filtrate was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 20 % to 40 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (16.0 g, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11−8.09 (m, 1H), 8.08−8.05 (m, 2H), 8.03−8.01 (m, 1H), 7.86−7.84 (m, 1H), 7.79−7.77 (m, 1H), 7.73−7.71 (m, 1H), 7.63−7.61 (m, 1H), 7.55−7.49 (m, 3H), 7.44−7.27 (m, 3H), 3.78 (q, J=6.8 Hz, 4H), 2.04−1.95 (m, 12H), 1.33−1.23 (br s, 6H), 0.93−0.86 (m, 18H), 0.27 (s, 9H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{55}H_{63}N_3O_4Si]^+$ 857.4588, found 857.4563.



3-Ethylpentan-3-yl 3-((3-(3,3-diethyltriaz-1-enyl)phenyl)ethynyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-ethynylphenyl)ethynyl)phenyl)ethynyl)benzoate (36)

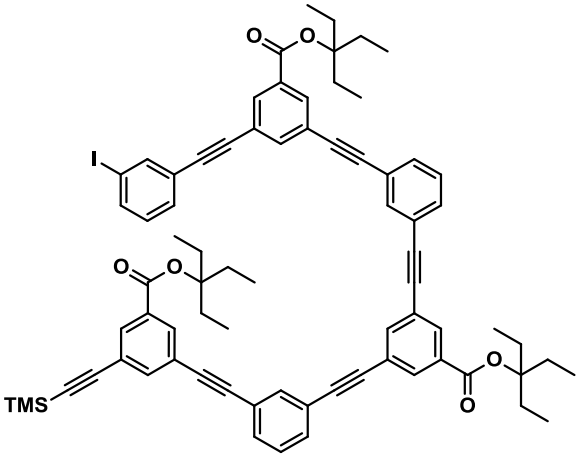
TMS-protected acetylene **35** (16.0 g, 18.6 mmol) was dissolved in CH_2Cl_2 (300 mL), followed by addition of MeOH (120 mL) and K_2CO_3 (2.0 g, 14.5 mmol). Reaction mixture was stirred at 25 °C for 2 hours. After completion, silica gel was added and reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 20 % to 60% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (14.3 g, 97%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.04 (m, 4H), 7.86−7.84 (m, 1H), 7.81−7.79 (m, 1H), 7.75−7.73 (m, 1H), 7.63−7.61 (m, 1H), 7.55−7.51 (m, 2H), 7.44−7.35 (m, 2H), 7.34−7.29 (m, 2H), 3.78 (q, J=6.9 Hz, 4H), 3.15 (s, 1H), 2.04−1.96 (m, 12H), 1.33−1.23 (br s, 6H), 0.93−0.86 (m, 18H) ppm. HRMS (CI positive mode) m/z: calculated for $[C_{52}H_{55}N_3O_4]^+$ 785.4193, found 785.4176.



3-Ethylpentan-3-yl 3-((3-(3,3-diethyltriaz-1-enyl)phenyl)ethynyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((trimethylsilyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl) benzoate (37)

A 500 mL round bottom flask was equipped with a magnetic stirring bar and charged with aryl iodide **33** (10.7 g, 19.7 mmol), acetylene **36** (14.3 g, 18.2 mmol), $Pd_2(dba)_3$ (366 mg, 0.4 mmol), PPh_3 (524 mg, 2.0 mmol), CuI (190 mg, 1.0 mmol). Reaction flask was evacuated and backfilled with argon 3 times, after which dry degassed Et_3N (350 mL) was added via cannula. Reaction mixture was stirred at 95 °C for 22 h. After completion, reaction mixture was cooled to 25 °C and the amount of Et_3N was reduced to ca 50 mL Diethyl ether (350 mL) was added and the reaction mixture was filtered through a plug of celite®. Filter cake was additionally washed with ether (2 x 50 mL). Combined filtrate was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 / hexanes (gradient 10 % to 60% of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was

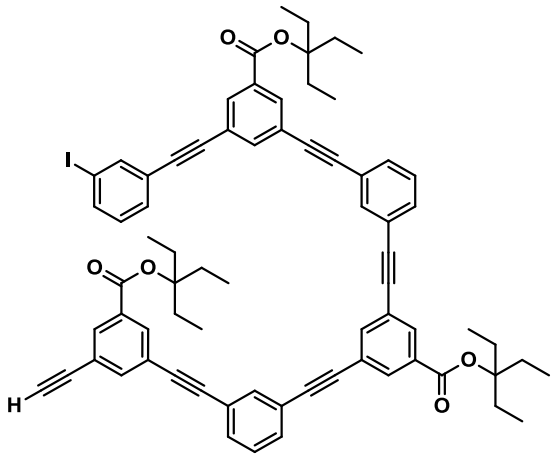
obtained as a yellow oil (17.5 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.05 (m, 5H), 8.02−8.01 (m, 1H), 7.87−7.84 (m, 2H), 7.79−7.72 (m, 3H), 7.63−7.61 (m, 1H), 7.56−7.50 (m, 4H), 7.44−7.35 (m, 3H), 7.34−7.30 (m, 2H), 3.78 (q, J=6.9 Hz, 4H), 2.04−1.94 (m, 18H), 1.33−1.21 (br s, 6H), 0.93−0.85 (m, 27H), 0.26 (s, 9H) ppm. HRMS (ESI positive mode) m/z: calculated for $[C_{158}H_{170}N_6O_{12}Si_2+2Na]^{2+}$ 1222.61000, found 1222.60800.



3-Ethylpentan-3-yl 3-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((3-iodophenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)-5-((trimethylsilyl)ethynyl)benzoate (38)

Pressure bomb equipped with magnetic stirring bar was charged with triazene starting material **37** (17.5 g, 14.6 mmol) and MeI (60 mL) added. Reaction mixture was thoroughly degassed by bubbling nitrogen gas, then sealed and placed in a preheated oil bath (115 °C). Reaction mixture was stirred at that temperature for 48 hours. After completion, reaction mixture was diluted with CH_2Cl_2 (300 mL) and dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 /

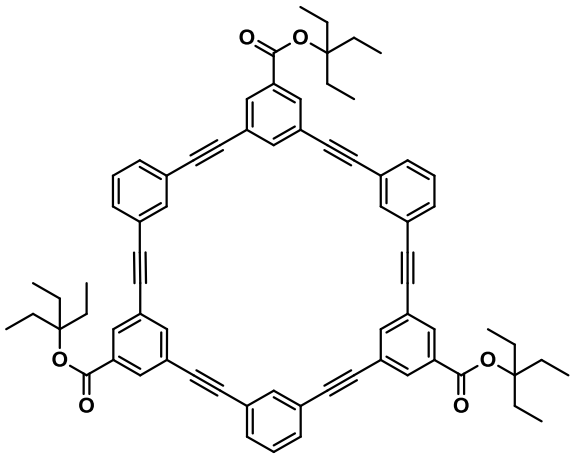
hexanes (gradient 20 % to 55 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a yellow oil (13.7 g, 79%).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.04 (m, 5H), 8.02−8.00 (m, 1H), 7.92−7.90 (m, 1H), 7.86−7.82 (m, 2H), 7.79−7.77 (m, 1H), 7.75−7.67 (m, 3H), 7.56−7.49 (m, 6H), 7.41−7.35 (m, 2H), 7.13−7.08 (m, 1H), 2.05−1.94 (m, 18H), 0.95−0.84 (m, 27H), 0.26 (s, 9H) ppm. HRMS (ESI positive mode) m/z: calculated for $[C_{150}H_{150}I_2O_{12}Si_2+2Na]^{2+}$ 1249.42700, found 1249.42440.



3-Ethylpentan-3-yl 3-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((3-((3-((3-ethylpentan-3-yloxy)carbonyl)-5-((3-iodophenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)phenyl)ethynyl)-5-ethynylbenzoate (39)

TMS-protected acetylene **38** (13.5 g, 11.0 mmol) was dissolved in CH_2Cl_2 (300 mL), followed by addition of MeOH (100 mL) and K_2CO_3 (2.0 g, 14.5 mmol). Reaction mixture was allowed to stir at 25 °C for 2 hours. After completion, silica gel was added

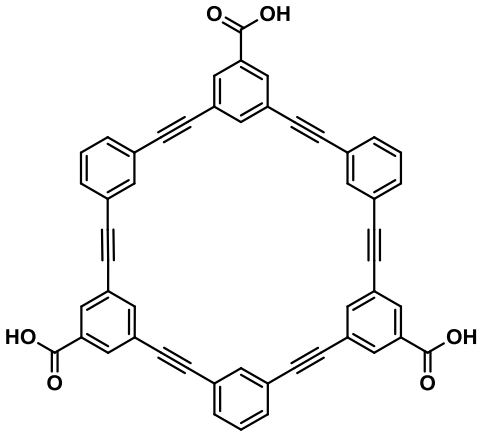
and reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2 as eluent and evaporation of the fractions containing the product, title compound was obtained as a colorless oil (12.7 g, 98%).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11−8.05 (m, 6H), 7.92−7.90 (m, 1H), 7.86−7.82 (m, 2H), 7.80−7.79 (m, 1H), 7.76−7.73 (m, 2H), 7.56−7.49 (m, 6H), 7.41−7.36 (m, 2H), 7.13−7.08 (m, 1H), 3.14 (s, 1H), 2.04−1.95 (m, 18H), 0.93−0.85 (m, 27H) ppm. HRMS (ESI positive mode) m/z: calculated for $[C_{144}H_{134}I_2O_{12}+2Na]^{2+}$ 1177.38750, found 1177.38350.



6,20,34-Tris(3-ethylpentan-3-yl) heptacyclo[37.3.1.1^{4},^{8}.1^{11},^{15}.1^{18},^{22}.1^{25},^{29}.1^{32},^{36}]octatetraconta-1(43),4,6,8(48),11,13,15(47),18,20,22(46),25,27,29(45),32(44),33,35,39,41-octadecaen-2,9,16,23,30,37-hexayne-6,20,34-tricarboxylate (40)

Inside a glovebox, a 100 mL Schlenk flask equipped with a magnetic stirring bar was charged with $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol), PPh_3 (0.13 g, 0.5 mmol), CuCl (0.02 g, 0.2 mmol), followed by dry degassed Et_3N (20 mL) and dry degassed toluene (30 mL).

Flask was capped with septum and taken out of the glovebox and placed in a preheated oil bath (80 °C). A solution of iodo acetylene **39** (1.19g, 1.0 mmol) in dry, degassed Et_3N (40 mL) was added to a Schlenk flask via needle attached to a gas tight-syringe at a rate 0.5 mL/hour against a positive pressure of nitrogen. After completion, silica gel was added and reaction mixture was dry-absorbed on silica gel. After purification by column chromatography on silica gel using CH_2Cl_2/ hexanes (gradient 20 % to 55 % of CH_2Cl_2) as eluent and evaporation of the fractions containing the product, title compound was obtained as a white solid (0.217 g, 21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.04 (m, 6H), 7.84−7.81 (m, 3H), 7.73−7.71 (m, 3H), 7.54−7.49 (m, 6H), 7.38−7.32 (m, 3H), 2.02 (q, J=7.3 Hz, 18H), 0.92 (t, J=7.3 Hz, 27H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 138.4, 135.2, 132.6, 132.0, 131.7, 128.7, 123.9, 123.3, 90.1, 90.0, 88.8, 27.1, 8.1 ppm. HRMS (ESI positive mode) m/z: calculated for $[C_{144}H_{132}O_{12}+2Na]^{2+}$ 1049.47520, found 1049.47630.



Heptacyclo[37.3.1.1^{4,8}.1^{11,15}.1^{18,22}.1^{25,29}.1^{32,36}]octatetraconta-1(43),4,6,8(48),11,13,15(47),18,20,22(46),25,27,29(45),32(44),33,35,39,41-octadecaen-2,9,16,23,30,37-hexayne-6,20,34-tricarboxylic acid (41)

A 100 mL flask equipped with magnetic stirring bar was charged with triester (0.96 g, 0.93 mmol) and CH_2Cl_2 (50 mL). Resulting clear solution was treated with trifluoroacetic acid (5 mL) under vigorous stirring. Reaction mixture was vigorously stirred at 25 °C for 20 hours. Resulting triacid that was formed during the reaction was filtered off and the solid was washed with fresh CH_2Cl_2 (3×30 mL). Obtained white solid was dried in vacuum for 2 hours to provide the product (0.65 g, 96% yield). ^{1}H NMR (500 MHz, DMSO-d_6 140 °C) δ 8.20−7.40 (m, 21H) ppm. HRMS (CI negative mode) m/z: calculated for $[C_{51}H_{24}O_6]^-$ 732.1573, found 732.1581.

Functionalization of arene and heteroarene C-H bonds

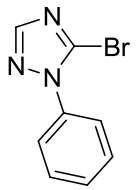
General considerations. Reactions were performed in 1-dram or 2-dram vials with PTFE/Liner caps. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Preparative plate chromatography was performed on Analtech silica gel plates 2000 microns with UV-254 indicator. Purification by HPLC was performed om Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column GCMS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a GE QE-300

spectrometer using TMS or residual solvent peak as a standard. Melting points are uncorrected. Hexafluorobenzene (1% in C_6D_6, δ = -164.9) was employed as an external standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on Fluka silica gel/TLC-cards with fluorescent indicator 254 nm.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: pentafluorobenzene, 1,3,5-trifluorobenzene, diphenyl disulfide, and 1,2,4,5-tetrafluorobenzene were bought from Oakwood. Carbon tetrabromide, iodine monochloride, caffeine, 4-chlorobenzaldehyde, and benzophenone were obtained from Acros. Potassium phosphate, *m*-xylene, pyridine-*N*-oxide, 1-butylimidazole, cyclohexanecarboxaldehyde, 1-phenylpyrazole, and pentachlorobenzene were purchased from Aldrich. Benzothiazole, benzoxazole, 2-chlorothiophene, carbon tetrachloride, 1,2-diiodotetrafluoroethane, and 2,3,5,6-tetrafluoroanisole were from Alfa Aesar. 2-Phenylpyridine, 3,5-difluorobenzonitrile, and 3-fluoronitrobenzene were obtained from Matrix Scientific. Potassium *t*-butoxide was bought from Fluka. Lithium *t*-butoxide was bought from Strem. Sulfur was bought from Spectrum.

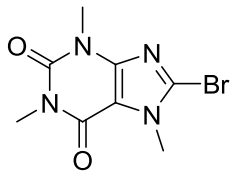
General procedure for halogenation. Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0 mmol) and halogenating reagent (1.5-4.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF or a mixture (1/1) of DMF and xylene

(1.0 mL) was added, followed by base (K_3PO_4 or t-BuOLi, 2.0-4.0 equiv). The sealed vial was taken out of the glovebox and placed in a preheated oil bath (60-130 ^oC) for the indicated time. The reaction mixture was allowed to cool to room temperature and subjected to flash chromatography on silica gel. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure halogenation product.



5-Bromo-1-phenyl-1H-1,2,4-triazole (Entry 1, Table 4.2.)

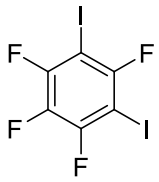
1-Phenyl-1H-1,2,4-triazole (145 mg, 1.0 mmol), dibromotetrafluoroethane (520 mg, 2.0 mmol), t-BuOLi (240 mg, 3.0 mmol), and DMF (2.0 mL), 100 ^oC, 3 hours. After preparative plate chromatography (30% AcOEt in hexanes) 173 mg (77%) of white solid was obtained. R_f=0.21 (SiO_2, hexanes/AcOEt 9/1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.61 (m, 5H), 8.05 (s, 1H).



8-Bromo-3,7-dihydro-1,3,7-trimethyl-1H-Purine-2,6-dione (Entry 2, Table 4.2.)

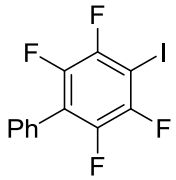
Caffeine (194 mg, 1.0 mmol), dibromotetrafluoroethane (780 mg, 3.0 mmol), t-BuOLi (320 mg, 4.0 mmol), and DMF (2.0 mL), 100 ^oC, 13 hours. After column

chromatography (gradient 10%-15% AcOEt in CH_2Cl_2) 176 mg (65%) of white solid was obtained. R_f=0.25 (SiO_2, hexanes/AcOEt 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.56 (s, 3H), 3.97 (s, 3H).



1,2,3,5-Tetrafluoro-4,6-diiodobenzene (Entry 3, Table 4.2.)

1,2,3,5-Tetrafluorobenzene (300 mg, 2.0 mmol), iodine (1524 mg, 6.0 mmol), t-BuOLi (640 mg, 8.0 mmol), and DMF (1.5 mL), 60 ºC, 3 hours. After column chromatography (pentane) 523 mg (95%) of a colorless oil was obtained. R_f = 0.68 (SiO_2, hexanes). ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.8-65.6 (m), 134.7.0-137.3 (m), 150.6-152.9 (m), 154.0-157.8 (m).

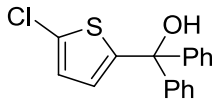


2,3,5,6-tetrafluoro-4-iodobiphenyl (Entry 4, Table 4.2.)

A 2 dram vial was charged with DMF (1.0 mL), 2,3,5,6-tetrafluorobiphenyl (226 mg, 1.0 mmol), I_2 (508 mg, 2.0 mmol), and t-BuOLi (240 mg, 3.0 mmol), 50 ºC, 3 hours. After column chromatography (10% CH_2Cl_2 in hexanes) 342 mg (97%) of a colorless solid was obtained. R_f = 0.49 (SiO_2, hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ7.40-7.55 (m, 5H).

General procedure for reaction with carbon electrophiles.

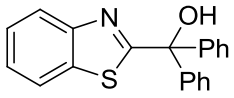
Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0-2.0 mmol) and aldehyde or ketone (3.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF (1.0-2.0 mL) was added, followed by base (K_3PO_4 or t-BuOLi, 1.5-3.0 equiv). The sealed vial was taken out of the glovebox and was placed in a preheated oil bath (60-105 ^oC) or stirred at RT for the indicated time. The reaction mixture was allowed to cool to room temperature, quenched with 15% citric acid, extracted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, filtered and subjected to flash chromatography on silica gel or preparative plate chromatography. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product.



(5-Chlorothiophen-2-yl)diphenylmethanol (Entry 1, Table 4.3.)

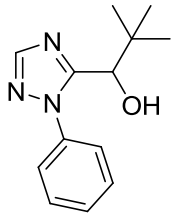
2-Chlorothiophene (118 mg, 1.0 mmol), benzophenone (474 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), 105 ^oC, 20 hours. After preparative plate chromatography (10% CH_2Cl_2 in hexanes) 123 mg (41%) of light pink solid was obtained. R_f=0.32 (SiO_2, CH_2Cl_2/hexanes 1/1). Analytical sample was recrystallized from hexanes, mp 112-114 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.92 (s, 1H), 6.48 (d, *J*=3.9 Hz,

1H), 6.75 (d, *J*=3.9 Hz, 1H), 7.25-7.45 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.4, 125.8, 126.2, 127.4, 128.1, 128.3, 130.5, 146.0, 150.8. FT-IR (neat, cm^{-1}) υ 3445, 1489, 1446, 1334, 1215, 1165, 1123, 1000, 902, 794, 753, 698. Anal calcd for $C_{17}H_{13}ClOS$ (300.80 g/mol): C, 67.88; H, 4.36; Found. C, 67.86; H, 4.26.



α,α-Diphenyl-2-benzothiazolemethanol (Entry 2, Table 4.3.)

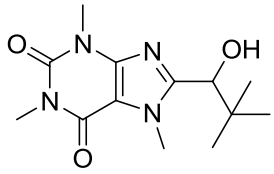
Benzothiazole (135 mg, 1.0 mmol), benzophenone (546 mg, 3.0 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMF (1.0 mL), 80 ºC, 13 hours. After column chromatography (gradient 10%-20% CH_2Cl_2 in hexanes) 247 mg (77%) of white solid was obtained. R_f=0.23 (SiO_2, CH_2Cl_2/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (s, 1H), 7.30-7.41 (m, 7H), 7.43-7.52 (m, 5H), 7.80-7.85 (m, 1H), 7.99-8.04 (m, 1H).



2,2-dimethyl-1-(1-phenyl-1H-1,2,4-triazol-5-yl)propan-1-ol (Entry 3, Table 4.3.)

1-phenyl-1H-1,2,4-triazole (145 mg, 1.0 mmol), pivaldehyde (258 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), 100 ºC, 12 hours. After preparative plate chromatography (10% AcOEt in CH_2Cl_2) 153 mg (66%) of white solid was obtained. R_f=0.38 (SiO_2, hexane/AcOEt 1/1). Analytical sample was recrystallized from hexanes/AcOEt, mp 108-110 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 9H), 2.95 (d,

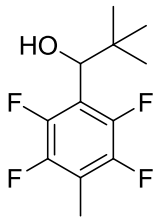
J=9.7 Hz, 1H), 4.55 (d, *J*=9.7 Hz, 1H), 7.24-7.58 (m, 5H), 8.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 37.1, 73.2, 126.2, 129.7, 129.8, 137.6, 151.0, 156.5. FT-IR (neat, cm^{-1}) υ 3294, 2955, 2901, 1597, 1504, 1473, 1386, 1297, 1273, 1185, 1104, 1063, 1037, 1018, 883, 810, 767, 694, 701. Anal calcd for $C_{13}H_{17}N_3O$ (231.29 g/mol): C, 67.51; H, 7.41; N, 18.17; Found. C, 67.64; H, 7.50; N, 18.19.



8-(1-Hydroxy-2,2-dimethylpropyl)-1,3,7-trimethyl-1H-purine-2,6(3H,7H)-dione (Entry 4, Table 4.3.)

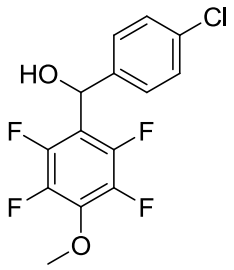
Caffeine (194 mg, 1.0 mmol), pivaldehyde (258 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), 105 ºC, 12 hours. After column chromatography (gradient 50%-60% AcOEt in CH_2Cl_2) 255 mg (91%) of white solid was obtained. R_f=0.26 (SiO_2, AcOEt/CH_2Cl_2 1/1). Analytical sample was recrystallized from hexanes/AcOEt, mp 169-171 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 9H), 3.04 (d, *J*=8.5 Hz, 1H), 3.39 (s, 3H), 3.55 (s, 3H), 3.99 (s, 3H), 4.47 (d, *J*=8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 28.1, 29.9, 33.0, 37.5, 73.7, 107.7, 147.6, 151.8, 154.0, 155.6. FT-IR (neat, cm^{-1}) υ 3446, 2952, 1694, 1641, 1541, 1435, 1366, 1220, 1080, 1037, 976, 758, 744. Anal calcd for $C_{13}H_{20}N_4O_3$ (280.32 g/mol): C, 55.70; H, 7.19; N, 19.99; Found. C, 55.80; H, 7.33; N, 19.97.

Control experiment: Performing the reaction under the conditions described above without added base no product formation was observed.



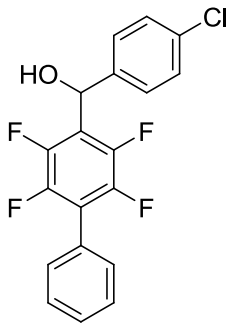
(2,2-Dimethyl-1-(2,3,5,6-tetrafluoro-4-methylphenyl)propan-1-ol (Entry 5, Table 4.3.)

2,3,5,6-Tetrafluorotoluene (164 mg, 1.0 mmol), pivaldehyde (258 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), RT, 12 hours. After preparative plate chromatography (50% CH_2Cl_2 in hexanes) 171 mg (68%) of white solid was obtained. Analytical sample was recrystallized from hexanes, mp 59-61 °C. R_f=0.53 (SiO_2, CH_2Cl_2/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, *J*=1.4 Hz, 9H), 2.27 (t, *J*=2.1 Hz, 3H), 2.47 (dt, *J*=10.0 Hz, 3.0 Hz, 1H), 4.78 (d, *J*=10.0 Hz, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.5- -146.9 (m, 2F), -145.2-144.7 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.5-8.0 (m), 25.9, 37.5, 76.1 (d, J_{C-F}=2.2 Hz), 115.0-115.6 (m), 117.3-117.8 (m), 142.0-144.3 (m), 145.6-147.4 (m). FT-IR (neat, cm^{-1}) υ 3474, 2964, 1479, 1393, 1369, 1279, 1259, 1095, 1050, 1022, 917, 868, 749, 727, 666. Anal calcd for $C_{12}H_{14}F_4O$ (250.23 g/mol): C, 57.60; H, 5.64; Found. C, 57.65; H, 5.67.



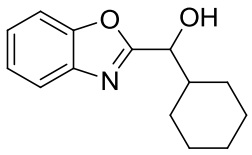
(4-Chlorophenyl)(2,3,5,6-tetrafluoro-4-methoxyphenyl)methanol (Entry 6, Table 4.3.)

2,3,5,6-Tetrafluoroanisole (180 mg, 1.0 mmol), 4-chlorobenzaldehyde (422 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), RT, 2 hours. After column chromatography (gradient 30%-60% CH_2Cl_2 in hexanes) 300 mg (93%) of colorless oil was obtained. R_f=0.45 (SiO_2, hexanes/CH_2Cl_2 1/4). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.64 (dt, *J*=7.5 Hz, 1.1 Hz, 1H), 4.08 (t, *J*=1.4 Hz, 3H), 6.18 (d, *J*=7.5 Hz, 1H), 7.33 (s, 4H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -160.6- -160.4 (m, 2F), -148.2- -148.0 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.6 (t, J_{C-F}=3.6 Hz), 67.4 (quintet, J_{C-F}=2.4 Hz), 114.5-115.4 (m), 127.4, 129.3, 134.4, 138.3-140.0 (m), 140.1, 142.8-143.9 (m), 146.6-147.3 (m). FT-IR (neat, cm^{-1}) υ 3387, 1651, 1491, 1438, 1416, 1196, 1132, 1092, 11014, 969, 916, 858, 808, 782. Anal calcd for $C_{14}H_9ClF_4O_2$ (320.67 g/mol): C, 52.44; H, 2.83; Found. C, 52.40; H, 2.88.



(4-Chlorophenyl)(2,3,5,6-tetrafluorobiphenyl-4-yl)methanol (Entry 7, Table 4.3.)

2,3,5,6-Tetrafluorobiphenyl (226 mg, 1.0 mmol), 4-chlorobenzaldehyde (422 mg, 3.0 mmol), t-BuOLi (120 mg, 1.5 mmol), and DMF (1.0 mL), 60 ºC, 6 hours. After column chromatography (gradient 30%-60% CH_2Cl_2 in hexanes) 311 mg (85%) of white solid was obtained. R_f=0.33 (SiO_2, hexanes/CH_2Cl_2 1/1). Analytical sample was recrystallized from hexanes/AcOEt, mp 142-144 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.69 (d, *J*=6.8 Hz, 1H), 6.30 (d, *J*=6.0 Hz, 1H), 7.34-7.56 (m, 9H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.3- -147.0 (m, 2F), -146.6- -146.4 (m, 2F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 67.5 (quintet, J_{C-F}=2.4 Hz), 120.5 (t, J_{C-F}=15.0 Hz), 120.8 (t, J_{C-F}=16.8 Hz), 137.1, 127.3, 128.9, 129.1, 129.5, 134.2, 139.6, 142.2-143.4 (m), 145.5-146.8 (m). FT-IR (neat, cm^{-1}) υ 3309, 1479, 1438, 1304, 1179, 1096, 1053, 1009, 961, 917, 819, 790, 760, 737, 695. Anal calcd for $C_{19}H_{11}ClF_4O$ (366.84 g/mol): C, 62.23; H, 3.02; Found. C, 62.38; H, 2.94.



Benzo[d]oxazol-2-yl(cyclohexyl)methanol (Entry 8, Table 4.3.)

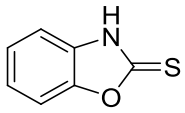
Benzoxazole (119 mg, 1.0 mmol), cyclohexanecarboxaldehyde (337 mg, 3.0 mmol), K_3PO_4 (636 mg, 3.0 mmol), and DMF (1.0 mL), 80 ^oC, 11 hours. After column chromatography (gradient 5%-15% AcOEt in CH_2Cl_2) 232 mg (50%) of yellow solid was obtained. R_f=0.53 (SiO_2, AcOEt/CH_2Cl_2 1/9). Analytical sample was recrystallized from hexanes/AcOEt, mp 121-123 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.40 (m, 5H), 1.53-1.87 (m, 5H), 1.91-2.06 (m, 1H), 3.70 (br s, 1H), 4.74 (d, *J*=5.9 Hz, 1H), 7.29-7.37 (m, 2H), 7.48-7.55 (m, 1H), 7.66-7.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.0, 26.2, 26.4, 27.8, 29.1, 43.3, 72.8, 111.0, 120.1, 124.7, 125.2, 140.6, 150.9, 167.7. FT-IR (neat, cm^{-1}) υ 3280, 2920, 2853, 1615, 1570, 1456, 1242, 1232, 1117, 1003, 976, 852, 834, 744. Anal calcd for $C_{14}H_{17}NO_2$ (231.29 g/mol): C, 72.70; H, 7.41; N, 6.06; Found. C, 72.85; H, 7.42; N, 6.03.

Control experiment: Performing the reaction under the conditions described above without added base, no product formation was observed.

General procedure for reaction with sulfur electrophiles.

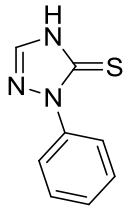
Outside the glovebox a 1-dram or 2-dram vial equipped with a magnetic stir bar was charged with substrate (1.0 -2.0 mmol) and sulfur electrofile (2.0-8.0 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture anhydrous DMF or DMPU (1.0-2.0 mL) was added, followed by base (K_3PO_4, t-BuOK or t-BuOLi, 1.5-3.0 equiv). The sealed vial was taken out of the glovebox and placed in a preheated oil bath (80-130 ^oC) for the indicated time. The reaction mixture was allowed to cool to room temperature, quenched with 15% citric acid, extracted with AcOEt, washed with brine, dried over anhydrous $MgSO_4$, filtered and subjected to flash chromatography on

silica gel or preparative plate chromatography. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product.



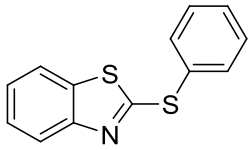
2(3H)-Benzoxazolethione (Entry 1, Table 4.4.)

Benzoxazole (119 mg, 1.0 mmol), sulfur (256 mg, 8.0 mmol), t-BuOLi (240 mg, 3.0 mmol), and DMF (1.0 mL), 80 ºC, 12 hours. After column chromatography (gradient 10 % to 20% AcOEt in hexanes) 136 mg (90%) of yellow solid was obtained. R_f=0.57 (SiO_2, AcOEt/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 4H), 10.88 (s, 1H).



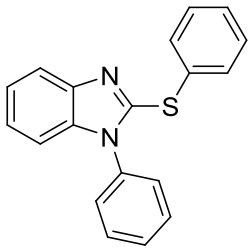
1,2-Dihydro-2-phenyl-3H-1,2,4-Triazole-3-thione (Entry 1, Table 4.4.)

1-Phenyl-1H-1,2,4-triazole (290 mg, 2.0 mmol), sulfur (512 mg, 16.0 mmol), t-BuOLi (320 mg, 4.0 mmol), and DMF (2.0 mL), 80 ºC, 12 hours. After column chromatography (40% AcOEt in hexanes) 264 mg (74%) of white crystalline solid was obtained. R_f=0.38 (SiO_2, AcOEt/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.47 (m, 1H), 7.48-7.56 (m, 2H), 7.92-7.98 (m, 3H), 13.11 (s, 1H).



2-Phenylsulfanyl-benzothiazole (Entry 3, Table 4.4.)

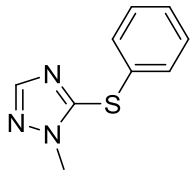
Benzothiazole (135 mg, 1.0 mmol), diphenyl disulfide (328 mg, 1.5 mmol), K_3PO_4 (636 mg, 3.0 mmol), and DMF (1.0 mL), 100 ^oC, 13 hours. After column chromatography (gradient 10%-20% CH_2Cl_2 in hexanes) 209 mg (85%) of yellow oil was obtained. R_f=0.39 (SiO_2, CH_2Cl_2/hexanes 1/1). ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dt, *J*=7.5 Hz, 1.1 Hz, 1H), 7.41 (dt, *J*=7.8 Hz, 1.6 Hz, 1H), 7.44-7.56 (m, 3H), 7.63-7.68 (m, 1H), 7.72-7.77 (m, 2H), 7.86-7.91 (m, 1H).



1-Phenyl-2-(phenylthio)-1H-benzimidazole (Entry 4, Table 4.4.)

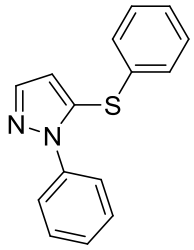
1-Phenylbenzimidazole (388 mg, 2.0 mmol), diphenyl disulfide (873 mg, 4.0 mmol), t-BuOLi (320 mg, 4.0 mmol), and DMF (2.0 mL), 130 ^oC, 12 hours. After column chromatography (30% CH_2Cl_2 in hexanes, CH_2Cl_2, then 30% AcOEt in CH_2Cl_2) 512 mg (84%) of light tan solid was obtained. R_f=0.52 (SiO_2, hexane/AcOEt 3/1). Analytical sample was recrystallized from hexanes/AcOEt, mp 92-94 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.09-7.15 (m, 1H), 7.17-7.54 (m, 12H), 7.56-7.80 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.2, 119.7, 122.9, 123.5, 127.6, 128.4, 129.1, 129.4, 129.7, 131.1, 132.4,

135.7, 137.5, 143.4, 149.5. FT-IR (neat, cm^{-1}) υ 1497, 1424, 1343, 1260, 1220, 761, 744, 696. Anal calcd for $C_{19}H_{14}N_2S$ (302.39 g/mol): C, 75.47; H, 4.67; N, 9.26; Found. C, 75.41; H, 4.60; N, 9.21.



1-Methyl-5-(phenylthio)-1H-1,2,4-triazole (Entry 5, Table 4.4.)

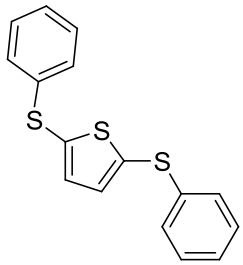
1-Methyl-1H-1,2,4-triazole (166 mg, 2.0 mmol), diphenyl disulfide (655 mg, 3.0 mmol), t-BuOLi (240 mg, 3.0 mmol), and DMF (2.0 mL), 80 ºC, 12 hours. After column chromatography (1:1 hexanes/CH_2Cl_2, then 1:1 AcOEt/hexanes) 212 mg (55%) of light yellow oil was obtained. R_f=0.53 (SiO_2, AcOEt/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.30-7.42 (m, 5H), 7.92 (s, 1H).



1-Phenyl-5-(phenylthio)-1H-pyrazole (Entry 6, Table 4.4.)

1-Phenyl-1H-pyrazole (144 mg, 1.0 mmol), diphenyl disulfide (437 mg, 2.0 mmol), t-BuOK (224 mg, 2.0 mmol), and DMF (1.0 mL), 130 ºC, 36 hours. After column chromatography (gradient 10%-20% AcOEt in hexanes) 204 mg (81%) of yellow oil was obtained. R_f=0.59 (SiO_2, hexanes/AcOEt 3/1).^{1}H NMR (300 MHz, $CDCl_3$) δ 6.61 (d,

J=1.7 Hz, 1H), 7.06-7.26 (m, 5H), 7.31-7.50 (m, 5H), 7.74 (d, *J*=1.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.9, 125.5, 127.0, 128.3, 128.7, 128.9, 129.4, 132.5, 135.4, 139.5, 140.7. FT-IR (neat, cm^{-1}) υ 3066, 1598, 1583, 1500, 1478, 1440, 1380, 1100, 1072, 1024, 987, 919, 791, 761, 739, 690, 664. Anal calcd for $C_{15}H_{12}N_2S$ (252.33 g/mol): C, 71.40; H, 4.79; N, 11.10; Found. C, 71.28; H, 4.74; N, 10.88.



2,5-bis(Phenylthio)thiophene (Entry 7, Table 4.4.)

2-Chlorothiophene (118 mg, 1.0 mmol), diphenyl disulfide (437 mg, 2.0 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMPU (1.0 mL), 130 ºC, 12 hours. After column chromatography (gradient 1%-10% CH_2Cl_2 in hexanes) and subsequent preparative plate chromatography (5% CH_2Cl_2 in hexanes) 248 mg (82%) of yellow oil was obtained. R_f=0.47 (SiO_2, hexanes/CH_2Cl_2 9/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.22 (m, 12H).

V. References

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