Synthesis and Reactivity of Aryl(trifluoromethyl)diazomethane Compounds

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Fluorine has a prominent role in organic chemistry and the pharmaceutical industry due to the unique properties it imparts. Naturally, trifluoromethyl groups (CF_3) share similar qualities and many methods have been developed for its inclusion into molecules. Historically, indirect trifluoromethylation was used until the advent of more robust direct methods. Of the three categories, direct electrophilic trifluoromethylation has grown slowly until relatively recently since the introduction of the Togni reagent, a hypervalent iodine (HVI) compound. HVI compounds have found interest as safer and cheaper alternatives to traditional metal-based reagents and benziodoxoles in particular are used for ligand transfer reactions.

Diazo groups are versatile functionalities that have a wide range of applications and syntheses. Apart from diazo group transfer reagents, hydrazones and their substituted derivatives serve as common precursors to diazo compounds. The Bamford-Stevens reaction of tosylhydrazones is one efficient pathway to the formation of diazoalkanes. The trifluoromethylation of diazo compounds and hydrazones as their precursors has found limited success and exploration into this area of research could serve useful towards the production of trifluoromethylated building blocks.

A simultaneous diazotization and trifluoromethylation of arylaldehyde tosylhydrazones has been found and the conditions of this procedure are explored in various venues. Discussions behind its mechanism are also speculated upon due to the formation of various side products. The reactivity and application of these trifluoromethylated diazo compounds will be investigated towards the recent rise in visible light-mediated reactions, especially for diazo compounds. The blue light photocatalysis of aryl(trifluoromethyl)diazomethane compounds is explored in the context of cyclopropanation and has seen initial success. Further investigation will prove useful in understanding this new area of photochemistry of diazo compounds.

Acknowledgements

I would first like to sincerely thank my supervisor, Prof. Graham Murphy, for his continual support and guidance over the past three years. I am forever thankful for this opportunity and have learned much more than I would have ever expected.

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To the members of the Murphy lab, past and present, I thank you for the support and company I have been given throughout the years. It would not have been possible without you all. I owe my deepest gratitude to Avery To for all he has done for me. For the companionship, indulging in my endless questions, and assuaging my constant doubts, I do not have enough words to express my appreciation for everything and I truly thank him. I would also like to take this opportunity to thank Dr. Leanne Racicot, without whom this experience would have been less manageable, and I will fondly remember the steady support, guidance, and kindness she has given me. I would like to thank Fabio Cuzzucoli and Dr. Zhensheng Zhao for the encouragement and fun times shared in the lab. I would also like to thank Tristan Chidley, Islam Jameel, and Liam Britt for their assistance, ideas, and inspiring passion for chemistry.

Lastly, I thank my friends and family for their continual support in keeping me hopeful towards this goal and the future. It has been quite the journey.

Dedication

For my loving family,
Wency, John, and Brian

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List of Abbreviations

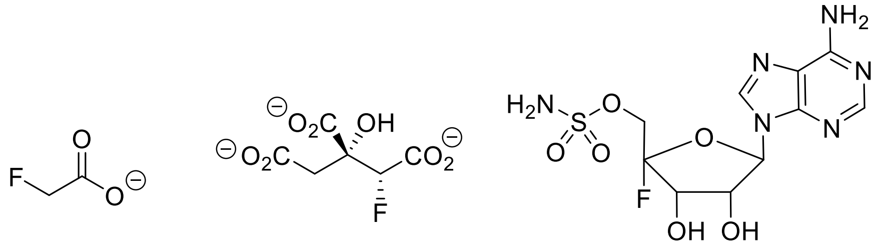
Ac	Acetyl
Ar	Aromatic ring
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
EDA	Ethyl diazoacetate
EDG	Electron-donating group
EWG	Electron-withdrawing group
FDA	Food and Drug Administration
HOMO	Highest occupied molecular orbital
HVI	Hypervalent Iodine
IBX	2-Iodoxybenzoic acid
In situ	In the reaction mixture
ISC	Intersystem crossing
IUPAC	International Union of Pure and Applied Chemistry
L	Ligand
LED	Light-emitting diode
MO	Molecular orbital
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
PFA	Perfluoroalkoxy alkane
PIDA	Phenyliodine diacetate
PIFA	Phenyliodine bis(trifluoroacetate)
phen	Phenanthroline
PPE	Personal Protective Equipment
R	Alkyl substituent
rt	Room temperature
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*tert*-Butyldimethylsilyl
TCICA	Trichloroisocyanuric acid
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Triflyl (trifluoromethylsulfonyl)
TFT	Trifluorotoluene
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMG	1,1,3,3-Tetramethylguanidine
TMS	Trimethylsilyl
Ts	Tosyl (4-methylbenzenesulfonyl)

Non scholae sed vitae discimus

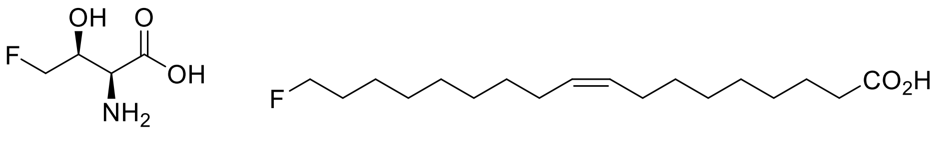
Chapter 1: Fluorine and Trifluoromethyl Groups

1.1 Fluorine Background

Fluorine is the 13th most abundant terrestrial element by weight percent (24th universal) and is found in nature bound to elements that it has a high affinity for, such as silicon, aluminum, calcium, and magnesium. This generates minerals such as cryolite, fluorite, and fluorapatite and its most common form is calcium fluoride, a main constituent of minerals like topaz and cryolite.[1] Despite being the most abundant halogen in Earth's crust, fluorine is mainly found as mineral fluorides with low aqueous solubility, demonstrated by a low concentration in ocean water (1.3 ppm).[2] As the smallest non-radioactive halogen, it has a very special place in the periodic table and since 1971 has had its own dedicated journal, the Journal of Fluorine Chemistry. This low availability of fluorides in solution has led to a lack of fluoroorganic motifs compared to the 5000 and increasing number of halogenated naturally produced compounds.[3] Thus, only five fluorinated compounds have been confirmed to be naturally occurring, along with the fluorinase enzyme responsible for their fluorination, while other compounds were determined to be minor metabolites or possible industrial bioaccumulation residue (Figure 1.1).[4]



Fluorocitrate **(2R, 3R)-Fluorocitrate** **Nucleocidin**

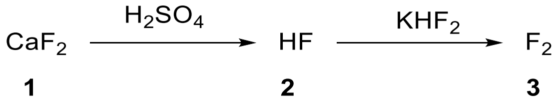


4-Fluorothreonine **18-Fluorooleic acid**

Figure 1.1 - The five fluorinated natural product compounds that have been identified.

As the most xenobiotic among the light elements, the lack of fluorination in natural compounds indicates an unrealized potential. As such, fluorine has found ever-growing importance in drug development where new pharmaceutical candidates are routinely scanned with fluorine substitution for favourable characteristics (e.g. increased biological activity, metabolic stability, etc.).[5] The percentage of fluorine-containing pharmaceuticals has been steadily increasing since the 1950s and it was estimated in 2010 that 20% of prescribed pharmaceutical drugs and 30% of agrochemicals contained one or more fluorine atoms.[6] Its importance can be further appreciated when considering that fluorine is present in up to 30% of top-selling drugs[6] and 15% of the 20 most profitable medicines ever introduced to the market,[7] including atorvastatin with over 104 million prescriptions by 2017.[8] As the pharmaceutical industry continues to develop, the number of fluorinated drugs can also be expected to rise. This was especially evident when examining the small molecule drugs approved by the Food and Drug Administration (FDA), where fluorine was present in ~29% of compounds in each of the past two years and more than a third of new chemical entities (NCEs) in 2019.[9] The breadth and large total of fluorinated compounds generated for commercial use so far still points to areas yet to be fully explored and new methods of fluorination are steadily being developed.

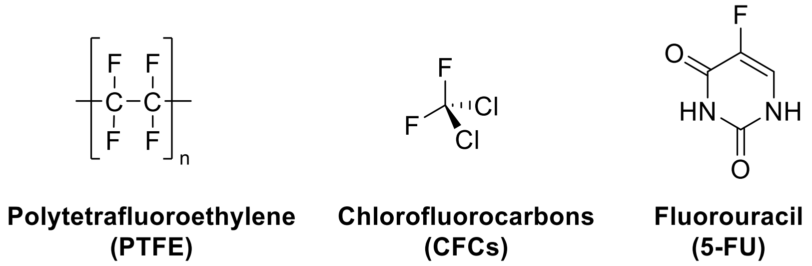
Terrestrial fluorine originates from the mineral fluorite or fluorspar (calcium fluoride, CaF_2), where it was first described by Georgius Agricola in 1529 as an additive to lower the melting point of metals for smelting during metalwork. Then in 1764, Andreas Sigismund Marggraf prepared the first instance of hydrofluoric acid (HF) when heating fluorite and sulfuric acid, which corroded its glass container. From then on, many chemists attempted to isolate elemental F_2 from hydrofluoric acid but were unsuccessful. It wasn't until 1886 that French chemist Henri Moissan, building upon on earlier chemists' attempts, managed to isolate fluorine gas by electrolysis of a mixture of potassium bifluoride (KHF_2) dissolved in anhydrous hydrofluoric acid, for which he won the 1906 Nobel Prize for Chemistry. Today, the world production of fluorine comes from the mining of mineral fluorite mainly in China and Mexico, with 35% of it still used in the smelting and refining of metals. Another large fraction is used for the generation of hydrofluoric acid from apatite rock (400,000 tonnes per year), with a subsequent portion of the acid used to produce fluorine gas (15,000 tonnes per year), through a modern version of Moissan's method (Scheme 1.1).[10]



Scheme 1.1 - The production of fluorine reagents from minerals.

Technology using HF and F_2 was developed during the 1930s by the Dupont company, leading to the discovery of Teflon (poly(tetrafluoroethene) or PTFE) for use as cable insulation and inert lining for vessels, and chlorofluorocarbons (CFCs) for use in aerosols, refrigerators, and air conditioning units (Figure 1.2). In the 1940s, fluorine was present extensively during the second World War, where chlorine trifluoride (ClF_3) was researched as an incendiary agent for flame-throwers. Around the end of the war, HF and F_2 gas were used generate uranium hexafluoride (UF_6) from uranium dioxide (UO_2), where the lighter uranium-235 (^{235}U) isotope could be separated from the uranium-238 (^{238}U) isotope by high speed gas centrifuge thereafter. This technique was used in the creation of the atomic bomb and is still currently used in nuclear power plants for energy production.[10]

Around 1956 is when the earliest biological applications using fluorine started with 5-fluorouracil finding use as an anticancer drug. Its similarity to the natural nucleobase uracil allows cellular uptake, but the change of the C-H to C-F bond inhibits the essential methylation necessary for DNA synthesis, thus halting cell growth.[11] By the 1970s and 1980s, organofluorine compounds had been produced regularly with compounds such as chlorine trifluoride (ClF_3) being used in the chemical industry to make inert, heat-stable, non-flammable, non-toxic fluorocarbon solvents. During that time, CFCs were also found to be accumulating in the atmosphere and damaging the ozone layer that protects the earth from the sun’s ultraviolet radiation, prompting a worldwide ban in 1987 in the Montreal Protocol. While the hydrofluorocarbons (HFCs) used as replacements do not damage the ozone layer, they are persistent greenhouse gases that are now contributing to global climate change, instigating their own respective ban in 1997 as part of the Kyoto Protocol.

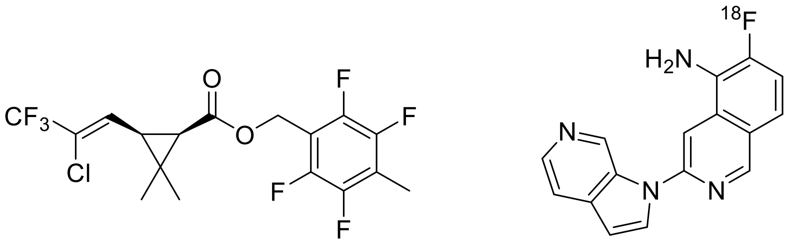


Polytetrafluoroethylene (PTFE) **Chlorofluorocarbons (CFCs)** **Fluorouracil (5-FU)**

Figure 1.2 - Early historical uses of fluorine.

The stability of fluorinated molecules lends to their remainder in the environment for far longer than intended, such that they are found in ecological niches far removed from their origin and nearly all humans contain traces (4 ppb) of these types of compounds now. On the contrary, fluoride is regarded as essential for humans in small doses, with the average person intaking ~0.3 to 3 mg of fluoride daily from dietary sources such as fluoridated tap water, seafood, and vegetables. It is even prescribed as preventative measures for osteoporosis in humans in some countries because fluoride converts the calcium phosphate of the bones to fluorapatite, a harder and more corrosion resistant material. However, an excess amount of fluoride generally causes fluorosis, which is known to hinder plant growth and reduce crop yields. For humans, this can result in excessive bone hardening which can lead to skeletal fluorosis and in high enough doses fluoride is poisonous, as is evident in its use as an insecticide for cockroaches and ants.

Nowadays, fluorine has become omnipresent in our society and everyday lives. It appears in a variety of pharmaceuticals like anti-fungal drugs, anti-depressants, and anaesthetics.[12] Other fluorinated compounds such as sulfur hexafluoride (SF_6) are used in the electrical power industry as an inert gas to insulate the surroundings of high-power electricity transformers. The incorporation of fluorine in highly ordered polymer chains has enabled advances in new functional materials like liquid crystal displays (LCD), while F_2 gas and nitrogen fluoride (NF_3) gas can each be used to etch LCD screens and semiconductors, respectively. The investigation into fluorine and fluorinated compounds has proved worthwhile and it is expected that further research will continue to innovate solutions for the production of new biomaterials and organofluorine compounds (Figure 1.3).



Tefluthrin
(pesticide)

[^{18}F]MK-6240
(PET tracer)

Figure 1.3 - Examples of modern fluorinated molecules.

1.2 Properties of Fluorine

Electronegativity & Metabolic Stability

Fluorine's incorporation into molecules alters electronic density and induces effects on rate of redox transformations, acidobasic behaviour, and Lewis basicity/acidity of neighbouring groups. It allows tuning of molecular properties such as polarity, steric size, lipophilicity, and hydrophilicity.[12] It imparts unique properties mainly due to the fact that it is the most electronegative element. The often-used electronegativity value of 3.98, assigned by Pauling in 1939, was derived from considerations of bond strengths and character in heteronuclear diatomic systems, corresponding similarly to Mulliken's earlier calculations based on an element's ionization energy and electron affinity.[13] Due to this, fluorine ($1s^2$, $2s^2$, $2p^5$) has one of the smallest atomic radii and removal of an electron to generate F^+ is extremely difficult (-401.2 kcal mol^{-1}).

In addition to its high electronegativity, fluorine has a strong reduction potential and tends to form strong bonds with all the other elements, other than the noble gases helium, neon, and argon. In organofluorine compounds, a C-F bond's highly polarized nature instills significantly different electrostatic character from a standard C-H bond. With the electron density situated mainly on fluorine, the strength of the bond can be credited to the electrostatic attraction between $F^{\delta-}$ and $C^{\delta+}$, rather than sharing of electrons in a classical covalent bond. This is the strongest single C-X bond in organic chemistry (BDE = 105.4 kcal mol^{-1}) and thus very resistant to chemical transformations.[14]

The C-F bond's resilience is particularly useful for increasing metabolic stability in pharmaceutical compounds. Metabolism in the human body principally occurs in the liver by the group of enzymes called cytochrome P450 monooxygenases, which oxidize drug molecules to lower their lipophilicity and increase clearance through the body. A preventative solution is fluorine substitution at metabolically labile sites to block enzyme oxidation to extend a molecule's bioavailability. A notable example of this is in the lead optimization of Ezetimib where fluorine was used to replace both a hydrogen and methoxy group to block metabolic oxidation (Figure 1.4).[15] In a similar fashion, fluorine substitution in glucose prevents glycolysis, allowing [^{18}F]FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose) to be trapped in cell tissues for positron emission tomography (PET) used in medical imaging.[16]

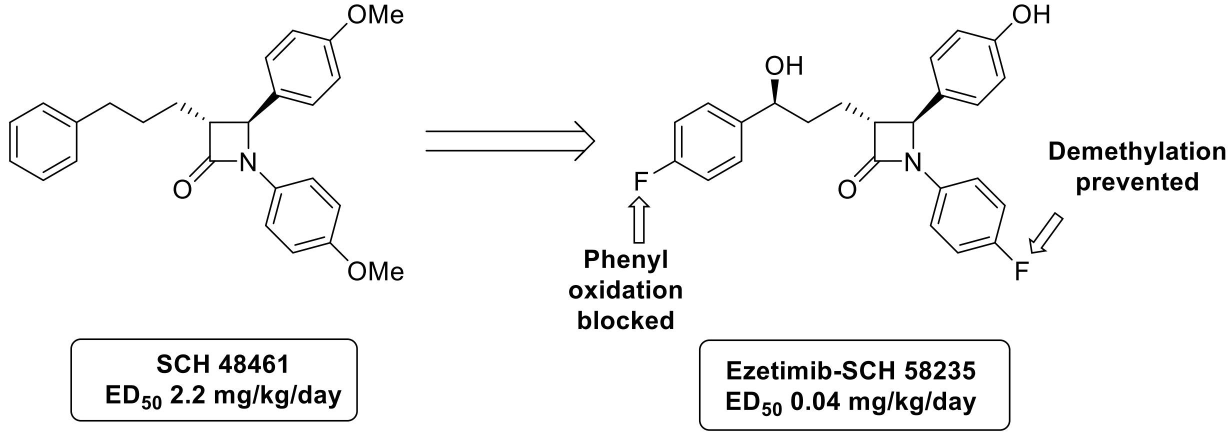


Figure 1.4 - Incorporation of fluorine to block metabolism during the lead optimization of Ezetinib.

Hyperconjugation & the Gauche Effect

It seems C-F bonds only interact weakly through dipoles and other electrostatic interactions, but its polarized nature indicates a low energy $\sigma^*_{C\text{-}F}$ antibonding orbital, similar to C-O bonds.

Therefore, similar to stabilization by electron rich π-bonds, oxygen/nitrogen lone pairs and nucleophiles should stabilize conformations, intermediates, or transition states. This can be observed in 2-fluorooxane, where the fluoro substituent prefers an axial conformation, contrary to the equatorial conformations typically preferred to avoid 1,3-diaxial interactions (Figure 1.5, Left). The theorized lone pair donation into the $\sigma^*_{C\text{-}F}$ antibonding orbital is consistent with the shortening of the C-O bond, the lengthening of the C-F bond, and the widening of the O-C-F angle in theory calculations.[17] Another classic example is 1,2-difluoroethane which is known to prefer a *gauche* conformation, different from the other 1,2-dihalogenated ethanes which prefer *anti* conformers (Figure 1.5, Right). The observation is rationalized by considering that each fluorine atom is antiperiplanar to a C-H bond, and the stabilizing hyperconjugation from two $\sigma_{C\text{-}H}$ to $\sigma^*_{C\text{-}F}$ interactions outweighs the repulsion between the two fluorine atoms.

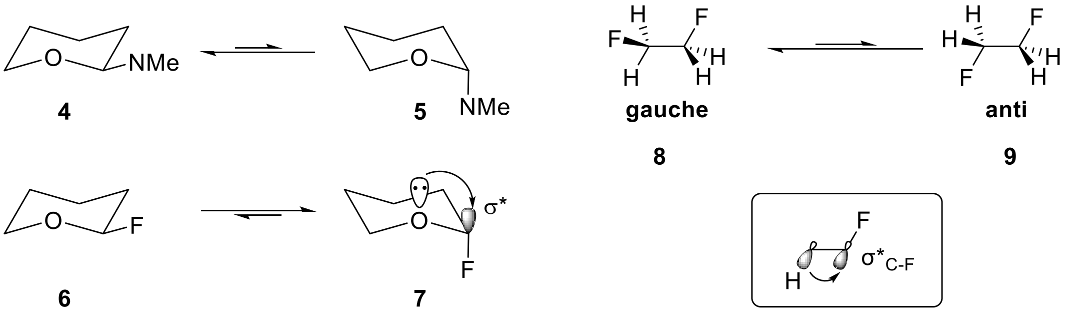


Figure 1.5 - Left: The preferred axial conformation of fluorine due to the anomeric effect. Right: 1,2-Difluoroethane's preference of a *gauche* over an *anti* conformation.

1.3 Physico-chemical and Conformational Effects of Fluorination

Size & Bioisosterism

Fluorine is most commonly used as a substitute for hydrogen or hydroxyl groups as fluorine's van der Waals radius (Bondi, r_v)[18] of 1.47 Å is between oxygen (1.57 Å) and hydrogen (1.20 Å). Thus, it yields similar steric demands as is evident in amino acid analogues where monofluorination is the most common substitution. However, despite being the most conservative steric substitution for hydrogen, their electronic properties have little parallel and properties of adjacent functional groups, such as pK_a, are affected.[14] Groups such as CHF_2 can act as bioisosteres for OH/SH, while still being acidic and interacting in hydrogen bonding (Figure 1.6). However, changing a C-OH for a C-F bond would result in the loss of an acidic hydrogen and hydrogen bonding donor, and this is a useful way to compare the inherent polarity of the C-O bond versus its hydrogen bonding. Other replacements like C=O for C-F or CF_2 would cause a change in the hybridization of the carbon atom, while hybridization is maintained in vinyl fluorides and have been found to be steric mimetics of amide (peptide) bonds. The lack of hydrogen bonding capability lends to polar hydrophobic properties instead,[19] which can be exploited in carbohydrate binding to proteins.[20]

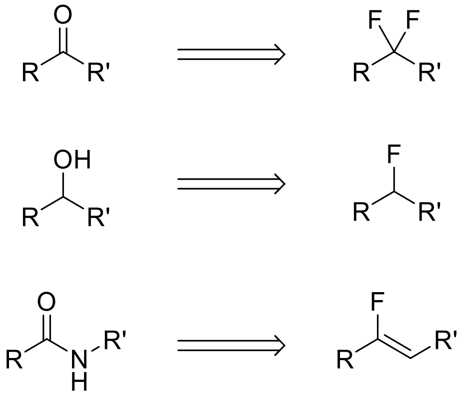
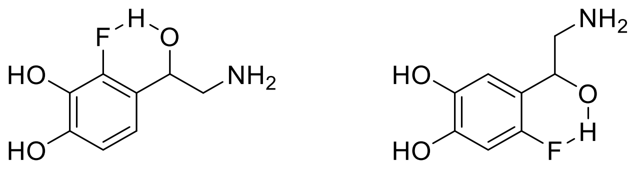


Figure 1.6 - Classical examples of fluorine being used as a bioisostere.

Dipole Interactions

Fluorine's high electronegativity causes a strong attraction of its lone pairs to the nucleus which results in high ionization potential but low polarizability. Thus, a C-F bond's intermolecular interactions are limited to weak interactions due to through-space electrostatic attraction that is more akin to neutral dipole interactions**.** In addition, properties are most prominently affected when a substitution causes a large change in electronegativity. For example, although going from hydrogen and fluorine has the smallest change in sterics, the substitution of a C-H to C-F bond reverses the dipole of the bond.[14] The large dipole from the bond often dictates intramolecular interactions and conformations of organofluorine compounds can be explained when considering these electrostatic interactions. For example, the large dipole causes C-F bonds to lie anti-planar to carbonyl groups, such as in amides, esters, ketones, and aldehydes.[21]

The polarization of the C-F bond also results in fluorine occasionally acting as a weak hydrogen bond acceptor. Although there is often insufficient evidence from crystallographic analyses, computational and spectroscopic experiments agree when considering the strength and existence of such an interaction. While intermolecular hydrogen-bond formation can be observed in simple systems like fluoromethane and water, the majority of interactions are intramolecular rather than intermolecular.[22] It was found that CH_2F groups are the strongest hydrogen bond acceptors compared to the more fluorinated CHF_2 and CF_3 groups.[23] However, even the energy of hydrogen-bond complex formation of a CH_2F moiety is less favorable than typical hydrogen bonds, which suggests that in environments with other competing hydrogen-bond acceptors, it would not be a dominant interaction.[24] In some systems, however, observed behaviors can only be explained by this weak hydrogen bond. One early noted intramolecular interaction is fluorinated norepinephrine, which has differing modes of action between its two isomers, both stabilized by hydrogen bonding (Figure 1.7).[25] There is an observed change in chemical shift in ^{19}F NMR spectroscopy when fluorine is acting as a hydrogen bond acceptor, and this can be used practically for fragment-based drug discovery (FBDD).[5,26]



10

2F-NE: β-agonist

11

6F-NE: α-agonist

Figure 1.7 - Fluorine involved in hydrogen bonding in the two structural isomers of fluorinated norepinephrine.

Fluorine can engage in charge-dipole interactions, a type of weak electrostatic interaction similar to hydrogen bonds. This short $CF\text{-}HN^+$ interaction (~2.4-2.5 Å) can be observed by the large axial preference in 3-fluoropiperidinium ring systems,[27] as well as *gauche* preference in protonated fluoroethylamine.[28] These interactions and conformations also occur in systems without hydrogen, as long as there is a formal charge such as in the fluoroethylpyridinium cation (Figure 1.8).[29] Similarly, there is a large amount of evidence that the C-F bond can coordinate metal cations preferentially. This charge-dipole interaction has been explored systematically with cryptand compounds.[30]

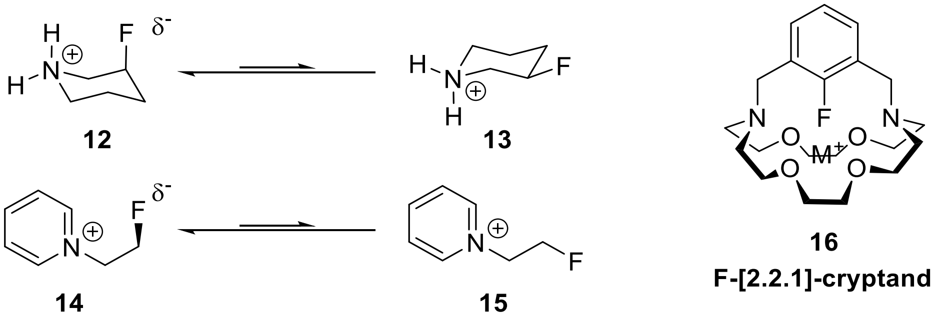


Figure 1.8 - The charge-dipole interactions between a C-F bond and a formally charged heteroatom (Left) or polarized metal cation (Right).

pK_a & Lipophilicity

Fluorine is often added to pharmaceutical agents to modify binding affinities and pharmacokinetic properties such as pK_a to impact bioavailability (percent of the dose to reach the circulatory system, denoted F). Intravenously administered drugs have 100% bioavailability but are more uncomfortable for patients compared to methods such as oral administration, which has lower bioavailability from either poor absorption or first-pass metabolism in the body. Fluorine's inclusion into molecules has strong effects on the acidobasicity of nearby functional group.[31] This enables molecules with poor bioavailability, such as a series of 3-piperidinylindole antipsychotic drugs, to be fluorinated into viability by reducing the pK_a of its amine group.[32] Similar effects of pK_a on bioavailability can be observed in a series of piperidinyl and piperazinyl indoles used for migraine treatment. The basicity of the amines was reduced by proximal fluorination which improved oral bioavailability in some cases, although ineffective in some fluorination cases.[33]

Another drug property to affect bioavailability is lipophilicity (log *P*), which affects permeability through a cell membrane and must be tuned to pass into a cell's lipid core but not be trapped within it. Fluorine's strong electronegativity may modulate lipophilicity in either direction. Mono- or difluorination of saturated alkyl groups decreases lipophilicity (Table 1.1), while aromatic fluorination, and perfluorination and fluorination adjacent to atoms with π-bonds increases lipophilicity due to the overlap of the carbon and fluorine orbitals making the C-F bond less polarized.[34]

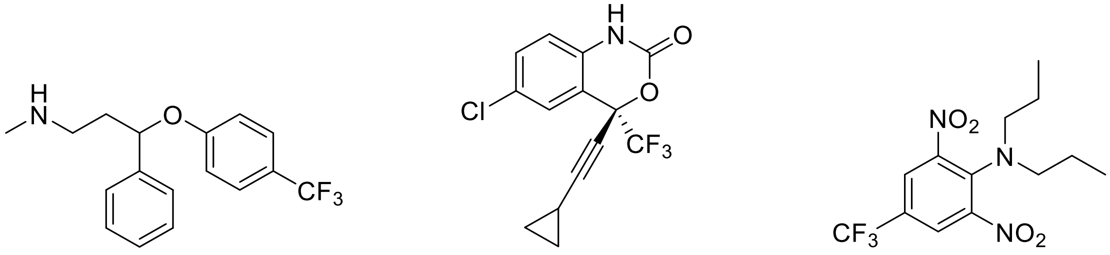
Compound	**Log *P* (octanol-water)**
CH_3CH_3	1.81
CH_3CHF_2	0.75
$CH_3(CH_2)_3CH_3$	3.11
$CH_3(CH_2)_3CH_2F$	2.33

Table 1.1 - The effect of fluorine substitution on lipophilicity (log P).

1.4 Trifluoromethyl Groups (CF_3)

In 1928, Lehmann described the first case of pharmacological activity from trifluoromethylated compounds affecting the nervous system of frogs.[35] Over the following decades, the biological significance of the trifluoromethyl group was recognized and in 1959 a dedicated review detailed the emergence of an assortment of new anaesthetic, ataractic, antiemetic, and diuretic agents from that past decade.[36] The increasing influence of the trifluoromethyl group has led to usage of this class of compounds in applications ranging from industrial use in polymers and dyes, to biological use in agrochemicals and pharmaceuticals. In agrochemical production, it was found that from 2010 to 2016, 96% of agrochemicals were halogenated, and of these compounds 52% were fluorinated and 35% were trifluoromethylated.[37] In 2008, ten of the top 30 best-selling pharmaceutical products were organofluorine compounds, two of which specifically contained the trifluoromethyl group (lansoprazole and celecoxib). Moreover, trifluoromethylated drugs such as fluoxetine and efavirenz (Figure 1.9) are included in the World Health Organization's List of Essential Medicines,[38] and in the past couple of years, 14 of the 33 fluorine-containing compounds approved by the FDA were trifluoromethylated,[9] showing the increased prominence of this specific group.

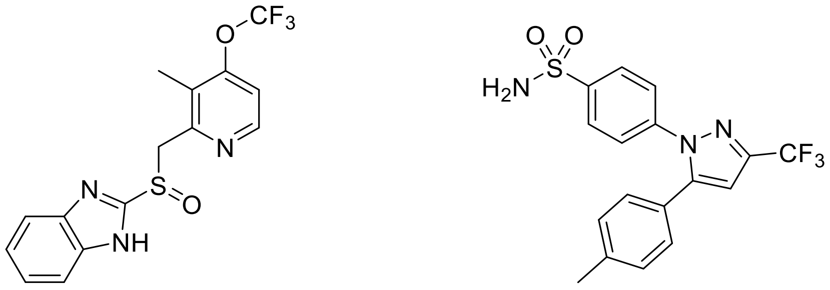
However, a recent review on the synthesis of fluorinated pharmaceuticals between 2001 and 2011 indicated that more than 90% of fluorinated drugs on the market were manufactured from fluorinated raw materials used as building blocks.[39] This continues to be evident in the present when looking at the synthetic routes of the 2019 FDA-approved drugs where instances of trifluoromethyl groups were all introduced via precursor molecules.[40] Although trifluoromethylation methods were necessary to synthesize the precursor molecules, the regular use of trifluoromethylated precursors points to a possible lack of efficient late-stage trifluoromethylation techniques.



Fluoxetine (Prozac)
anti-depressant

Efavirenz (Sustiva)
anti-retroviral

Trifluralin
herbicide



Lansoprazole (Prevacid)
antacid

Celecoxib (Celebrex)
anti-inflammatory

Figure 1.9 - Examples of trifluoromethylated pharmaceuticals and agrochemicals.

Many of the strong electronic properties imbued by monofluorination expectedly overlap with trifluoromethylation. The qualities of trifluoromethyl groups include generally increased Brønsted acidity and improved general bioavailability through increased lipophilicity and protection against oxidation. Many of these properties are measured through comparison to their non-fluorinated counterpart (*i.e.* methyl groups), showing a change simply through fluorinations rather than trifluoromethylations, in cases like lipophilicity (log *P*).[12] Electronically, both F and CF$_3$ are quite high on the electronegativity scale (Pauling 4.0/3.5), with CF$_3$ being slightly lower and comparable to oxygen. Both F and CF$_3$ are electron-withdrawing inductively as strong σ-acceptors (-I$_\sigma$). However, F is a strong π-donor (+I$_\pi$), while CF$_3$ groups are strong π-acceptor (-I$_\pi$) due to possible negative hyperconjugation (Figure 1.10). This results in F and CF$_3$ having similar electron-withdrawing inductive properties (σ_I), but opposite electronics through resonance (σ_R), as evidenced by their differing Hammett values of -0.34 and 0.10 for F and CF$_3$, respectively.[41] Interestingly, the ^{19}F NMR chemical shifts of CF$_3$ groups in alkyl and aromatic moieties are nearly identical, indicating that the delocalization of electrons from an aromatic ring has almost no effect.[23]

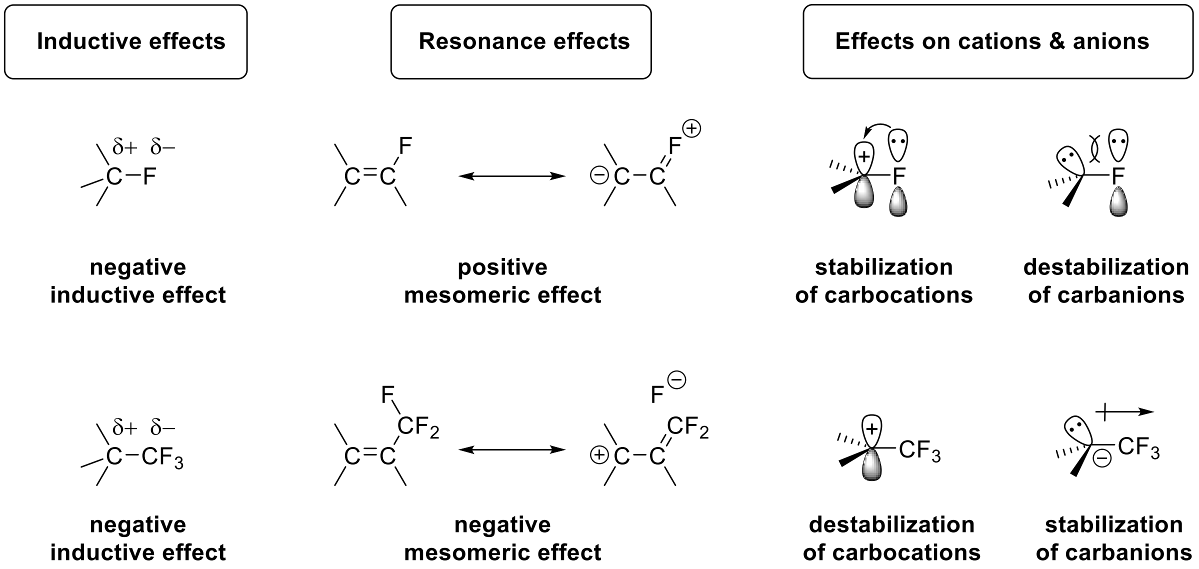
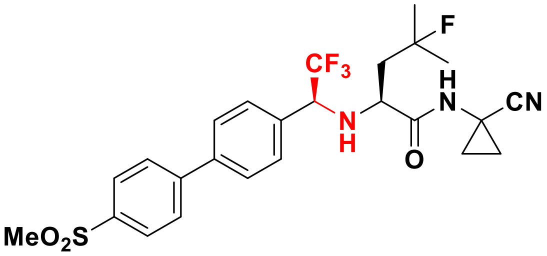


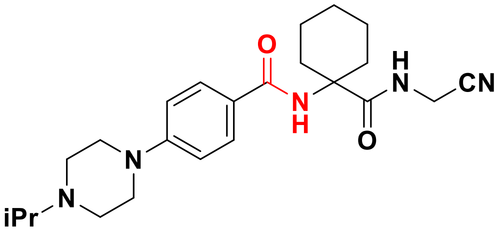
Figure 1.10 - The electronic effects of a fluorine atom versus trifluoromethyl group in organofluorine compounds.

In classical bioisosterism, trifluoromethyl groups were used to replace methyl groups with the rationale that hydrogen to fluorine interchange was the mildest possible steric replacement, despite actually being closer in size to oxygen.[18] Due to this steric difference, bioactivity assessments now use trifluoromethyl groups more often to replace amine, hydroxyl, and chlorine groups instead.[42] A substitution from C-CH_3 to a C-CF_3 bond has a minor effect on bond length, but the van der Waals volume is estimated to become around twice as large (21.6 $Å^3$ versus 39.8 $Å^3$, respectively)[43] This difference in steric bulk can be observed when comparing methoxybenzene which adopts a planar conformation, and trifluoromethoxybenzene where the O-CF_3 group is almost orthogonal to the aromatic ring.[44]

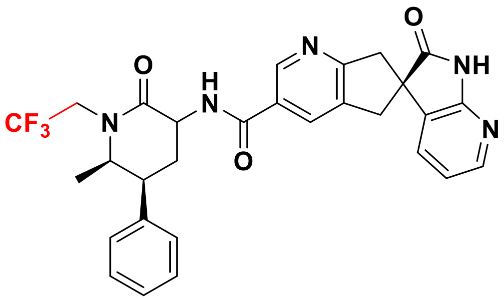
The steric size of the methyl group has been compared to some hydrocarbon alkyl groups such as ethyl or isopropyl groups, despite their seemingly different shapes. This seems plausible when considering conformational energies (*i.e.* A-values) in which trifluoromethyl groups are comparable to isopropyl or cyclohexyl groups.[45] In relatively recent years, the steric parameters for trifluoromethyl groups were indeed found to be much larger than a methyl group (~0.7 kcal mol^{-1}), but only slightly larger than an isopropyl group (~0.2 kcal mol^{-1}) and with an equal effective van der Waals radii (2.20 Å).[46] Even when considering rotational barriers (ΔG^{tors}) in biphenyl derivatives, trifluoromethyl substitution (21.9 kcal mol^{-1}) was only slightly less than isopropyl substitution (22.2 kcal mol^{-1}). However, the rotationally symmetric trifluoromethyl group is much smaller in van der Waals volume (39.8 $Å^3$ versus 56.2 $Å^3$), and thus only comparable by effective steric bulk but not in shape and size to the axially anisotropic isopropyl group.[43]

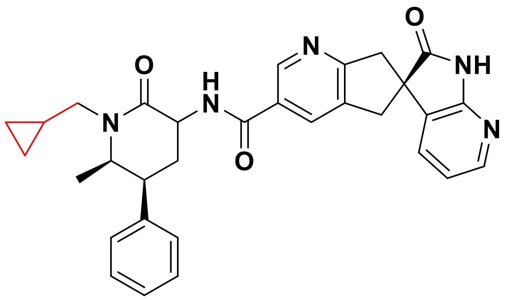
Towards non-classical bioisosteres, trifluoromethyl groups in conjunction with other functional groups can be used, such as trifluoroethylamine moieties which can act as amide isosteres with C=O bonds mimicked by C-CF_3 bonds (Figure 1.11).[47] Other recent examples include notable non-fluorinated derivatives of 2019 FDA-approved drugs ubrogepant, upadacitinib, and pexidartinib, where systematic structural variations comprised of interchanging trifluoroethyl with *sec*-butyl and cyclopropylmethyl groups or trifluoromethyl with cyclopropylmethyl and methoxy moities.[40] In all these cases, the trifluoromethyl group itself was used as a steric substitute for cyclopropyl and methoxy groups, and a double-bond oxygen atom.



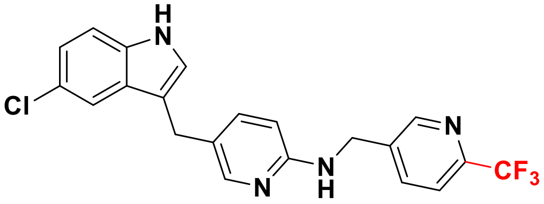


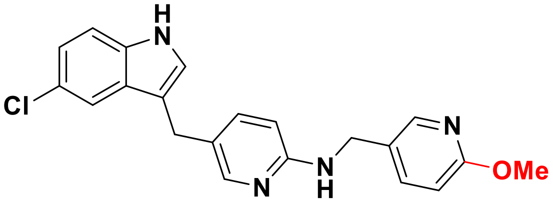
odanacatib





ubrogepant (MK-1602)



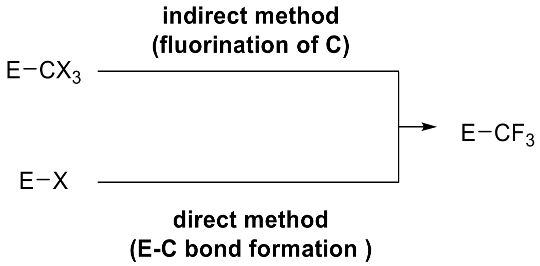


pexidartinib

Figure 1.11 - Examples of non-classical bioisosteres of CF_3 in drug development.

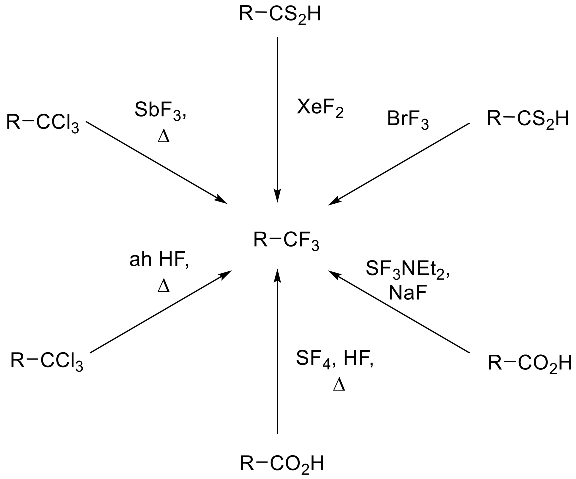
1.5 Indirect Trifluoromethylation

The earliest fluorinating agents hail from the synthesis of HF by Marggraf in 1764 and Moissan's preparation of elemental F_2 in 1886. Their extreme reactivity limited widespread use in standard organic chemistry laboratories due to the specialized equipment, methods, and safety precautions needed to address the dangers of these fluorination tools. Thus, their adoption has been limited mainly to industrial scale productions. However, reactive fluorine sources (e.g. SbF_3, HF, SF_4, etc.) could be derived from HF and F_2 and used to triply fluorinate a carbon atom. This is referred to as "indirect" trifluoromethylation where an E-CX_3 group is fluorinated at a suitably reactive carbon centre already joined to the rest of the compound (i.e. functional group interconversion). In contrast, "direct" trifluoromethylation refers to forming an E-CF_3 bond between an element (E) and an already assembled CF_3 entity (Scheme 1.2).



Scheme 1.2 - Indirect versus direct methods of trifluoromethylation.

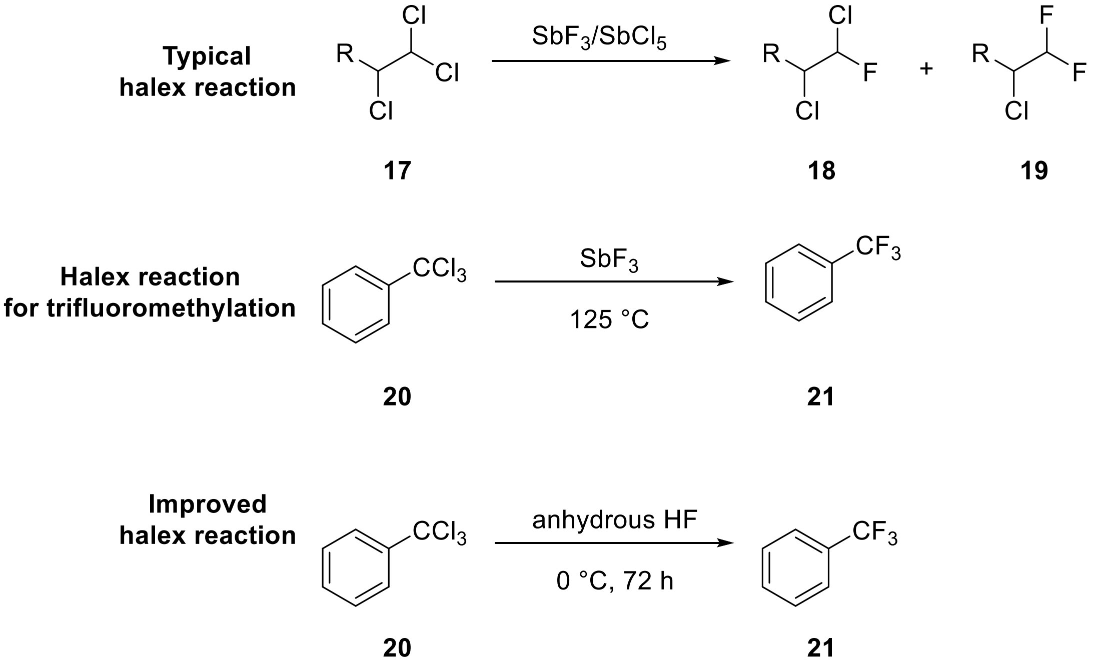
It was not until the 1980s that reliable direct trifluoromethylation methods were available. Thus, early historical approaches to synthesize CF_3 group mainly consisted of indirect methods (Scheme 1.3). These procedures often employed harsh reaction conditions, such as high temperatures and pressure, long reaction times, and highly acidic conditions, which could only be tolerated by the most robust of functional groups. Therefore, there were two strategies: (1) the fluorinations had to occur early in the stages of compound synthesis to accommodate other functional groups, often limiting the complexity of target molecules; or (2) to apply the building block approach where smaller and simpler molecules are directly trifluoromethylated before being forged together into complex compounds.



Scheme 1.3 - Various fluorination reactions used to produce a CF_3 group from a suitable electrophile precursor. Adapted from ref.[48]

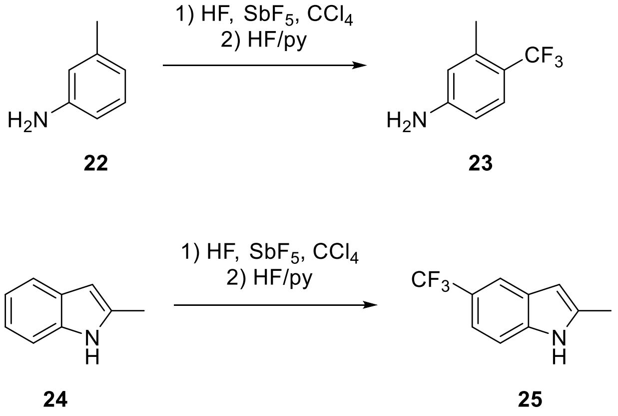
Halex and Related Reactions

The synthesis of organofluorine compounds were developed from practical fluorination and fluoroalkylation techniques. Some well-known C-F bond formation reactions included the likes of the Swarts reaction, Balz-Schiemann reaction, Halex reaction, and Simons electrochemical fluorination. The oldest indirect trifluoromethylation is a variation of the Swarts reaction which used antimony trifluoride (SbF_3) with chlorine to partially fluorinate halogen-substituted aliphatic compounds (usually chlorine or bromine) (Scheme 1.4). It was found that on aromatic trichloromethyl compounds ($ArCCl_3$), the three chlorine atoms could be replaced with three fluorine atoms using SbF_3 to form trifluoromethylated aromatic compounds, popularly referred to as a halogen-exchange (Halex) reaction.[49] This procedure has since fallen out of regular use due to the toxicity of antimony, but in 1938, Simons demonstrated a better method under harsher conditions using only anhydrous hydrogen fluoride.[50] This method is still used for the industrial scale production of aromatic trifluoromethyl compounds like trifluorotoluene (benzotrifluoride) but is also limited in widespread use because of the danger of anhydrous HF and the excess of HCl produced.[48]



Scheme 1.4 - The Halex reaction and its use for indirect trifluoromethylation of trichloromethylaryl compounds.

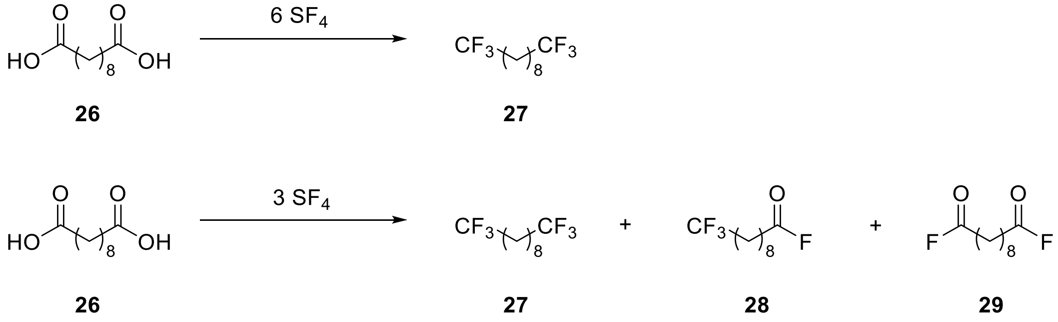
These methods were further elaborated for the production of benzotrifluorides, where substituted anilines underwent a two-step regioselective electrophilic aromatic substitution using a combination of anhydrous HF and antimony pentafluoride (SbF_5) with CCl_4 (banned today). This produced a mixture of fluorinated and partially fluorinated chloromethyl substituted products which could be subsequently fully fluorinated using HF/pyridine with remarkably good regioselectivity (Scheme 1.5).[51] This method is applicable for the installation of aromatic CF_3 groups in indoles, oxindoles, and indolines in the presence of amide and lactone moieties, thus viable as a late stage trifluoromethylation method for a small group of functional groups.[52]



Scheme 1.5 - Regioselective aromatic electrophilic trifluoromethylation of aryl compounds.

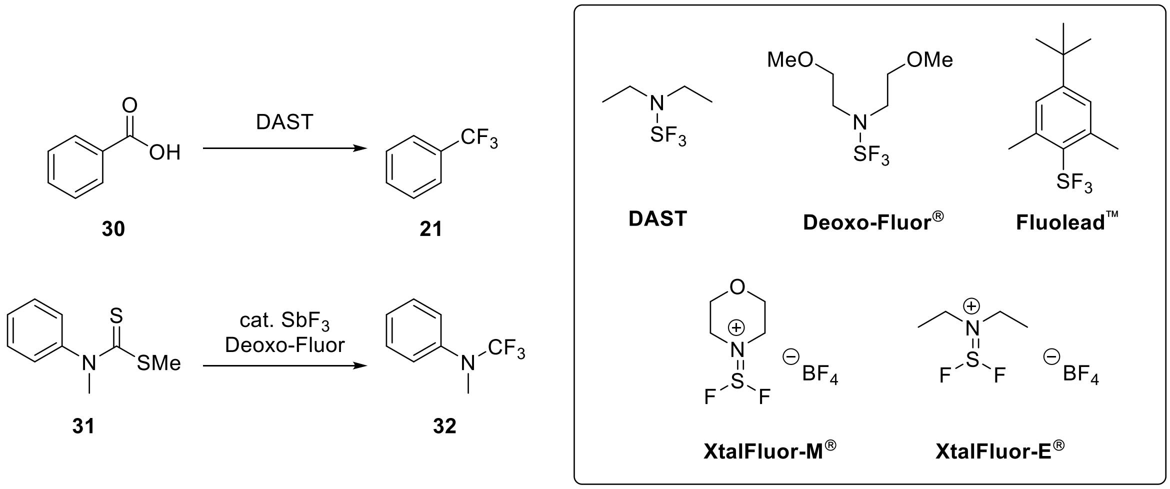
SF_4-based Reagents

The next set of methods used sulfur tetrafluoride (SF_4), a hazardous and difficult-to-handle gas. It is commercially available but can also be synthesized from sulfur dichloride (SCl_2) and sodium fluoride (NaF) with heat.[53] By end of 1950s, the reactivity of SF_4 was known to transform carboxylic acids to CF_3 groups and could also work with esters and anhydrides with more stable yields and broader substrate scopes (Scheme 1.6).[54] Fluorinations on aldehydes and ketones also gave the corresponding difluoromethyl (RCF_2H) and difluoromethylene (RCF_2R') products. Unfortunately, this reactive method can only mainly be tolerated by chlorides, nitro groups, and aliphatic alkenes/alkynes.



Scheme 1.6 - Complete and incomplete fluorinations using SF_4.

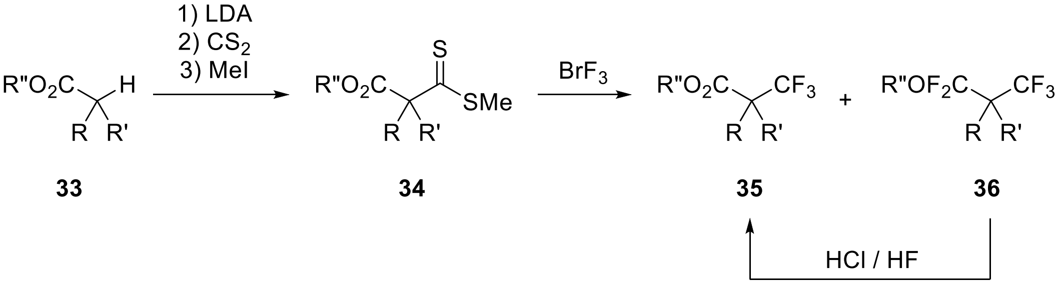
A decade later, another class of fluorination reagents emerged—dialkylaminosulfur trifluorides, derived from SF_4 and dialkylamino trialkylsilanes (R_2NSiR_3'). These reagents could be used in the same manner as SF_4 (Scheme 1.7), often employing harsh conditions of heating and long reaction times to convert quantitatively. The most well-known reagent of this class is diethylaminosulfur trifluoride (DAST), which is unwieldy in industrial processes because it decays around 140 °C very exothermically. This class of compounds has seen many additions and improvements in order to improve scope and stability. For example, aliphatic or aromatic acyl fluorides can be transformed to alkyl or aryl trifluorides using Deoxo-Fluor (bis(2- methoxyethyl)aminosulfur trifluoride), which has higher thermal stability.[55]



Scheme 1.7 - Fluorinations and examples of DAST-type reagents.

Oxidative Desulfurization-Fluorination

Another method is the oxidative desulfurization-fluorination of dithiocarboxylic acid derivatives. The most expensive reagent for this may be the reagent xenon difluoride (XeF_2), a commercially available and easy-to-handle white solid. First discovered in 1962 along with other compounds of noble gas Xe,[56] it is able to transform dithiocarboxylic acid compounds into the corresponding aromatic trifluoromethyl compounds.[57] Likewise, bromine trifluoride (BrF_3) is the more cost-efficient method, which is also commercially available and can be stored indefinitely in Teflon vessels. It has parallel reactivity and can also transform sulfur-containing functional groups into trifluoromethyl groups (Scheme 1.8).[58] Additionally, it is able to convert some carbon-based substituents in the alpha position of ester compounds into trifluoromethyl groups.[59] Finally, HF/pyridine (Olah's reagent) and tetrabutylammonium dihydrogentrifluoride can also be used with oxidants to convert dithiocarboxylate derivatives to trifluoromethyl compounds.[60]



Scheme 1.8 - Indirect trifluoromethylation via oxidative desulfurization-fluorination using BrF_3.

1.6 Direct Trifluoromethylation

The products of indirect trifluoromethylation like Halex reactions brought the advent of trifluoromethylated building blocks like trifluoroacetic acid and benzotrifluoride. Slowly, newer methods using such reagents allowed direct trifluoromethylations to become quicker, cheaper, and safer. Furthermore, not only was the direct formation of C-CF_3 bonds important, but the construction of heteroatom E-CF_3 bonds (E = N, P, O, S) also grew in importance. Especially in the past few decades, the synthetic community has been rapidly expanding its variety of trifluoromethylating tools and their range of applications.

The direct addition of a trifluoromethyl group can be subdivided into nucleophilic, radical, or electrophilic pathways depending on the target. However, radical- and electrophilic trifluoromethylation methods often result in the same products, blurring the distinction between the two pathways. Historically, the nucleophilic pathway was the most used and heavily studied with the rise of reagents such as M-CF_3 complexes and Ruppert-Prakash reagent ($TMSCF_3$). The electrophilic pathway is considered the least thoroughly investigated, although the field has been progressing rapidly in the past few decades with new reagents reported regularly. Thus, the exploration for cheaper reagents with different pathways of reactivity continues to grow. In some ways the community has developed reagents and procedures for many situations, but areas such as asymmetric catalytic trifluoromethylations can always be improved on. The Toste group has published a review in 2015 on catalytic enantioselective fluorinations with a section dedicated to trifluoromethylations, which mainly consisted of $TMSCF_3$ and nucleophilic trifluoromethylations but also the inclusion of a few reports of enantioselective reactions using electrophilic reagents like Togni reagent.[61] For enantioselective trifluoromethylations specifically, the Shibata group has written a review in 2008.[62]

1.6.1 Nucleophilic Reagents

Trifluoromethyl Metal Complexes (M-CF_3)

The use of metal for trifluoromethyl metal complexes were among the first direct trifluoromethylation methods reported. With reactivity patterns akin to the well-known alkyl organometallic tools such as Grignard and organolithium reagents, these M-CF_3-type reagents have examples involving lithium, main group metals (Sn, Bi), and late transition metals (Cu, Zn, Cd, Hg) to stabilize the charge of the CF_3 anion. Initial approaches to metal complexes were unfortunately ineffective when using reagents like methyllithium on compounds such as CF_3I.[63] These reactions would result in the formation of tetrafluoroethylene and its polymers, suggesting a 1,1-elimination event of the CF_3 anion to difluorocarbene with subsequent dimerization and polymerization. The destabilization of the CF_3 anion is due to strong electrostatic repulsion between the lone pairs of fluorine and carbanion. However, in the carbene form, the fluorine lone pair instead stabilizes the empty orbital on the carbon atom, thus shifting the equilibrium towards the formation of the carbene species (Figure 1.12). Similarly, the Grignard analogues CF_3MgI and CF_3MgBr were accessible but in minor amounts and were difficult to control. They were even more reactive to electrophiles and prone to simply form trifluoromethane.[64] Instead, main group and late transition metals are more suited for stabilization of the CF_3 anion by partial delocalization of the electron density into the low-lying unoccupied d-orbitals on the metal. Most M-CF_3 compounds are no longer important nor used in synthesis either due to toxicity, laborious synthesis, or low stability. Copper and $CuCF_3$ complexes remain as the most often used and discussed reagents, with a comprehensive review by Burton and Yang detailing the use of other main group and late transition metals.[65] A 2011 review by Tomashenko and Grushin also has some examples with nickel and palladium for aromatic trifluoromethylation specifically.[66]

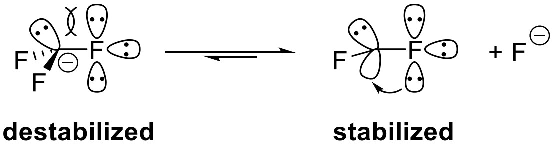
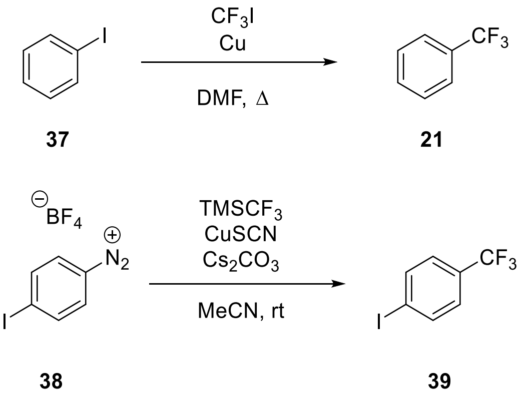


Figure 1.12 - Electrostatic repulsion between the filled orbitals of a CF_3 anion compared to the more stable carbenoid species.

One of the earliest examples of selective trifluoromethylation was described by McLoughlin and Thrower in 1969 using copper to form a trifluoromethyl-copper complex *in-situ* to couple perfluoroalkylhalides with aromatic iodides (Scheme 1.9, Top).[67] This has evolved into using CF_3I and activated copper as the most regular method of *in situ* generation of $CuCF_3$, with stabilizing ligands (often DMF or HMPA) then transmetallation to Cu(I) using other metals such as mercury, zinc, or cadmium.[68] CF_3I and CF_3H were often used as simple sources of CF_3 anions, but in the early 1980s, trifluoroacetate was also discovered as a useful source of CF_3 groups. Release of the CF_3 fragment by decarboxylation under elevated temperatures allowed its use in reactions like the Cu(I)-mediated trifluoromethylation of aryl iodides.[69]

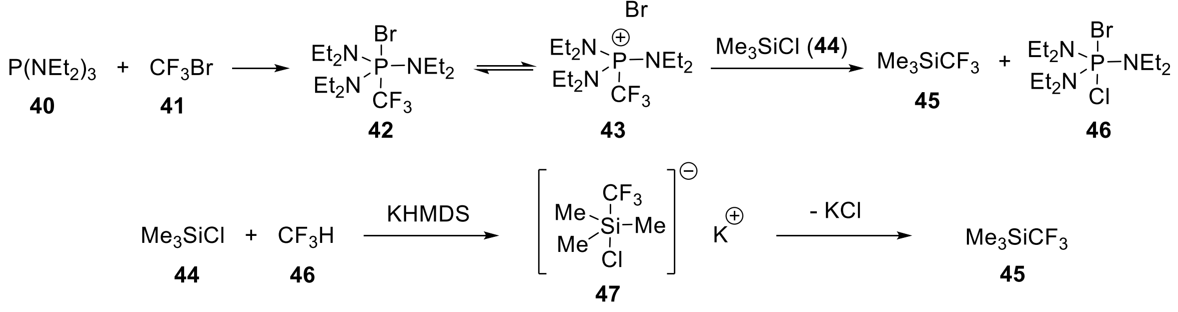
The usage of copper has also been reported in conjunction with other popular trifluoromethylation reagents for other coupling types such as Ullmann-type coupling with R_3SiCF_3, KF and CuI,[70] or Sandmeyer-type coupling on aryl diazonium salts using CuSCN, Cs_2CO_3, and $TMSCF_3$ to be transformed into trifluoromethyl arenes (Scheme 1.9, Bottom).[71] Within the past few decades, methods for metal catalyzed trifluoromethylation have improved considerably since the time of McLoughlin and Thrower and are detailed in a review by the Ritter group.[72]



Scheme 1.9 - Top: The McLoughlin-Thrower reaction using excess amounts of copper. Bottom: Sandmeyer-type coupling catalyzed by copper reagents.

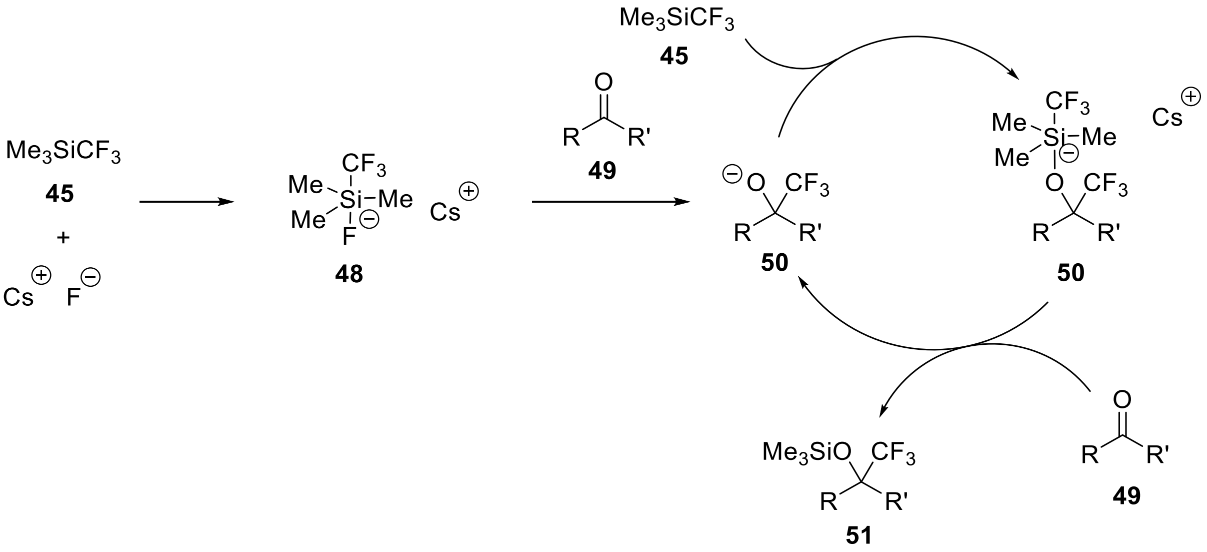
Ruppert-Prakash Reagent (TMSCF$_3$)

The most studied and reliable system in this area is trifluoromethyl trimethylsilane (Ruppert-Prakash reagent, TMSCF$_3$). This is the most prominently used source for CF$_3$ fragments and is often used in the synthesis of many modern trifluoromethylation reagents, like during the umpolung process in making electrophilic CF$_3$ reagents. It is an easy-to-handle liquid, first made by Ruppert in 1984 using CF$_3$Br with electron rich phosphine (P(NEt$_2$)$_3$) and trimethylsilyl chloride (TMSCl) (Scheme 1.10).[73] Since the prohibition of the ozone-depleting CF$_3$Br by the Montreal Protocol shortly thereafter, routes and methods have vastly improved. Current industrial procedures follow methods based on Prakash's improved modern route using trifluoromethane, a powerful greenhouse gas produced in large volumes as a by-product of industrial synthesis of fluoropolymers and refrigerants.[74]



Scheme 1.10 - Top: Ruppert's first reported preparation of TMSCF$_3$.
Bottom: Prakash's modern preparation of TMSCF$_3$ starting from trifluoromethane.

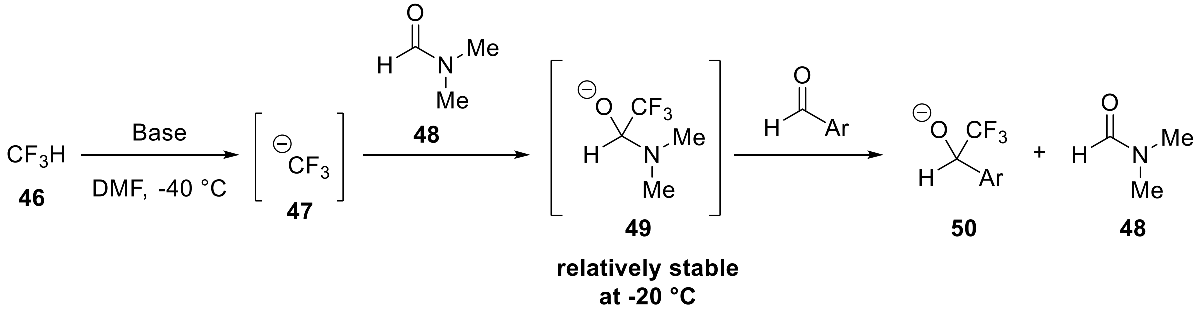
Nonetheless, Ruppert had not described it in synthesis as a reagent and it was not until Prakash in 1989 who described a fluoride-initiated nucleophilic trifluoromethylation on aldehydes and ketones using the reagent.[75] These addition reactions are often activated by nucleophilic fluoride sources, most often CsF or tetrabutylammonium fluoride (TBAF), with the proposed mechanism showing the catalytic amount of fluoride generating a pentavalent silicate (Scheme 1.11). This intermediate then reacts with the carbonyl electrophile while concomitantly releasing trimethylsilyl fluoride and the resulting alkoxide sustains the reaction cycle by attack of the silicon centre of the next $TMSCF_3$ molecule. This mechanism has been well explored and competent activators have expanded to hard Lewis bases (e.g. carbonate),[76] Lewis acids (e.g. TiF_4),[77] and softer activators like phosphines.[78] While Prakash originally explored and implemented his strategy on mainly carbonyl electrophiles, the target scope now extends to a variety of functional groups, with recent examples being detailed by Liu *et al.* in a dedicated trifluoromethyl trimethylsilane review.[79] Additionally, the usefulness of the Ruppert-Prakash reagent in total synthesis is well reported, as a tool to alter biological activity of the compounds when implemented as drugs.[80]



Scheme 1.11 - General scheme for the catalytic nucleophilic trifluoromethylation of carbonyl compounds using Me_3SiCF_3.

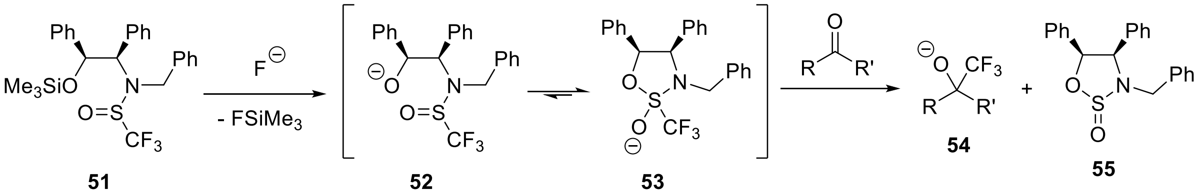
Masked CF_3 Equivalents

The smallest and simplest source of CF_3 anions is in trifluoromethane (fluoroform), from which a base can simply abstract a proton as the most atom efficient, sustainable, and green process for CF_3 fragment generation. However, as a gas with a boiling point of -84 °C, the handling of the reagent and equipment proves complicated. Additionally, as stated earlier, the destabilization of the CF_3 anion and resulting tendency towards forming the carbenoid species requires more refined methods. These issues are tackled by binding the unstable trifluoromethyl anion to a molecule to act as the vehicle for adding it to the electrophile. Tertiary formamides, most prominently DMF, can act both as the solvent and the stabilizing reservoir to transfer these masked CF_3 groups to electrophiles such as aldehydes and ketones as first shown by the Shono group in 1991 (Scheme 1.12).[81] The hemiaminal-like adduct formed *in situ* from CF_3^- and DMF (or structurally similar molecules) was investigated shortly after.[82]



Scheme 1.12 - Tertiary formamides, shown as DMF, as a reservoir for CF_3 anions for the trifluoromethylation of carbonyl compounds.

Due to the reagent's high basicity, this method is restricted in scope to aldehydes and non-enolizable ketones. However, this concept served as inspiration for the synthesis of more stable and better compounds, not only to avoid gaseous CF_3H, but also to enhance the CF_3 fragment's reactivity. This was well explored in a series of articles by the Langlois group who reported silylated hemiaminals as the choice adduct, synthesized using inexpensive and easily-handled chemicals. Further work using *N*-formylmorpholine and *N*-formylpiperazine had similar scope and drawbacks.[83] These masked CF_3 anion equivalents have marked reactivity towards ketones, aldehydes, and disulfides similar to previous nucleophilic methods. This method requires only a catalytic amount of fluoride towards the silylated reagents, in contrast to the plain hemiacetal. The trifluoromethyl transfer mechanism proceeds via a metal hemiamidate intermediate, where the authors suggest a dimeric aggregate forming a loose six-membered transition state with the carbonyl substrate to explain the necessity of two equivalents of the reagents for quantitative yield. Furthermore, the Langlois group's solution to circumvent the problems of high basicity and competing Cannizaro-type disproportionation reactions was to use an intramolecular substrate of *N*-trimethylsiloxyethyl-*N*-alkyl-trifluoroacetamides or -sulfinamides treated with fluoride sources. This intramolecular cyclizative approach used a cyclic and less basic vehicle for the CF_3 group, which allowed for trifluoromethylation of enolizable ketones (Scheme 1.13).[84] It was also expanded upon later into an enantioselective trifluoromethylation method.[85]



Scheme 1.13 - Langlois' intramolecular generation of CF_3 anions capable of trifluoromethylating enolizable ketones.

1.6.2 Radical Reagents

Radical trifluoromethylation has a rich history with many sources for trifluoromethyl radicals and an almost equally diverse number of radical activators. Below in Figure 1.13 are some CF_3-radical sources, formed under thermal, photolysis, and electrochemical conditions, or by chemical induction in the presence of a radical acceptor. CF_3-radicals behave formally as electrophiles and it is often difficult to discern their pathways from CF_3 cations. In fact, some of the reagents typically used as formal nucleophilic or electrophilic trifluoromethylation reagents may act as sources of CF_3 radicals as well. This section will only briefly cover a few concepts and reagents out of the ocean of radical trifluoromethylations developed. Curiosity in the details in this area of trifluoromethylation can be sated by these dedicated reviews on fluoroalkyl radicals[86] and trifluoromethyl radicals.[87]

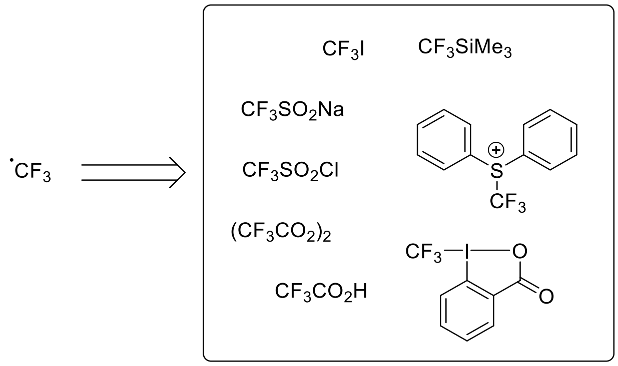
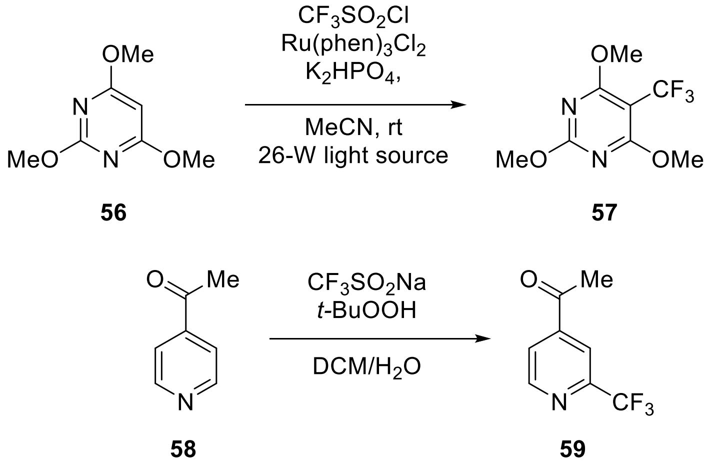


Figure 1.13 - Examples of sources of radical CF_3 groups.

The generation of trifluoromethyl radicals was first reported in the late 1940s by Haszeldine using CF_3I and ethylene with initiation by either irradiation or heat.[88] CF_3I continued to be a prominent source for CF_3 radicals and other initiation sources have been reported such as Et_3B, Et_2Zn, and many metal photoredox catalysts. However, as an inconvenient gas, it becomes difficult to control parameters such as the concentration especially at elevated temperatures. Thus, other reagents were devised such as bis(trifluoroacetyl) peroxide, CF_3SO_2SPh, and CF_3SO_2Cl. Trifluoromethanesulfonyl chloride in particular has been well investigated upon by the MacMillan group for radical trifluoromethylation using commercially available $Ru(phen)_3Cl_2$ as a photocatalyst in mild conditions.[89] Simpler organofluorine molecules like trifluoroacetate and trifluoroacetic acid could also generate CF_3 radicals using relatively more expensive catalysts like TiO_2 and XeF_2.[90]

Perhaps the most well-known radical trifluoromethylation reagent would be the Langlois reagent—sodium trifluoromethanesulfinate. Originally reported in 1991 to generate trifluoromethyl radicals in the presence of *t*-BuOOH and $Cu(OSO_2CF_3)_2$ (Scheme 1.14),[91] methods using this reagent have been heavily refined to metal-free procedures[92] and even simply with the mild oxidants like phenyliodine diacetate (PIDA).[93] The other types of reagents typically used for formal nucleophilic and electrophilic trifluoromethylation have also been reported to generate trifluoromethyl radicals, such as $TMSCF_3$,[94] Yagupolskii-type sulfonium salts,[95] and Togni-type iodane reagents.[96]



Scheme 1.14 - Application of CF_3SO_2Cl and Langlois' reagent for the trifluoromethylation of arene compounds.

As the field of trifluoromethylation chemistry progresses, reports of new reagents not based on previous iterations are produced regularly (Figure 1.14). This past decade has seen steady invention of new radical trifluoromethylation reagents, many of which become commercially available on multi kilogram scales, such as Baran's zinc trifluoromethanesulfinate (TFMS)[97] and Hartwig's (Phen)Cu-CF_3 reagents.[98] Other reagents like the persistent perfluoroalkyl radical (PPFR) were first discovered in 1984, but did not find application until very recently,[99] and we can be sure that the field of radical trifluoromethylation will continue to grow swiftly.

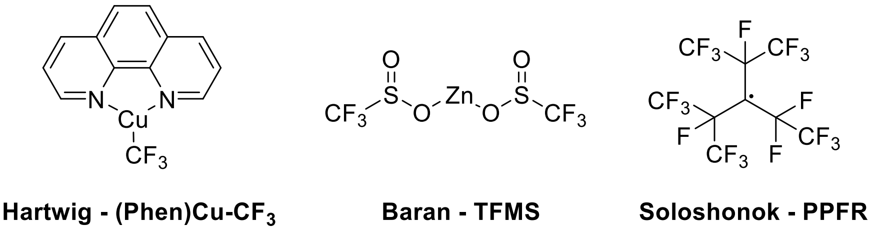


Figure 1.14 - Recently developed radical trifluoromethylation reagents.

1.6.3 Electrophilic Reagents

The youngest of the three branches of direct trifluoromethylation is the electrophilic approach, starting their development in the mid-1980s.[100] From the beginning, successful reagents were based on the chalcogen group (S, Se, Te) and it was not until after the turn of the millennium, that the class of iodine-based reagents has emerged.[101] In this still-growing field of electrophilic trifluoromethylation, there has been relatively rapid development in the last two decades. These recently developed methods have grown the library of electrophilic trifluoromethylating reagents (Figure 1.15), and many have become regular tools in an organic chemist's toolkit—produced in multi kilogram scales in industrial processes as commercially available reagents. A computational exploration of the trifluoromethylating power of the various electrophilic reagents has good alignment with experimentally observed results and can serve as a quick summary.[102] Further detail and references for electrophilic trifluoromethylation can be found in a 2010 review by the Shibata group.[103]

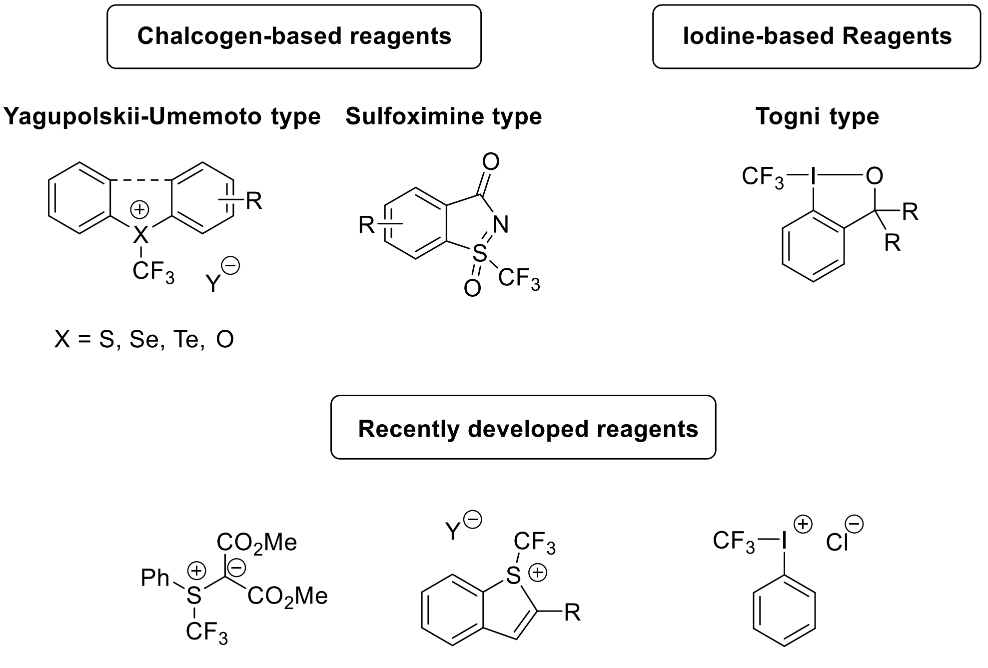


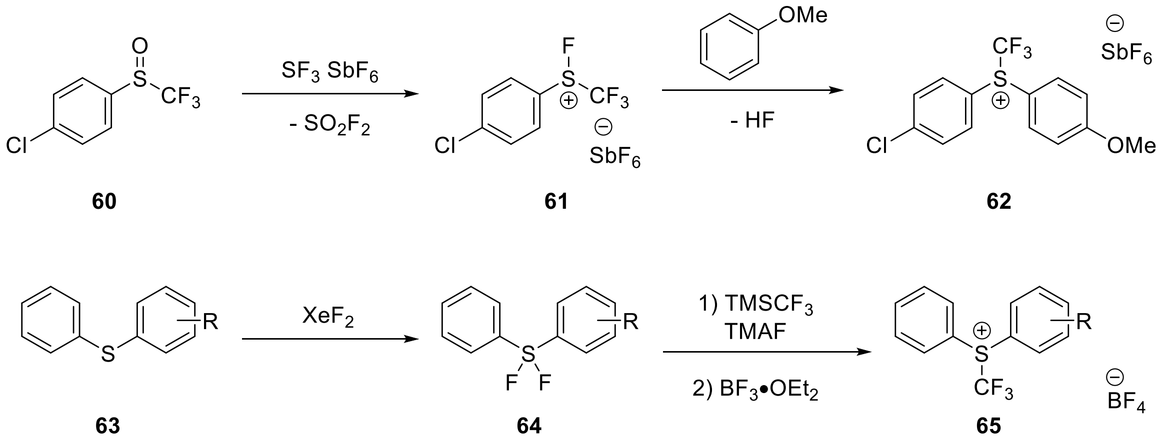
Figure 1.15 - Classifications of electrophilic trifluoromethylation reagents, along with newly developed classes and reagents.

1.6.3.1 Chalcogen-based Reagents

Yagupolskii-type

The earliest electrophilic-type reagents were the chalcogenium-based salts first reported by Yagupolskii *et al.* in 1984.[100] The diarylsulfonium salts were synthesized starting from (trifluoromethyl)aryl sulfoxide by deoxyfluorination with trifluorosulfonium hexafluoroantimonate (SF_3SbF_6) then subsequent fluoride abstraction with antimony pentafluoride to the corresponding S-fluoro *S*-trifluoromethylsulfonium salt. This electrophilic compound would then undergo electrophilic aromatic substitution with electron-rich arenes such as m-xylene or anisole to yield the corresponding *S*-(trifluoromethyl)diarylsulfonium salt (Scheme 1.15). These salts were stable under ambient conditions and were found to act as a formal CF_3^+ source when reacting with sodium p-nitrothiophenolate to form the corresponding trifluoromethyl thioether, although the nature of the reaction mechanism was unclear at the time.

Development in this class of reagents was slow and it was not until the late 1990s that the Shreeve group improved the synthetic routes[104] and allowed for more diversity in the aryl ring substitution patterns using *in situ* aromatic substitution. The Wakselman group further improved routes again, reporting a solvent-free one-pot procedure for the aryl substitution in addition to a simple synthesis of phenyl trifluoromethyl sulfoxide starting from benzene.[105] More recently, the Yagupolskii group continued to refine the synthetic methods to make aryl- and hetaryl(trifluoromethyl)sulfonium salts, including a formal umpolung step involving $TMSCF_3$ to the final trifluoromethylating reagent. The enhanced diversity of this class of reagents enabled a larger substrate scope, with the trifluoromethylation of iodide, trivalent phosphorus, and other soft nucleophiles. Interestingly, trifluoromethylation always occurred at the softer centre in a molecule, such as the sulfur in thiourea compounds.[106]



Scheme 1.15 - Top: Yagupolskii's first preparation of electrophilic trifluoromethylating reagents. Bottom: Yagupolskii's improved synthesis route over two decades later.

Umemoto-type

Inspired by the initial work from by Yagupolskii, the Umemoto group published a series of articles for the synthesis of (trifluoromethyl)dibenzochalcogenium salts. These heterocyclic analogues of the Yagupolskii-type salts were initially based on a dibenzothio- and selenophenium frameworks,[107] and were quickly expanded to tellurium analogues as well.[108] They were the most broadly applicable electrophilic CF_3-transfer reagents for a long period of time. The main advantage of these Umemoto-type reagents is their crystalline stability which allows for good storage and commercial production (albeit expensive), with the main disadvantages being low solubility in less polar solvents and poor atom economy coupled with lack of recyclability. An important trait of this class of compounds is that the general reactivity depended on the electronegativity of the chalcogenide bearing the CF_3-group and the aromatic ring substituents. The reactivity and stability of the (trifluoromethyl)dibenzochalcogenium salts were shown to be inversely related such that reactivity increased and stability decreased from Te < Se < S (Figure 1.16). Reactivity, stability, and solubility could be further adjusted with the incorporation of electron withdrawing groups (e.g. nitro groups) on the aryl rings.[107-108]

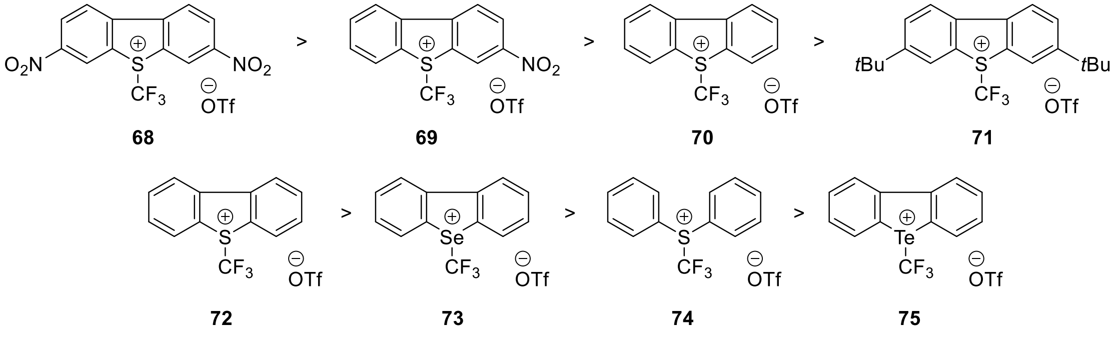
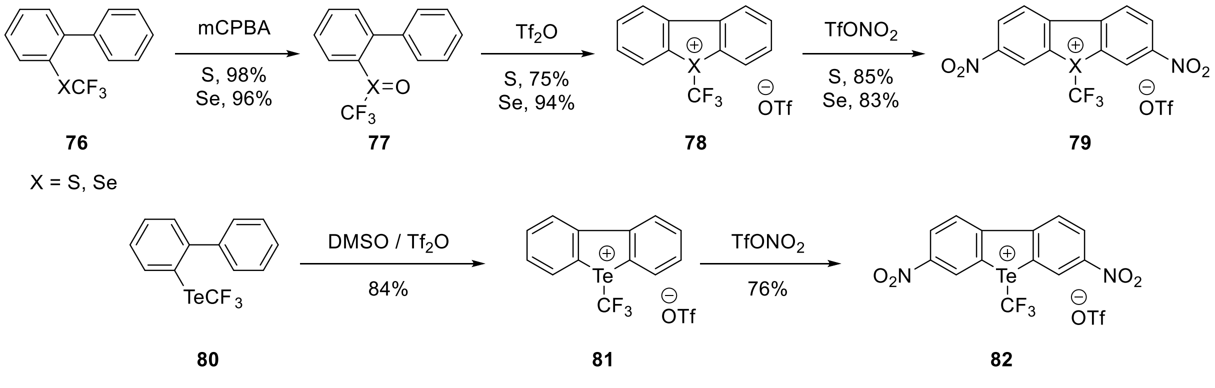


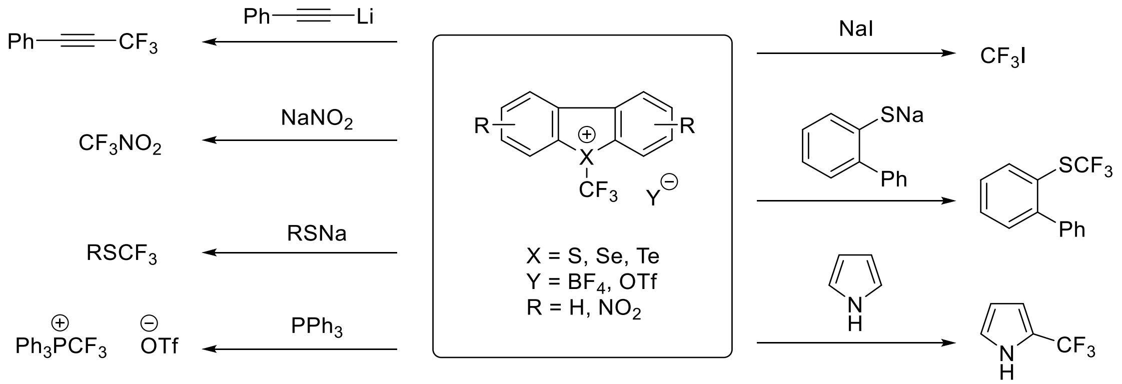
Figure 1.16 - Trifluoromethylation power of Yagupolskii- and Umemoto-type reagents sorted in descending strength.

The synthesis route of this new heterocyclic class of compounds was also appealingly simple, starting from the trifluoromethylthio- or selenoethers, followed by oxidative activation with F_2 and TfOH or HBF_4 to produce the trifluoromethyldibenzothio- and selenophenium salts in good yield with few side reactions occurring (Scheme 1.16 - General procedure for the synthesis of Umemoto-type reagents). Some derivatives required oxidation to the sulfoxide and selenoxide first before electrophilic aromatic substitution using Tf_2O to produce the thiophenium or selenophenium salt. The telluroether analogue followed a similar set of steps for synthesis using milder reagents, presumably because of tellurium's higher nucleophilicity.[108] Substitution of the aryl rings was also simple, despite harsh reaction conditions.[109] Much later, the Magnier group reported a one-pot procedure starting from unsubstituted biphenyl derivatives using potassium trifluoromethanesulfinate and triflic acid, further lowering production costs for the reagent.[110]



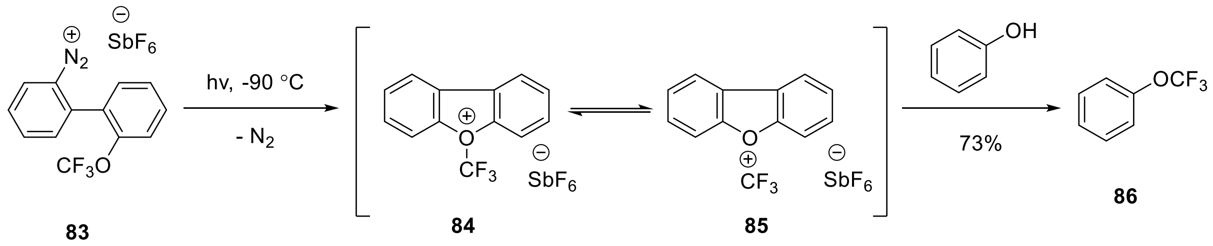
Scheme 1.16 - General procedure for the synthesis of Umemoto-type reagents.

When originally reported, the lower reactivity of the selenium- and tellurium-based reagents were more successful than their sulfur-based counterpart for the trifluoromethylation of softer nucleophiles, such as enamines, thiolates, and electron rich arenes that tended to undergo oxidative side reactions.[107-109] The substrate scope of these salt compounds has been readily explored, including both carbon- and heteroatom-centered nucleophiles (Scheme 1.17).[111] They have seen applications in adjusting physico-chemical properties in drug compounds,[112] and are still being used to explore couplings such as Sandmeyer reactions.[113]



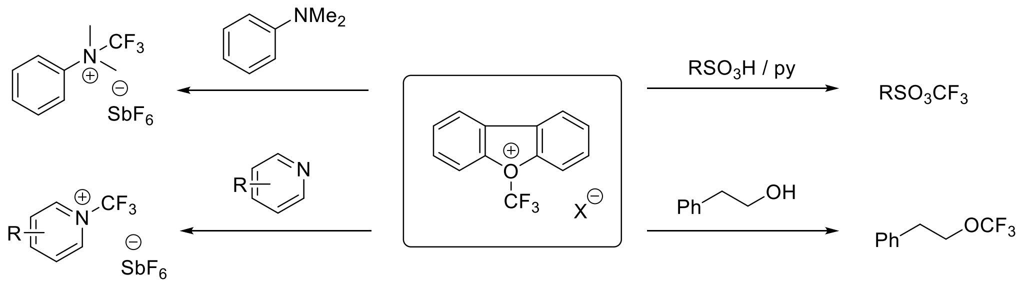
Scheme 1.17 - Various applications of the Umemoto-type trifluoromethylating reagents.

While the sulfur-, selenium-, and tellurium-based salts were applicable to soft nucleophiles, hard nucleophiles proved more challenging for direct trifluoromethylation. Since the trifluoromethylating reactivity of the chalcogenium salts was established as Te < Se < S in order of electronegativity, it was then postulated that oxygen, the most electronegative of the chalcogens, would be the most reactive. The O-(trifluoromethyl)dibenzofuranium salts (sometimes referred to as Meerwein-type salts) were reported by the Umemoto group in 2007. They were synthesized by photochemical decomposition of diazonium salt substrates from similar trifluoromethoxy scaffolds as the precursors of the other chalcogenium salts (Scheme 1.18).[114] These rare species are inherently very unstable with reported half-lives ranging from 29 min to 415 min depending on the counterion and required low temperatures of -100 °C for their *in-situ* formation, limiting their synthetic application and commercially availability.



Scheme 1.18 - Synthesis and application of the oxygen-based Umemoto-type reagents.

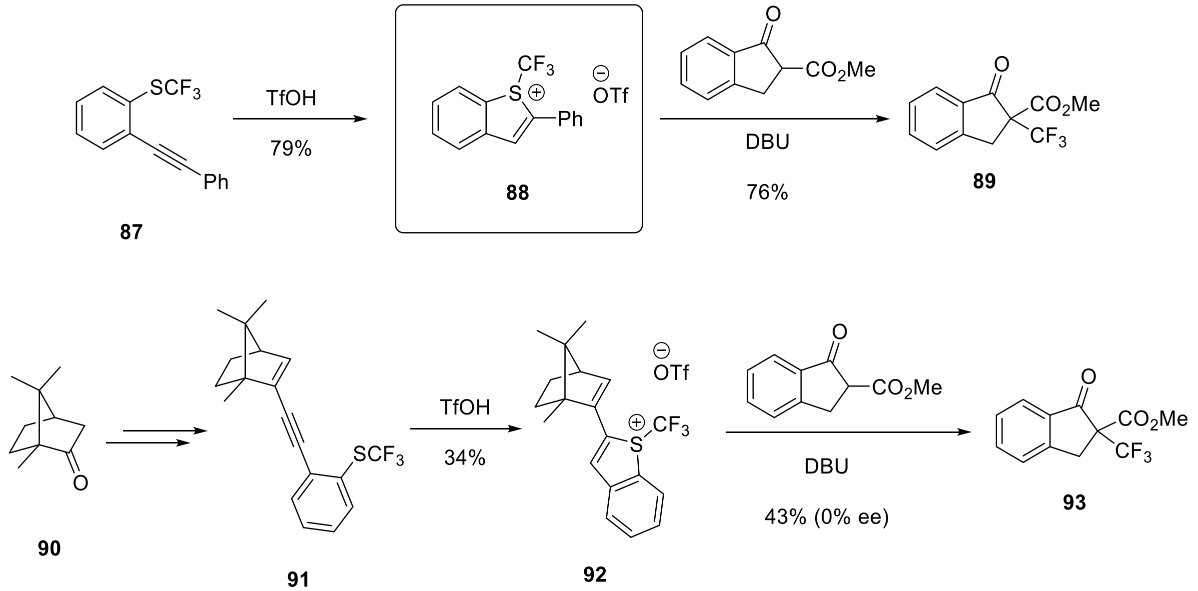
These O-CF_3 salts were uniquely capable of direct O- and N-trifluoromethylation of alcohols, phenols, sulfonates, amines, anilines, pyrrolidines, and pyridines (Scheme 1.19). This is in contrast to the S- and Se-CF_3 salts, with which aromatic trifluoromethylation and/or oxidation would occur instead, suggesting a different reaction mechanism for the more reactive oxonium species. It was suggested that the different reacting species varies from CF_3• to CF_3^+ depending on the reactivity of the nucleophiles, the trifluoromethylating power of the salts, and reaction conditions. The mechanism was proposed to more dissociative rather than S_N2-like.



Scheme 1.19 - Application of the dibenzofuranium derivatives of Umemoto-type reagents.

Extended Yagupolskii-Umemoto-type (Shibata-type)

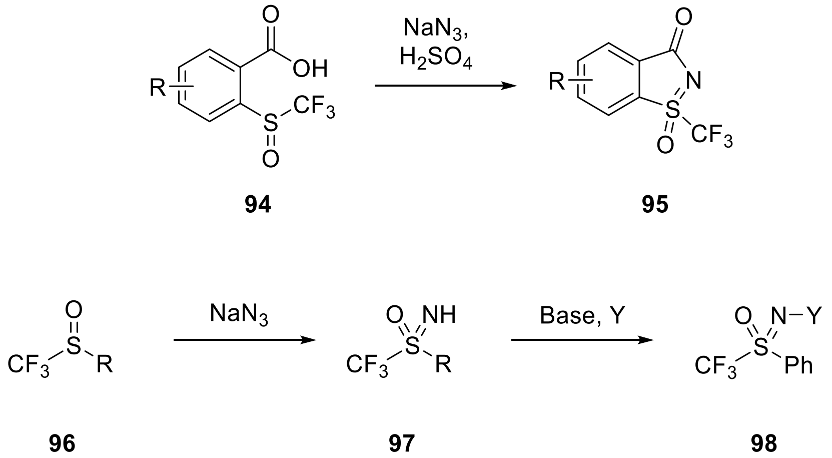
In 2010, the Shibata group developed a novel route towards Yagupolskii-Umemoto-type reagents—benzothiophenium salts rather than dibenzo analogues.[115] This was achieved through intramolecular cyclization of o-ethynylaryl- and alkyl-trifluoromethylsulfanes catalyzed strictly by triflic acid (TfOH) (Scheme 1.20). It was noted that cyclization failed with other Brønsted and Lewis acids. These Shibata-type reagents could be applied for the trifluoromethylation of carbon centered nucleophiles like β-keto esters and cyclic dicyanoalkylidenes in good yields, much higher than the commercially available Umemoto- or Togni-type reagents. One advantage of these benzothiophenium salts was envisioned to be the enantioselective trifluoromethylation by the simple modification of chiral groups on the 2-position of the thiophene. This potential allowed for selectivity acting from an internal component of the molecule rather than an external chiral reagent, however, initial attempts were unsuccessful and yielded a racemic mixture of diastereomers.



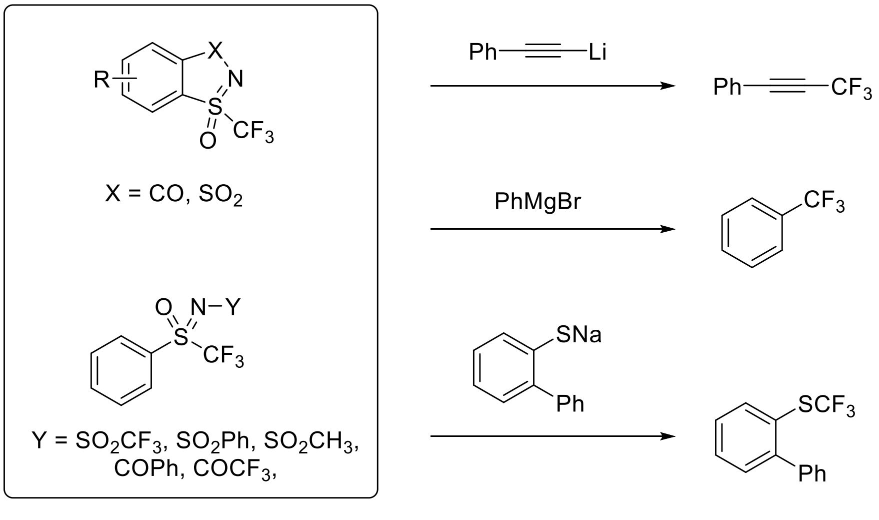
Scheme 1.20 - Synthesis of benzothiophenium salts by Shibata and initial attempts at enantioselective trifluoromethylations.

Sulfoximines, Sulfoximinums & Sulfonium Ylides

The preparation of fluorinated sulfoximines has history back to when Yagupolskii reported his other trifluoromethylating salt reagents in 1984.[116] It was not until 2003 that further progress was made by Magnier and Wakselman. who reported an alkylated version of the trifluoromethyl sulfoximines.[117] That same year, Adachi and Ishihara at Daikin Laboratories patented procedures for a neutral cyclic arylsulfoximine reagent[118] and just two years later, reported the first trifluoromethylation using both the cyclic sulfoximines and derivatives of Yagupolskii's acyclic sulfoximine reagent (Scheme 1.21).[119] These sulfoximine compounds (occasionally referred to as Adachi-type reagents) are reactive towards nucleophiles like Grignard reagents, sodium thiophenolates, and alkynyl lithium with low to moderate success (Scheme 1.22).

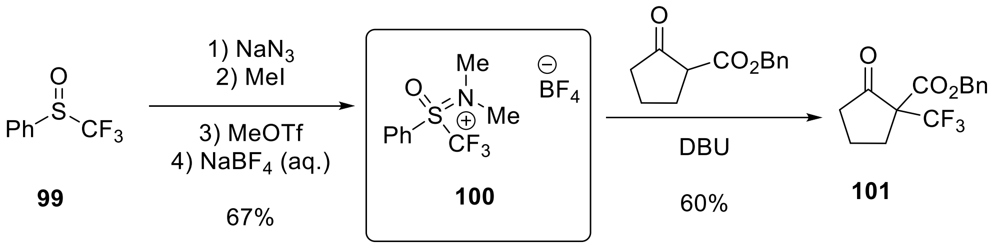


Scheme 1.21 - Synthesis of electrophilic trifluoromethylating sulfoximine (Adachi-type) reagents.



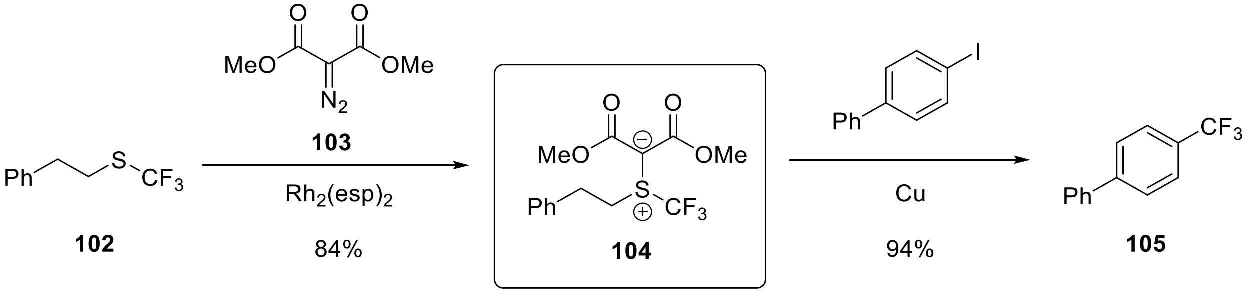
Scheme 1.22 - Applications of electrophilic trifluoromethylating sulfoximine reagents.

In 2008, the Shibata group reported a fluorinated analogue of the Johnson methylene-transfer reagent. This sulfoximinium reagent was synthesized from phenyl trifluoromethyl sulfoxide using sodium azide, then methylation and anion exchange to the desired reagent as a crystalline solid (Scheme 1.23). Similar to the benzothiophenium salts, these fluorinated-Johnson-type reagents could be used to trifluoromethylate carbon-centered nucleophiles like β-ketoesters and dicyanoalkylidenes in moderate to good yields.[120] Unfortunately, further work on scope expansion by the Shibata group proved challenging. Further details on fluorinated sulfoximines can be found in a few independent reviews.[121]



Scheme 1.23 - Synthesis and application of fluorinated Johnson-type (sulfoximiniums) reagents.

The variety of sulfur-based trifluoromethylating reagents continued to grow with the emergence of new trifluoromethylthiolating reagents and methods.[122] A recent addition to this class of compounds came in the form of bench-stable sulfoniums ylides, synthesized from the addition of a Rh-catalyzed carbenoid to a trifluoromethylthioether (Scheme 1.24).[123] Able to be produced on multi-gram scales in high yield, these reagents can be used in the electrophilic trifluoromethylation of β-ketoesters under basic conditions or to trifluoromethylate aryl iodides in a single-electron transfer mechanism mediated by copper via $CuCF_3$.



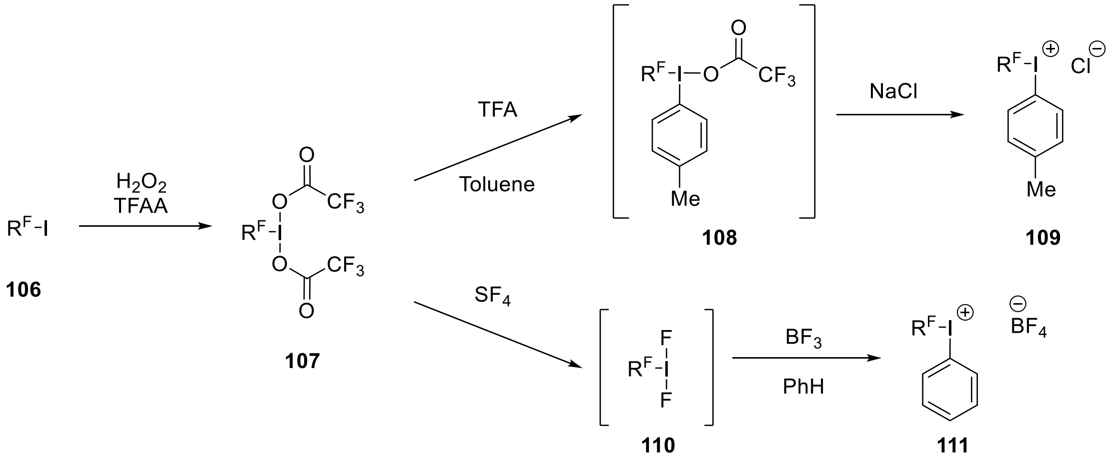
Scheme 1.24 - Synthesis and application of sulfonium ylide reagents
for electrophilic trifluoromethylation.

1.6.3.2 Iodine-based Reagents

Initial Efforts

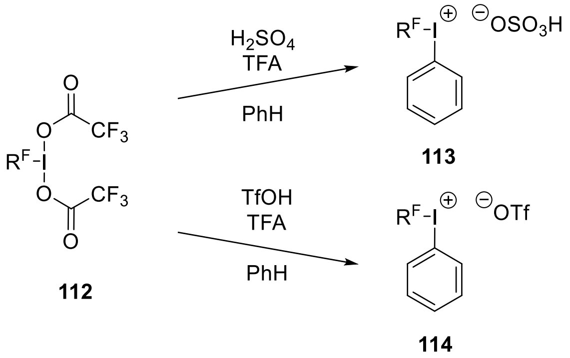
Before the polyvalent chalcogen-based trifluoromethylation reagents were first developed by the Yagupolskii group in 1984, work was conducted on other hypervalent compounds. Yagupolskii first reported perfluoroalkylated hypervalent iodine compounds in Russian literature as early as 1971,[124] and later published the results in English chemistry journals in 1978.[125] These compounds originated from perfluoroalkyliodides, which were oxidized by trifluoroperoxyacetic acid *in situ* to form bis(trifluoroacetoxy)iodoperfluoroalkane compounds. Then by activation with trifluoroacetic acid, these would react with arenes in Friedel-Crafts electrophilic aromatic substitution to afford the perfluoroalkyl-aryliodine trifluoroacetates intermediates. Substitution with a chloride anion would yield the final perfluoroalkylating iodonium reagent (Scheme 1.25).

These reagents were able to be used for electrophilic perfluoroalkylation due to the high withdrawal of electrons from the perfluoroalkyl group. However, in some cases the chloride anion of the iodonium was capable of acting as a nucleophile for the formation of perfluoroalkyl chlorides as by-products.[125] Therefore, synthetic routes towards a non-nucleophilic counterion were attempted and achieved by deoxofluorination of the bis(trifluoroacetoxy)iodoperfluoroalkanes with SF_4 followed by the addition of boron trifluoride with benzene as the solvent. The resulting phenyl perfluoroalkyliodonium tetrafluoroborates had larger separation of charges and were therefore more effective perfluoroalkylating agents than its chloride counterpart.[126]



Scheme 1.25 - Synthesis of perfluoroalkylating reagents by Yagupolskii.

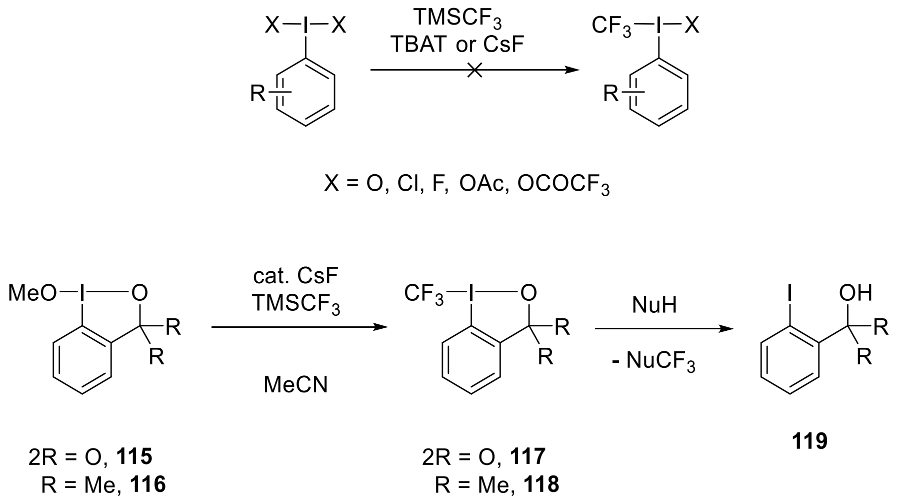
Later on, the bis(trifluoroacetoxy)iodoperfluoroalkanes were further elaborated upon by the Umemoto group using sulfuric acid and triflic acid to introduce different counterions, named as (perfluoroalkyl)phenyliodonium sulfates (FIS) and triflates (FITS reagent) respectively (Scheme 1.26).[127] In contrast to Yagupolskii's perfluoroalkyl aryliodoniums used for the perfluoroalkylation of soft nucleophiles, the FIS- and FITS-type reagents were more reactive and capable of perfluoroalkylation of harder nucleophiles such as Grignard reagents and lithium acetylides.[127a] Noticeably in these early works, the directly trifluoromethylated hypervalent iodine reagents could not be accessed by these methods, arguably due to the incompatibility of the trifluoromethylated intermediate with the harsh conditions necessary for the arene substitution step.



Scheme 1.26 - Synthesis of FIS- and FITS-type perfluoroalkylating reagents by Umemoto.

Togni-type

It was not until more than two decades later that a directly-trifluoromethylated reagent could be synthesized. Since the trifluoromethyl derivative of the earlier bis(trifluoroacetoxy) iodane reagents were moderately stable at low temperatures, initial attempts by the Togni group employed mild conditions towards the synthesis of the trifluoromethylated iodonium salt. In contrast to perfluoroalkyl iodide precursors, hypervalent iodine scaffolds similar to the target product were used, with CF_3-substitution as the final ligand exchange step.[128] Unfortunately, similar results were drawn for the instability of such a compound, and it was postulated additional cyclic structure was necessary. Thus, the incorporation of a benziodoxole framework granted sufficient rigidity and stability, enough for the isolation of the first iodine-based electrophilic trifluoromethylating compound (Scheme 1.27). Starting from 2-iodobenzoic acid, oxidation to the cyclic hydroxy-, acetoxy-, then methoxy-substituted benziodoxolone was followed by installation of the CF_3 moiety in a final umpolung step using $TMSCF_3$.[101] For the alcohol-based reagent, the precursor was a chlorine-substituted dimethylbenziodoxole instead.

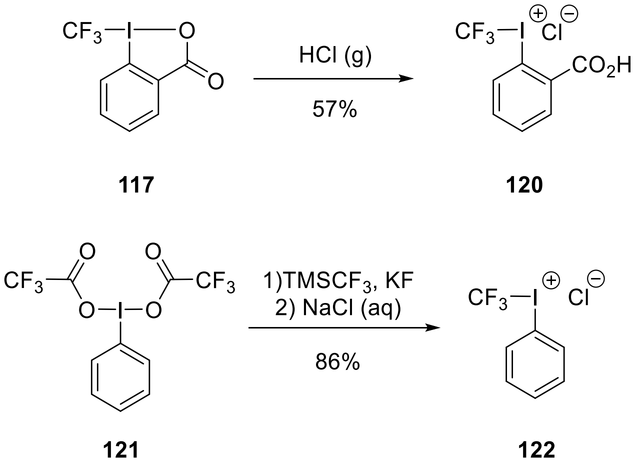


Scheme 1.27 - Top: Initial attempts at synthesizing an iodine-based trifluoromethylating reagent. Bottom: Synthesis and application of Togni-type trifluoromethylating reagents.

The reactivity of the Togni reagents (and all hypervalent iodine compounds) relies on the reduction of the hypervalent iodine atom to a more stable oxidation state such as in 2-iodobenzoic acid or 2-(2-iodophenyl)-propan-2-ol. Although initially applicable mainly to soft sulfur-, phosphorus-, and carbon-centered nucleophiles, further research has found that through proper Lewis or Brønsted acid activation, hard oxygen-, and nitrogen-centered nucleophiles were also suitable substrates for trifluoromethylation. Additional transformations promoted by transition metals include trifluoromethylation of aromatic cores, allylic alkenes, and terminal alkynes, among many others.[129] Further discussion of the Togni-type reagents will be elaborated upon later in this thesis.

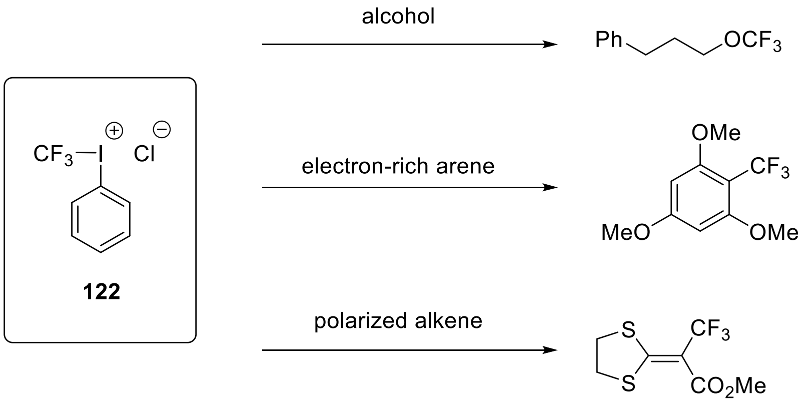
Iodonium Salts

It was recently reported by the Toste group that through the action of HCl gas, CF_3-iodonium salts derived from the conventional Togni reagents could be isolated as crystalline solids, as the first example of a non-cyclic iodine-based reagent (Scheme 1.28, Top). The choice of counterion was the key factor in stability of the resulting compound, with other halides (Br, I) and pseudo-halides (OTf) being ineffective. These salts were able to perform electrophilic trifluoromethylation on an array of hard nucleophiles include azoles, olefins, enolates, and sulfonates.[130] Even more recently, the Wang group demonstrated the first direct preparation of non-cyclic trifluoromethylated iodine-based compounds starting from $PhI(OCOCF_3)_2$ (PIFA).[131] Initial attempts using phenyliodine diacetate (PIDA) resulted only in phenyliodine products, but the product $PhICF_3Cl$ could be prepared by direct ligand-exchange of PIFA using $TMSCF_3$ and NaCl as the source for ligands, ultimately requiring -45 °C temperatures and precise quench procedures for product isolation (Scheme 1.28, Bottom).



Scheme 1.28 - Recent advances in the synthesis of non-cyclic iodine-based electrophilic trifluoromethylating reagents.

The resulting iodonium salt reagent was an air-stable solid with chloride-bridging interactions observed in the formation of a tetramer, and could be synthesized at gram-scale, proving efficient and practical. However, it slowly degraded in organic solvents and the similar $PhICF_3Br$ derivative was even less stable, degrading during storage. These compounds exhibited properties similar to the perfluoroalkylating reagents developed by Yagupolskii and Umemoto, with long I-Cl bonds (~2.828 Å) suggesting similar iodonium character. This endows it enhanced electrophilicity and its strong trifluoromethylating ability enables it to perform catalyst-free CF_3-transfers on a variety of heteroatom- and carbon-centered nucleophiles (Scheme 1.29).



Scheme 1.29 - Applications of the non-cyclic iodine-based electrophilic trifluoromethylating reagents.

Chapter 2: Hypervalent Iodine (HVI)

2.1 Background and Properties

Iodine is the heaviest, least electronegative, and most polarizable of the non-radioactive halogens in the periodic table. Like the other group 17 elements, iodine is most commonly found in organic compounds with an oxidation state of -1. However, its large atomic radius allows more filled orbitals than the other stable halogens which enables it to exist in polyvalent forms with other stable oxidation states ranging from -1 to +7 (Figure 2.1). Known today as hypervalent iodine (HVI) compounds, these reagents have been steadily gaining popularity since the first organic HVI compound $PhICl_2$ was discovered in 1886 by Willgerodt.[132]

Their wide range of reactivity and mild reaction conditions have brought them into the spotlight for the chemistry community, especially in the last three decades. Applications of this broad class of reagents includes oxidative transformations and ligand transfers, often mirroring the reactivity profiles of transition metals. HVI reagents are particularly attractive as they combine the high reactivity typically associated with transition metals together with the lower toxicity and costs of main group elements. The field of hypervalent iodine chemistry continues to grow steadily as the reagents are less hazardous, inexpensive, and have a smaller environmental impact compared to classical reagents.

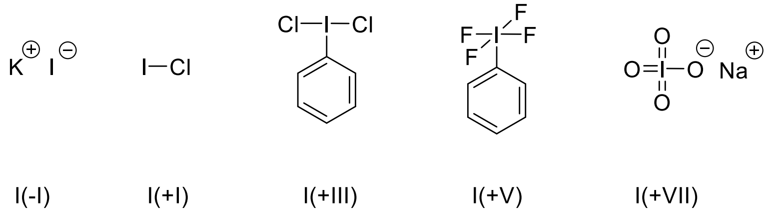


Figure 2.1 - Examples of iodine in its most common oxidation states.

Hypervalent compounds were originally named according to the *N-X-L* notation introduced by the research groups of Martin, Arduengo, and Kochi in 1980,[133] wherein *N* represented the number of electrons around the central atom *X* and *L* represented the number of ligands (e.g. 10-I-3). The naming convention currently most used for hypervalent iodine particularly is the lambda notation established by IUPAC in 1983, wherein the superscript of the lambda represented the iodine atom's oxidation state (e.g. λ^3 and λ^5 for iodine (III) and iodine (V) compounds, respectively) (Figure 2.2).[134] The term hypervalent was first defined by Musher in 1969 as any group 15-18 element that has a valence other than its lowest stable oxidation state.[135] Currently, hypervalency has been formally defined by IUPAC as "the ability of an atom to expand its valence shell beyond the standard Lewis octet rule" (i.e. more than eight electrons).[136] For iodine atoms, this is most commonly observed as the +3 and +5 oxidation states with 10 and 12 electrons, respectively.

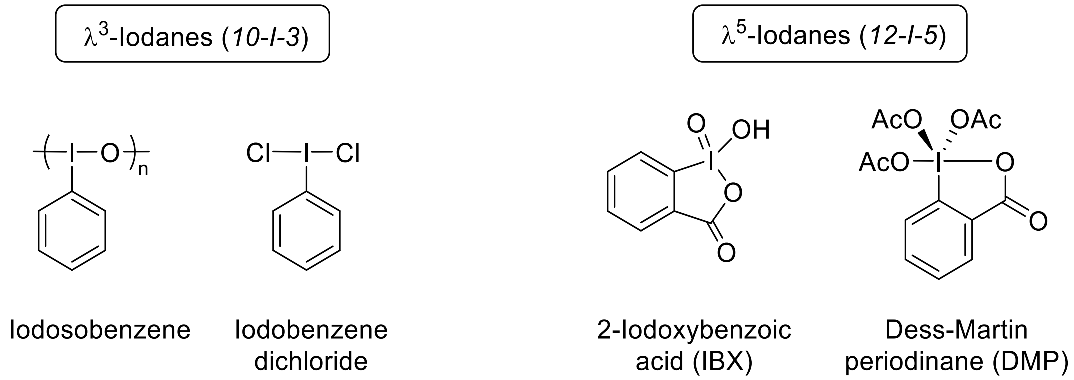


Figure 2.2 - Naming conventions and examples of iodine (III) and iodine (V) compounds.

The occurrence of hypervalency in iodine compounds has a few prevailing theories. The first theory was proposed by Pauling in 1939 before the term hypervalent was even coined. He proposed an expanded octet model with the promotion of electrons into the vacant d-orbitals of iodine to form sp^3d or sp^3d^2 hybrid orbitals with its ligands.[13] However, it was argued that iodine's d-orbitals are often larger and disproportionate, displaying poor orbital overlap with its ligand's smaller s- or p-orbitals.[137] The second theory is the valence bond description proposed by Coulson in 1964 to explain the structures of other hypervalent molecules such as XeF_2. This theory describes a positive central atom and a negatively charged ligand, and the true structure is a combination of all the possible resonance structures, placing formal charges on each atom as the electrons are not equally shared between them (Figure 2.3, Left).[138]

Today, the more widely accepted description for hypervalent molecules like iodine compounds is the 3-centre 4-electron (3c-4e) bond model first proposed by Pimental and Rundel in 1951, based on molecular orbital (MO) theory (Figure 2.3, Right).[139] This description involves the overlap of the filled 5p orbital of iodine with the half-filled orbitals of the two ligands without the involvement of iodine's d-orbitals. There are four electrons are shared across the colinear L-I-L bond, two from iodine and one from each ligand. This positions the electron pairs in one bonding and one non-bonding MO, resulting in a node at the central iodine atom. The theory predicts approximately 0.5 bond order for each I-L bond, giving rise elongated and highly polarized hypervalent bonds where the electron density is localized at the most electronegative atoms placed in the apical positions, leaving the central iodine to be highly electrophilic. In the equatorial positions are two lone pairs and the least electronegative substituent which is most often an aryl group for a stabilizing effect. The overall geometry is thus a distorted trigonal bipyramid, viewed in molecules as a T-shape, as predicted by the valence shell electron pair repulsion (VSEPR) model.[140]

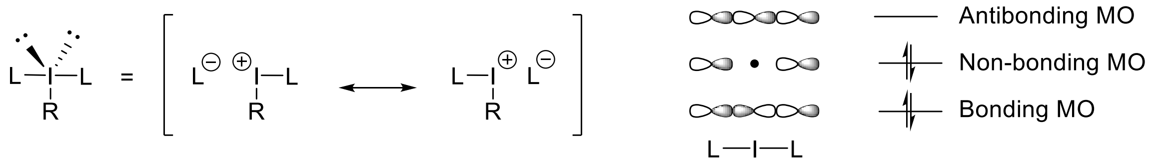
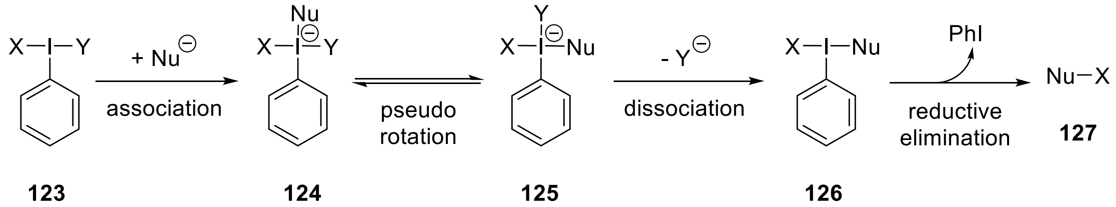


Figure 2.3 - Left: The valence bond description of hypervalent molecules. Right: The molecular orbital diagram of the 3c-4e bond in λ^3-iodanes.

2.2 Reactivity and Applications

Since the reactivity patterns of hypervalent iodine compounds have been described to parallel that of transition metals, terminology such as oxidative addition, ligand exchange, reductive elimination, and ligand coupling is commonly borrowed to discuss HVI chemistry. Reactions are initiated by virtue of the iodine atom's high electrophilicity which induces nucleophilic attack and results in exchange of one of the ligands and the nucleophile. This exchange occurs with cleavage of the hypervalent bond which are generally longer and weaker than normal covalent bonds, mirroring metal-ligand bonds in metal complexes.

For this initial ligand exchange reaction, two mechanistic pathways have been proposed: an associative and a dissociative pathway. In the dissociative pathway, one ligand is eliminated first to form the dicoordinated iodonium ion, which then reacts with the nucleophile to form the substituted iodane. In the associative pathway, the external nucleophile attacks the iodine atom to form a trans square planar species, which then isomerizes to the cis form. This is followed by ligand dissociation to form the substituted iodane. Of the two pathways, the associative pathway is the most accepted due to the fact that the dissociative pathway forms a highly unstable dicoordinated iodonium cation that has not been observed. Conversely, tetracoordinated iodine species have been isolated, giving additional credence to the associative pathway.[141] Thus, the ligand exchange process between the heteroatom ligand and the external nucleophile is widely considered an addition-elimination sequence (Scheme 2.1).[142]

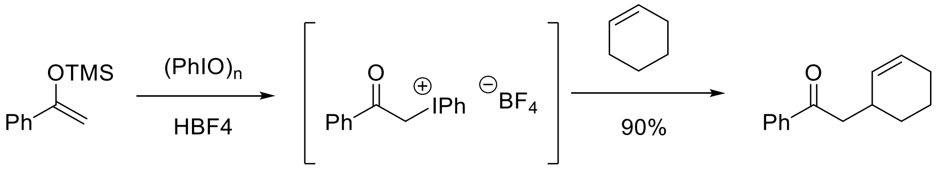


Scheme 2.1 - Ligand exchange and reductive elimination pathways for aryl-λ^3-iodanes.

All processes involving iodanes are thermodynamically driven by the reduction of the hypervalent iodine atom to a lower and more stable oxidation state, described in transition metal chemistry as reductive elimination. For trivalent iodanes, this reduction to monovalent iodine is so thermodynamically favourable that the λ^3-iodanyl group has been described as a hypernucleofuge, with a leaving group ability found to be 10^6 times greater than a triflate group.[143] Reductive elimination is paired with covalent bond formation either between the two iodane ligands or elsewhere on the substrate.

The most commonly used hypervalent iodine compounds are the λ^5- and λ^3-iodanes. Iodine (V) compounds like 2-iodoxybenzoic acid (IBX) and Dess-Martin periodinane (DMP) have uses primarily for mild oxidative processes.[144] Conversely, the iodine (III) compounds are a much more diverse class of reagents with equally diverse applications. While some λ^3-iodanes like (diacetoxyiodo)benzene

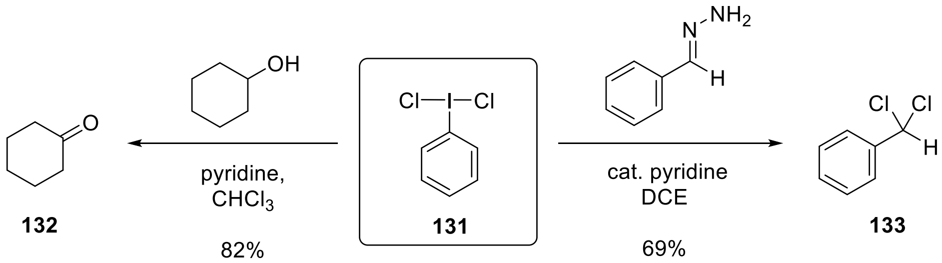
($PhI(OAc)_2$, PIDA) can be used as mild alcoholic oxidants,[145] the extent of the oxidative capabilities of λ^3-iodanes can be displayed in a wide array of reactions ranging from the ring expansions of alcohols[146] to the coupling of carbon nucleophiles (Scheme 2.2).[147] The high nucleofugality of iodanes can be exploited for time-sensitive reactions like radiofluorination[148] and has been used as the driving force for umpolung reactions such as the oxidative dearomatization of phenols.[149]



128 **129** **130**

Scheme 2.2 - Oxidative coupling of carbon nucleophiles using λ^3-iodanes.

The umpolung nature of many iodane reactions may possibly be the most interesting trait of λ^3-iodanes, as they can be used for the oxidative functionalization of organic substrates as formal electrophilic group transfer reagents. This is most commonly performed by acyclic aryl-λ^3-iodanes, which are able to transfer ligands such as phenyl groups,[150] aryl groups,[151] and tosyloxy groups.[152] It may be postulated that whether the ability of an iodane compound to perform mainly an oxidative role or to transfer its ligands pertains to the nature of its ligands. Intriguingly, many of the acyclic λ^3-iodane compounds capable of oxidative reactions also display a capacity for ligand transfer, thus moderate overlap is observed for the type of reactions that any certain type of λ^3-iodane may perform. For example, iodobenzene dichloride ($PhICl_2$) can be used both for oxidative processes such as oxidation of alcohols to ketones,[153] and for transfer of both chlorine ligands[154] (Scheme 2.3).



132 **131** **133**

Scheme 2.3 - Oxidation and ligand transfer reactions using the same iodine (III) reagent.

In contrast, the cyclic iodine (III) compounds are less reactive and instead used chiefly as atom transfer reagents, leaving oxidations mainly to iodine (V) derivatives like DMP and IBX. Cyclic aryl-λ^3-iodane reagents are used under electrophilic or radical conditions to deliver their exocyclic ligand and are able to transfer similar ligands to their non-cyclic counterparts, such as tosyloxy groups[155] and chloronium cations.[156] However, the main attraction of benziodoxoles is the ability to provide rare electrophilic synthons that are otherwise difficult to prepare and isolate, such as alkynyl groups,[157] azido groups,[158] and alkylperoxy groups[159] (Figure 2.4, Left). The electrophilic transfer of classical nucleophilic groups such as these were typically performed *in situ* or by iodonium salts, and the increased stability of the benziodoxole compounds allows harsher conditions to be employed. Some functional groups such trifluoromethyl groups could only be prepared in a cyclic compound until relatively recently,[131] and new electrophilic synthons of groups are regularly reported like carboxylic acids[160] and isocyano groups (Figure 2.4, Right).[161]

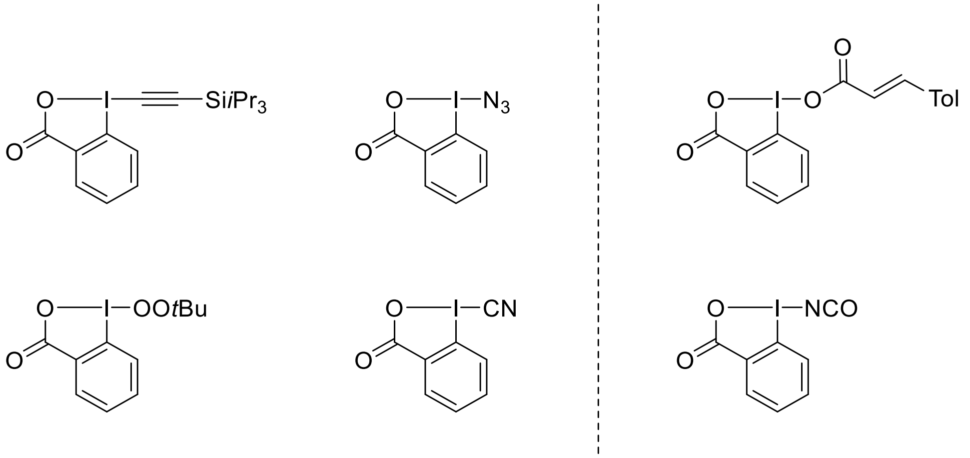
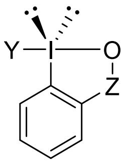


Figure 2.4 - Left: Specific examples of benziodoxoles used for group-transfer reactions. Right: Recently developed benziodoxole reagents.

2.3 Benziodoxoles

Benziodoxoles are the collective group of heterocycles with iodine and oxygen atoms in a five-membered ring fused with a benzene ring. The name "benziodoxolones" is used for benziodoxole rings with a carbonyl substituent, which is common since benziodoxoles are primarily derived from 2-iodobenzoic acid or the corresponding dimethyl or bis(trifluoromethyl) alcohols. While the majority of known heterocyclic iodanes are five-membered heterocycles (including cyclic iodonium salts), examples of four- and six-membered iodine (III) heterocycles are also known. Additionally, iodine-based heterocycles containing other atoms such as nitrogen, boron, sulfur, and phosphorus have been reported,[140] but benziodoxoles are undoubtably the most studied class of cyclic hypervalent iodine compounds and have found significant practical application as synthetic reagents. Accordingly, the chemistry of benziodoxoles and other cyclic iodanes have been reviewed several times in the past couple of decades.[162]

The defining feature of benziodoxoles is the rigid cyclic backbone which confers exceptional stability compared to other hypervalent iodine compounds (Figure 2.5). This stabilization, like that of hypervalent phosphorus and sulfur compounds, is derived from two factors. Firstly, the bridging between the apical and equatorial positions of the hypervalent iodine atom provides an inherent steric hindrance to prevent its premature reduction. Secondly, the benziodoxole ring provides better overlap between the iodine lone pairs and benzene ring p-orbitals.[156] Moreover, in benziodoxoles with gem-dimethyl and bis(trifluoromethyl) substituents, additional stabilization is observed from steric effects (Thorpe-Ingold effect)[163] and from the electron-withdrawing CF_3 groups which stabilize the 3c-4e bond.



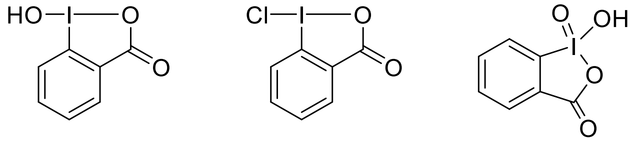
Y = aryl, alkynyl, OH, OAc, Cl, F, CF_3, N_3, etc.

Z = CO, CMe_2, $C(CF_3)_2$

Figure 2.5 - The structure and bonding of benziodoxol(on)es which react as Y^+ equivalents.

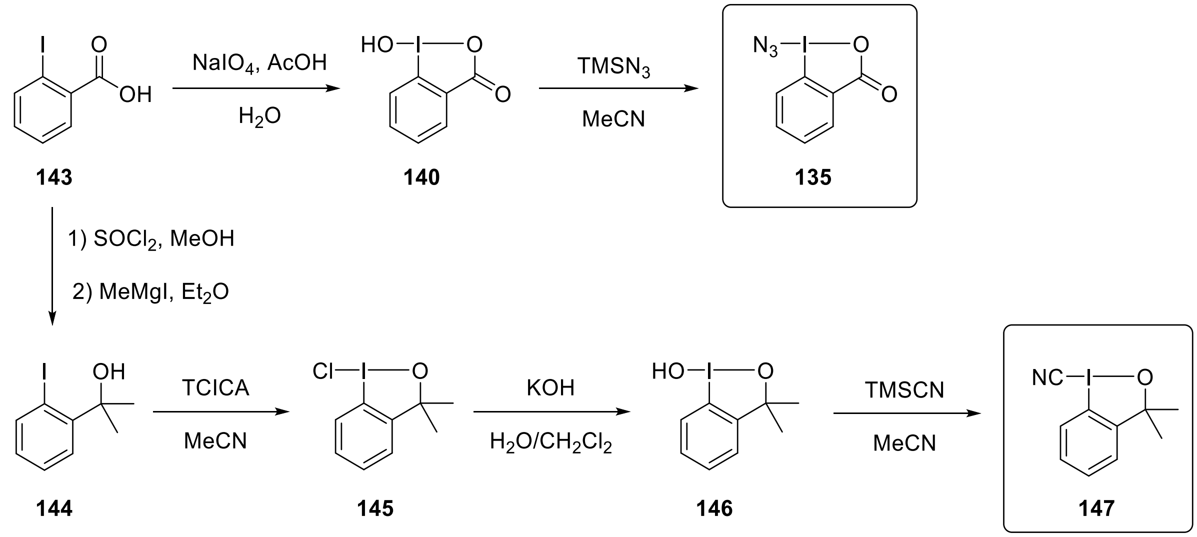
Some common HVI reagents like iodosylbenzene (PhIO), 2-iodoxybenzoic acid (IBX), and iodonium ylides ($PhICX_2$) create polymeric networks through intermolecular bonding and consequently have lower thermal stability, reactivity, and solubility. However, the cyclic ring structure of benziodoxoles innately prevents these secondary interactions and polymeric potential, and thus possess comparably higher thermal stability and solubility. Similar stabilizing effects of the benziodoxole ring can also be observed in the weaker intramolecular coordination of pseudocyclic iodine (III) compounds. This class of iodanes possesses higher thermal stability and better solubility than non-cyclic iodanes as well. They have mainly found synthetic application as effective oxidants and will not be covered, but further detail can be found in this recent review.[164]

The first benziodoxole compounds were reported over 120 years ago, shortly after the synthesis of the first HVI compounds by Willgerodt. Starting from 2-iodobenzoic acid, 1-hydroxy-1,2-benziodoxol-3-(1H)-one and 1-chloro-1,2-benziodoxol-3-(1H)-one could be prepared,[165] with overoxidation generating 2-iodoxybenzoic acid (IBX) (Figure 2.6).[166] The general methods to prepare cyclic aryl-λ^3-iodanes are still currently very similar by starting from commercially available aryl iodides—most often 2-iodobenzoic acid or alcohols derivatized from it. The initial oxidative ring formation also regularly employs either the hydroxy- or chlorobenziodoxole as key intermediates before subsequent derivatization and/or ligand exchange. The substitution of a wide variety of ligands (e.g. F, Cl, OH, AcO, TsO, Br, ethynyl, CF_3) allows the preparation of other reagents (Scheme 2.4). However, hydroxybenziodoxole compounds are occasionally derivatized to the acetoxy- or methoxybenziodoxole forms before ligand exchange. This stems from the fact that upon dehydration, they are prone to form polymeric networks, similar to iodosylbenzoic acid (PhI=O), rendering it difficult to manipulate. In fact, the strong λ^5-benziodoxole oxidant DMP is synthesized by the acetylation of IBX using acetic anhydride and acetic acid for similar reasons.



140 **141** **142**

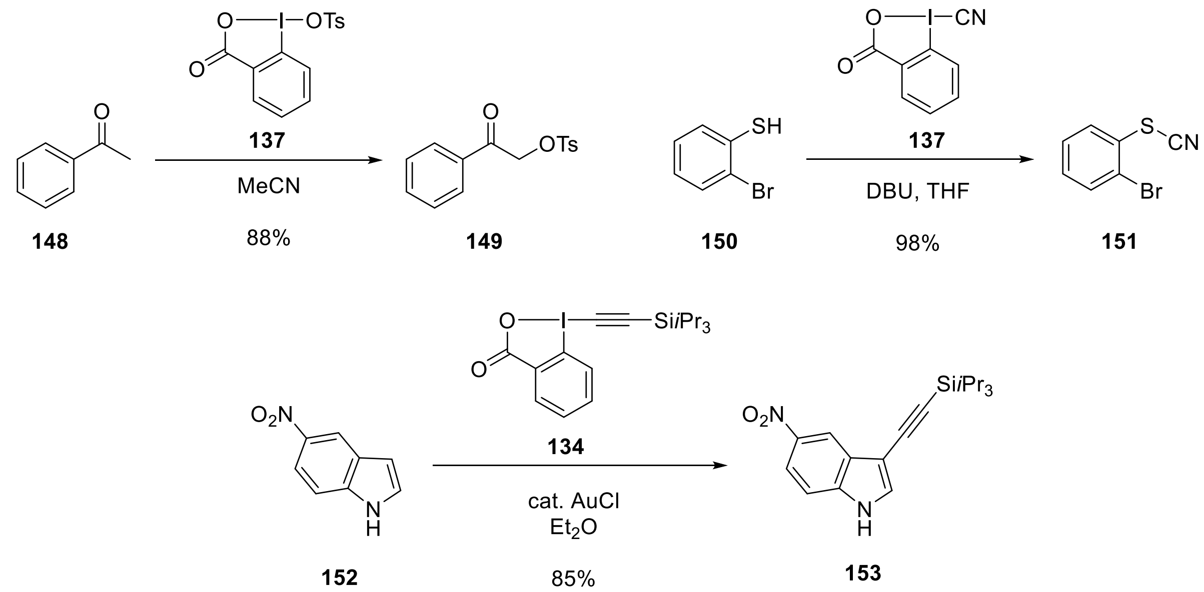
Figure 2.6 - The earliest known synthesized benziodoxole compounds.



Scheme 2.4 - Common synthetic routes for the preparation of benziodoxole compounds. Adapted from ref.[162c]

The development of Dess-Martin periodinane (DMP) in 1983 brought interest to the cyclic HVI compounds as efficient oxidants of alcohols under mild conditions.[167] Hydroxybenziodoxoles also attracted interest in the mid-1980s due to their catalytic activity in the cleavage of reactive esters and toxic phosphates.[168] Starting in the 1990s that the class of benziodoxoles began to grow in size with the advent of ethynyl, azido, and cyano ligands becoming available.[157,169] Despite this growth, applications were scarce and there was little incentive to use these cyclic group-transfer reagents over more popular HVI alternatives like non-cyclic iodonium salts.[170]

However, the seminal publication in 2006 by the Togni group reported the synthesis of the first CF_3-containing hypervalent iodine compound,[101] which brought renewed interest to benziodoxole-derived reagents. Thus, over the past 15 years, there has been a renaissance of cyclic λ^3-iodanes and many older methods to prepare many benziodoxoles have been improved to highly efficient and optimized one-pot procedures.[171] Many benziodoxole compounds were previously difficult to handle or used only for oxidative processes, often requiring external reagent combinations to provide the necessary functional group.[172] As the discovery of new reagents continues to progress, the re-examination of these older benziodoxole reagents yielded new applications in transferring their ligands (Scheme 2.5).[173]

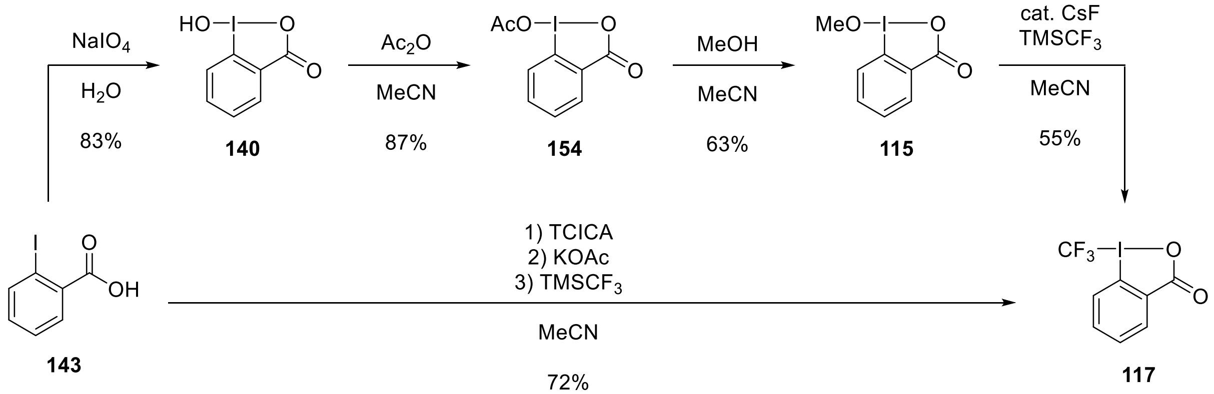


Scheme 2.5 - Recent examples of the applications of benziodoxole-derived reagents.

Since electrophilic trifluoromethylation methods were scarce, the advent of CF_3-benziodoxole compounds by the Togni group brought particular interest to carbon-based ligands and hypervalent iodine chemistry. As mentioned in the previous chapter, perfluoroalkylation methods using HVI compounds were attempted by the Yagupolskii and Umemoto groups in the 1980s.[125,127a] They were successful in synthesizing stable iodonium reagents for transferring most perfluoroalkyl substituents but the trifluoromethyl group alone remained elusive. This was attributed to the weak I-CF_3 bond and when the Togni group initially followed ligand exchange methods on similar iodine (III) scaffolds, their attempts were unsuccessful until they ingeniously incorporated the stabilizing cyclic backbone of a benziodoxole ring. This led to the creation of 3,3-dimethyl-1-trifluoromethyl-1,2-benziodoxole and 1-(trifluoromethyl)-1,2-benziodoxol-3(1H)-one, which are now popularly referred to as Togni reagents. Since then, this new class of reagents has been well explored in its synthetic routes and applications, principally by the Togni group. Discussion of the research behind the compounds and an overview of other historical trifluoromethylation methods are detailed in the various PhD dissertations of the past members of the Togni group.[128,174]

2.4 Togni Reagent

The synthesis of the Togni reagents are not patented and they are available from several commercial suppliers. They can be produced on a large multikilogram scale, which is beneficial for industrial scale production of pharmaceutical compounds. The benziodoxolone Togni reagent is more commonly used in research laboratories due to its simpler synthesis route, which relies on simple and readily available materials. Its one-pot preparation[171a] starts from 2-iodobenzoic acid followed by oxidation and subsequent ligand exchange to the chlorobenziodoxole, performed by trichloroisocyanuric acid (TCICA) as an inexpensive oxidant and source of Cl^+. The subsequent ligand exchange uses potassium acetate (KOAc) and the final step for the umpolung of the trifluoromethyl anion is performed using Ruppert-Prakash reagent ($TMSCF_3$) (Scheme 2.6, Top). Also starting from 2-iodobenzoic acid, the dimethyl alcohol derivative is accessed by esterification then subsequent addition of methylmagnesium iodide (MeMgI). The chloro- and acetoxybenziodoxole compounds are used as intermediates in this preparation as well, before the final trifluoromethylation using $TMSCF_3$. The advantages and scalability of these highly revised synthesis routes stems from using TCICA and KOAc, allowing ease of purification by the simple filtration of their by-products even on a large scale. In addition, safer and simpler reagents could be used to avoid hazardous or expensive reagents such as tert-butyl hypochlorite (tBuOCl), silver acetate (AgOAc), and sodium periodate ($NaIO_4$) that are more difficult to handle. The previous routes leading up to these optimized procedures are described in the comprehensive review of the Togni-type reagents by the eponymous group.[129]

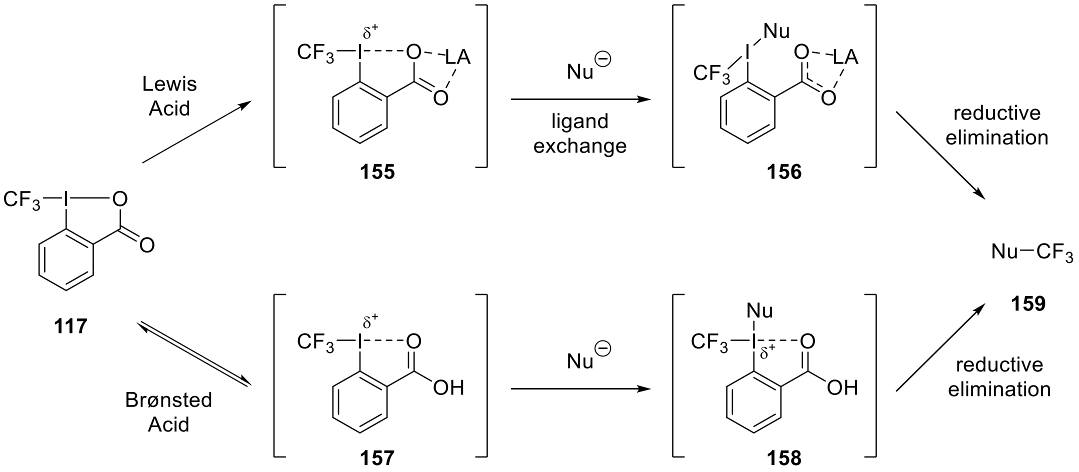


Scheme 2.6 - The original synthesis route (Top) compared to the most recent one-pot procedure (Bottom) for the synthesis of the benziodoxolone Togni reagent. Adapted from ref.[129]

The Togni reagents are both air-stable crystalline solids and non-explosive under typical laboratory and reaction conditions. Like other HVI compounds, they are energetic molecules and decompose exothermally when heated to elevated temperatures. Some samples seemed to be impact sensitive similar to other benziodoxole compounds[175] and the dimethyl compound was found to have a shock sensitivity similar to TNT.[176] However, the sensitivity of the reagents is likely overstated and differences amongst reports are attributed to the amount and nature of impurities contained between samples. It was noted by the Togni group that up to 2015, no incidents involving the Togni-type reagents had been reported even when synthesized and applied on large scales by both undergraduate students and experienced chemists in academic and industrial settings.[129]

Similar to other λ^3-iodanes, the compounds hold a t-shape geometry emerging from the pseudotrigonal-bipyramidal geometry as predicted by VSEPR theory but are distorted due to the iodine lone pairs and benziodoxole ring. The torsion angles are close to 0°, signifying a mostly planar molecule, while the dimethyl compound shows an expected twisting out of the plane. In the benziodoxolone derivative, the observed bond angle for the hypervalent CF_3-I-O bond is 170.43° and the other bond angles between the apical and equatorial positions are 93.74° and 76.79°, all deviating from the expected 180° or 90° angles. The I-O bond length is 2.283 Å—well between the expected range of 2.11 Å and 2.48 Å for benziodoxolones—and indicates considerable changes in the ionic character of this bond. Longer I-O bonds are concomitant with a shorter and stronger I-CF_3 bond but nevertheless the trifluoromethyl groups are strongly electron-poor, as indicated by the high ^{19}F NMR chemical shifts of the compounds (-33.8 and -40.1 ppm) when compared to classic organic CF_3 moieties (generally between -50 and -70 ppm).

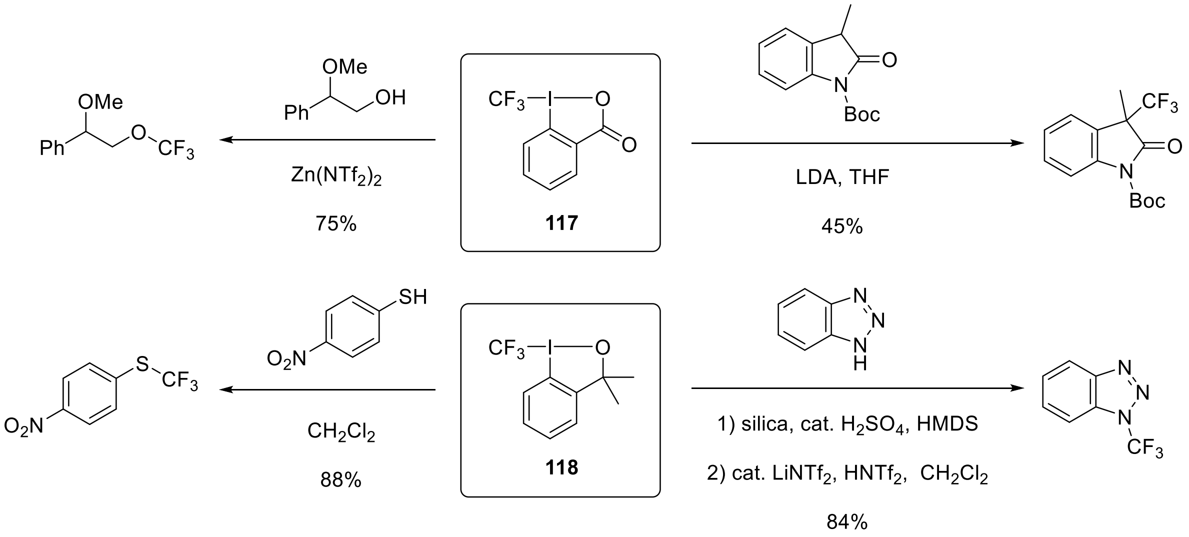
The Togni reagents are able to react directly with nucleophiles, although it is not uncommon for reactions to require an auxiliary to proceed adequately, such as Brønsted or Lewis acid. Although it was initially speculated that an iodonium intermediate was formed as the reactive species, it was found that activation of the molecule weakens the I-O bond to promote the release of the CF_3 unit. In both the activations by Brønsted acid[177] and by Lewis acid,[178] it was found that protonation or complexation by the acid lengthens the I-O bond, vacating a coordination site on iodine to be taken by the substrate whereupon reductive elimination forms the trifluoromethylated product as the rate-determining step (Scheme 2.7). Incidentally, protonation of Togni reagent using HCl was the method used recently to isolate the first CF_3-containing iodonium salt.[130]



Scheme 2.7 - Proposed mechanisms for the Lewis/Brønsted acid activation of Togni reagents.

For copper-catalyzed reactions, coordination to the carboxylate group is unlikely as copper has a poor affinity for it. Weak secondary bonding, like those observed in pseudocyclic iodanes, and mere elongation of the I-O bond is more likely. Many reports have suggested radical or single electron transfer (SET) mechanisms as well. Unfortunately, mechanistic studies are sparse and often claim the addition of the radical scavenger TEMPO ((2,2,6,6-Tetramethylpiperidin-1-yl)oxyl) halting product formation as confirmation, yet the Togni group has reported rather that the trifluoromethylation of TEMPO as a competing reaction.[179] In any case, the mechanisms involving the Togni reagents are likely highly dependent on the reagents and reaction conditions.

The Togni reagents are used as formally electrophilic reagents for the transfer of the CF_3 group to nucleophiles like heteroatoms and carbon atoms. The abundance of transformations described in the review by the Togni group has made clear the scope of applications possible.[129] This class of reagents is regularly iterated upon with considerable amounts of unexplored prospects, but below is a brief overview of the territory covered so far. Sulfur-centered nucleophiles were among the first to be studied and trifluoromethylation was effective on alkyl and aromatic compounds (Scheme 2.8).[180] The lack of interference with other functional groups such as amines, alcohols, and alkynes indicated possible application in late-stage synthesis. Bis- and monotrifluoromethylation of primary and secondary phosphines has also been explored[181] with some applications of the chiral phosphines as ligands for asymmetric catalysis.[182] Trifluoromethylation of oxygen and nitrogen atoms are more difficult to perform and are typically formed under harsh conditions or functional group interconversions.[114] The use of Lewis acids are necessary for the efficient direct trifluoromethylation of alcohols[178] and N-heterocycles.[183] Arguably, the most important targets are carbon-centered nucleophiles for C-C bond formation, which were also among the first compounds to be tested using the Togni reagents.[180] Amongst the various applications are the trifluoromethylation of aryl, heteroaryl, enolate, terminal alkyne, and vinylic compounds. Stereoselective methods have also been examined in combination with the chiral auxiliaries of imidazolidinones[184] and Evans-type acyloxazolidinones.[185]



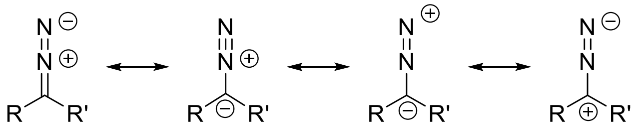
Scheme 2.8 - Application of the Togni reagents on various types of nucleophiles.

Chapter 3: Aryl(trifluoromethyl)diazomethane Compounds

3.1 History and Properties of Diazo Compounds

Diazo groups are an organic functionality consisting of two terminally linked nitrogen atoms. When bound to a carbon atom, they are charge neutral compounds referred to as diazoalkanes ($R_1R_2C=N_2$), not to be confused with azo compounds (R-N=N-R) and diazonium compounds ($R-N_2^+$). These compounds display a broad range of reactivity and are versatile functionalities that are useful in organic synthesis. Diazo compounds have a deep and rich history starting over 150 years when Peter Griess synthesized the first diazo compound.[186] Interest has since grown substantially upon the advent of the diazo reagents ethyl diazoacetate (EDA) and diazomethane (CH_2N_2) in 1883 and 1894, respectively.[187]

Diazoalkanes have an open linear structure and can be distinguished from their cyclic valence isomers (diazirines) by colour and reactivity—diazirines are mostly colourless and less reactive while most diazoalkanes are intensely yellow to red and highly reactive. When considering the resonance structures of diazo compounds (Figure 3.1), their ambiphilic nature is revealed by the nucleophilic carbon atom and electrophilic terminal nitrogen atom. In addition, substitution of the carbon atom renders diazoalkanes electrophilic due to the possible leaving group of dinitrogen and this expulsion of nitrogen gas (N_2) explains their high reactivity. Due to this, diazoalkanes are broadly considered to be explosive and thus, diazo compounds often contain stabilizing groups to render them less reactive and safer.



160 **161** **162** **163**

Figure 3.1 - The resonance structures of diazo compounds.

The stability of diazo groups increases with the number of electron-withdrawing groups (EWG) (Figure 3.2, Left) such as carbonyl groups, or aromatic substituents, which increases thermal stability through the electronic interaction between the aromatic π-system and the diazo group. With sufficient conjugation, the dipole moment of molecules such as diazomalononitrile (**164**) can begin to resemble diazonium compounds (**165**) rather than diazo compounds (Figure 3.2, Right).[188] This increase in stability is illustrated in ethyl diazoacetate where the inclusion of a carbonyl moiety provides it thermal stability below 120 °C and at room temperature it does not decompose upon treatment of glacial acetic acid.[189] Compounds like (trimethylsilyl)diazomethane ($Me_3SiCH{=}N_2$) are also more thermally stable than diazomethane for similar reasons and can be used as substitutes in many applications. Despite this, the potential safety risk is certainly one of the reasons for the scarcity of commercially available diazo compounds. In addition, reactions involving diazo compounds are generally performed with appropriate precautions such as submolar reaction scale and the use of glass vessels without ground-glass joints or rough surfaces. For industrial scale processes, the risk of diazo compounds is reduced by their in-situ generation and consumption to minimize the quantity of reagents like diazomethane or EDA in solution at any one time.[190]

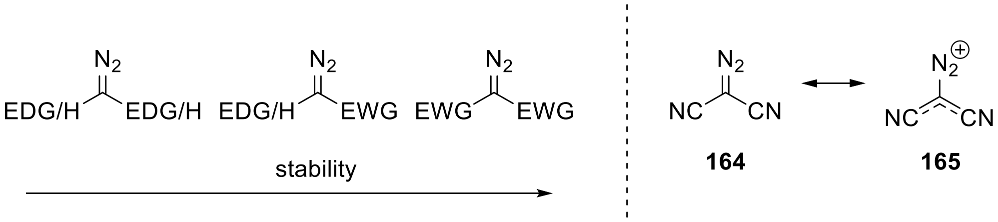
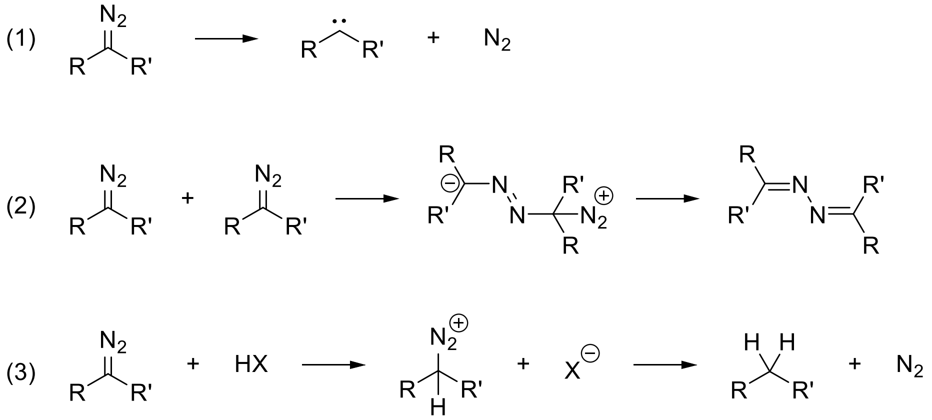


Figure 3.2 - Left: The stability trend of diazo compounds.
Right: The diazonium-like nature of diazomalononitrile.

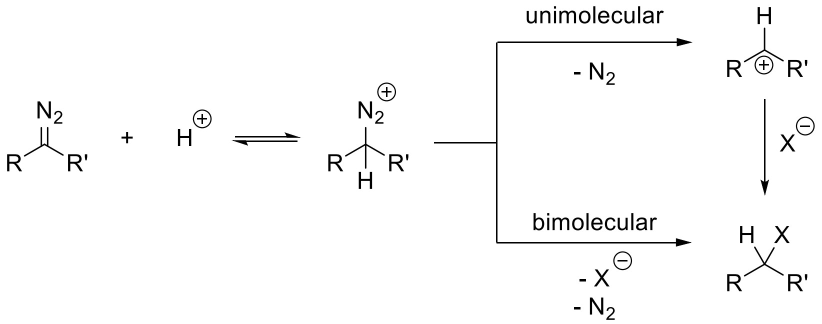
The broad reactivity of diazo compounds has been known since the discovery of the Wolff rearrangement in the early 20th century.[191] Since then, diazo compounds have been observed to act as 1,3-dipoles in cycloadditions, as nucleophiles in reactions like the Buchner-Curtius-Schlotterbeck reaction, and most prominently as carbene precursors for a large array of reactions. Nowadays, transition-metal-catalyzed reactions are of particular interest due to the high degrees of stereo-, regio-, and chemoselectivity possible. The distribution of various products from the reactions involving diazo compounds can provide insight towards their mechanistic pathways and signal the effects of solvents or other reaction partners. In principle, the decomposition of alkyl- and aryl-substituted diazomethanes occurs by one of three pathways (Scheme 3.1): (1) unimolecular decomposition leading to a carbene and dinitrogen; (2) bimolecular decomposition leading to azines; and (3) reaction with solvent or suitable reagents and subsequent nitrogen cleavage.



Scheme 3.1 - General decomposition pathways of diazo compounds.

In the acid-catalyzed decomposition of diazoalkanes, the protonation of the diazo compounds is considered the first step and decreasing the basicity of the azomethine carbon by inclusion of inductively-withdrawing or mesomeric substituents decreases the rate of decomposition. In addition to the inherent structural effects of diazoalkanes, the influence of solvents and acidity must also be considered. The rate of hydrolysis of acid-sensitive diazoalkanes can be decreased by minimizing the concentration of protons in solution, although even in basic solutions this possibility cannot be entirely suppressed.[192] Interestingly, the interaction of diazoalkanes with certain alcohols or phenols does not necessarily lead to decomposition, but instead the diazoalkane merely acts as a basic catalyst for the addition of the alcohol to other electrophiles.[193]

Additionally, the nature of the solvent can have significant effects on the kinetics and mechanism of the acid-catalyzed decomposition of diazo compounds. While protonation of the diazo carbon to form a diazonium ion is always the first step, there are three possible rate-determining steps (Scheme 3.2). The rate of decomposition of the diazonium ion versus its deprotonation is determined by the nature of the substituents and the stability of the carbenium ion intermediate. For aryldiazoacetates and (aryldiazomethyl)phosphonates, decomposition of the diazonium ion is quick and thus the protonation step occurs the slowest. To distinguish between the rate-determining pathways, one can also compare between specific acid catalysis (i.e. H_3O^+ ions or protonated solvent ions (lyonium ions)) and general acid catalysis (undissociated acids and lyonium ions as the catalyst).



Scheme 3.2 - Mechanistic pathways for the acid-catalyzed decomposition of diazo compounds.

3.2 General Synthesis of Diazo Compounds

There is a wide assortment of synthetic methods for the preparation of aliphatic diazo compounds. Aside from some unique methods, there are three major routes (Figure 3.3):[188,194] (1) compounds with one nitrogen-containing functional group are condensed with another nitrogen-containing reagent; (2) the diazo group is transferred to a suitable carbon atom from a donor compound; and (3) compounds with two nitrogen atoms are converted to diazo compounds. The very first procedure by Griess in 1858 in synthesizing diazo compounds was in fact an amine diazotization of aminonitrophenol compounds.[186] For α-acceptor-substituted primary aliphatic amines, reaction with nitrous acid, aqueous sodium nitrite, or a similar reagent produces the desired diazo group. This approach is still the method of choice for the production of ethyl diazoacetate from glycine ethyl ester. A similar reaction is the Forster reaction in which ketoximes are diazotized upon reaction with chloramine (Scheme 3.3, Top).[195]

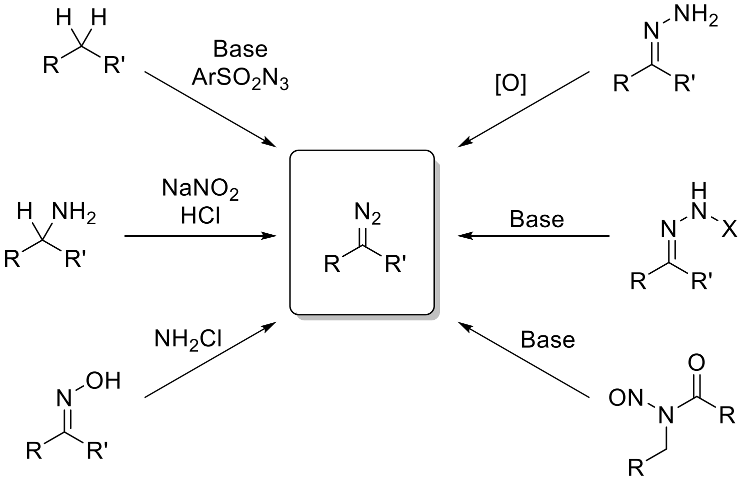
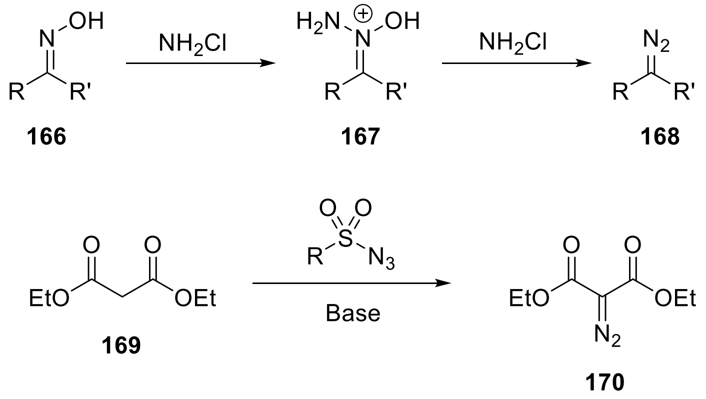


Figure 3.3 - Several synthetic routes towards diazo compounds.

The most popular method for synthesizing diazo compounds is the diazo group transfer, where an intact N_2 group is transferred by a donor to an acceptor either by exchange or addition (Scheme 3.3, Bottom). First described by Dimroth in 1910,[196] this method was popularized in the 1960s by Regitz and his collaborators upon their extensive studies and is now the main method for synthesizing diazocarbonyl compounds.[188,197] For active methylene compounds, multiple adjacent carbonyl groups are ideal for smooth diazo group transfer. In cases with compounds containing only one carbonyl group, the deformylative variant of the Regitz diazo transfer can be used instead, where a second carbonyl functionality is installed temporarily to aid in the diazo transfer, before it is removed again.[198] Diazo group transfer reagents consist mainly of sulfonyl azides, with tosyl azide being the most commonly used.[197a] In terms of azides used for diazo transfer, it was been established that reagents with larger amounts of steric bulk have increased thermal stability, and thus increased ease of handling and safety.[199] As such, reagents such as *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) have become commercially available and are advantageous for their safety and ease of product separation.[200]

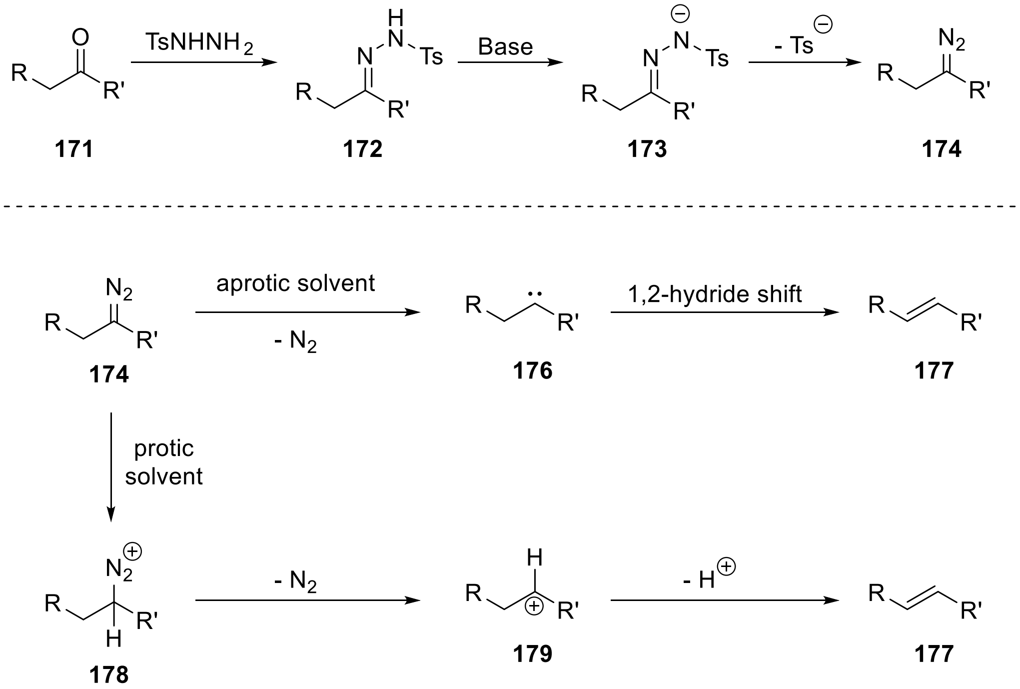


Scheme 3.3 - Top: The Forster reaction of ketoximes using chloramine. Bottom: Diazo group transfer using sulfonyl azides.

3.3 Hydrazones and the Bamford-Stevens Reaction

The dehydrogenation of hydrazones is one of the oldest methods for preparing diazo compounds.[201] Historically, the synthesis of diazo compounds by dehydrogenation was performed by heavy-metal-based oxidizing reagents such as silver (I) oxide, manganese dioxide, and lead (IV) acetate.[202] More recently, chlorodimethylsulfonium chloride (Swern reagent) and hypervalent iodine reagents ($PhI(OAc)_2$,$TolIF_2$, iodosobenzene, and IBX) have been reported as safer metal-free alternatives.[203] The main advantage of this dehydrogenation method is the facile synthesis of hydrazones from the addition of hydrazine (H_2NNH_2) to a carbonyl compound and heating in a suitable solvent whereupon precipitation of the hydrazone compound occurs upon cooling.

Adjacent to hydrazone dehydrogenation, another versatile method for the conversion of carbonyl compounds to diazo compounds is the Bamford-Stevens reaction. This was first reported in 1952 by Bamford and Stevens for the conversion of carbonyl compounds towards alkenes through an intermediate tosylhydrazone generated from tosyl hydrazide and aldehydes or ketones (Scheme 3.4).[204] Under basic conditions, the *p*-tolyl sulfonyl group is cleaved to form diazoalkanes which thermally decompose to alkenes upon loss of dinitrogen and removal of the α-proton. In substrates without an α-proton, this thermal elimination cannot occur, and the diazo intermediate can react *in situ* or be isolated.



Scheme 3.4 - Top: Formation and decomposition of tosylhydrazones to diazo compounds. Bottom: Decomposition of the diazoalkane depending on the solvent.

The Bamford-Stevens reaction also tolerates the alkaline cleavage of other substituted hydrazones such as methylsulfinyl- and 2-nitrophenylsulfenyl hydrazones.[205] The use of other *N*-substitutions may sometimes be advantageous as the cleavage of groups such as 2,4,6-triisopropylbenzene sulfonyl (trisyl) groups are faster than that of the standard tosyl groups.[206] Alternatively, the use of silyl-substituted hydrazones for diazoalkane formation has also been reported using (difluoroiodo)benzene for the oxidation.[203b,207] Some stable diazoalkanes are easily accessible through the Bamford-Stevens reaction, when difficult to attain otherwise (Figure 3.4). For example, the base-induced reaction of α-diketone tosylhydrazones to form α-diazocarbonyl compounds can take place at room temperature.[208] Additionally, thermally stable diazo compounds such as α-diazophosphonates, α-diazophosphinates,[209] and even silyl- and germyl-substituted diazoalkanes can be generated through the Bamford-Stevens reaction.[210]

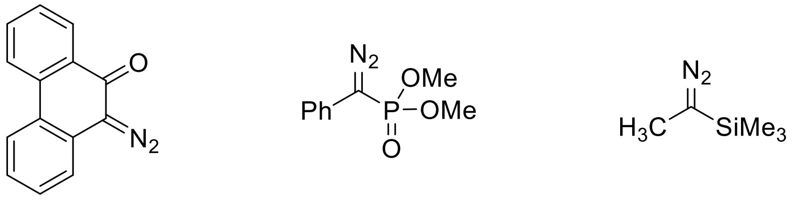
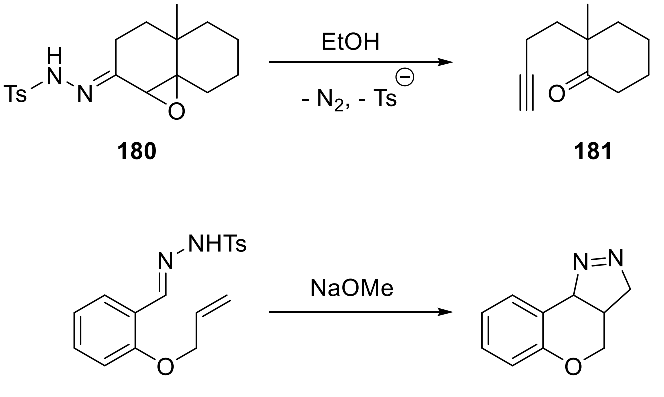


Figure 3.4 - Examples of stable diazo compounds formed by the Bamford-Stevens reaction.

In contrast, diazo compounds without electron-withdrawing groups, such as alkyl-substituted diazoalkanes, are generally unstable under the conditions of the Bamford-Stevens reaction even in aprotic solvents. The elevated temperatures required for diazotization of the tosylhydrazones is naturally disadvantageous for these thermolabile diazo compounds which may be isolated only in trace amounts.[211] Thus, protocols to form unstabilized diazo compounds have been developed for the Bamford-Stevens reaction. These techniques call for the *in situ* generation of the diazo group from tosylhydrazones and are used to make metallocarbenes for reactions like insertions and cyclopropanations. In particular, an array of Pd-catalyzed cross-coupling reactions starting from tosylhydrazones in this manner has been developed.[212] This has emerged as an advantageous alternative to typical cross-coupling using partners like triflates, due to the easy formation and handling of the bench-stable tosylhydrazones. These reactions act as a complement to the widely used Shapiro reaction[213] in allowing coupling with other functionalities such as aryl, vinyl, and alkynyl groups.

There are many other reactions that may occur from tosylhydrazones and the Bamford-Stevens reaction. Due to the elevated temperatures often employed, the formation of carbenes and carbenium ions can take place. For example, *N*-alkylation of the starting hydrazone is possible through the carbenium ion formed by the protonation of the formed diazoalkane.[214] Another observed reaction is the Eschenmoser fragmentation of α-β-epoxyketone tosylhydrazones which form carbonyl compounds and alkynes upon the release of the nitrogen gas and toluene sulfinate (Scheme 3.5).[215] The diazo functionality formed by the Bamford-Stevens reaction is also highly reactive and may perform intramolecular cycloadditions or cyclizations in the presence of alkenes and α-imino groups.[216] Additionally, for α,β-unsaturated tosylhydrazones, preparation of the respective diazo compound is limited because formation of the vinyldiazoalkane may produce cyclopropenes and 3*H*-pyrazoles.[217]

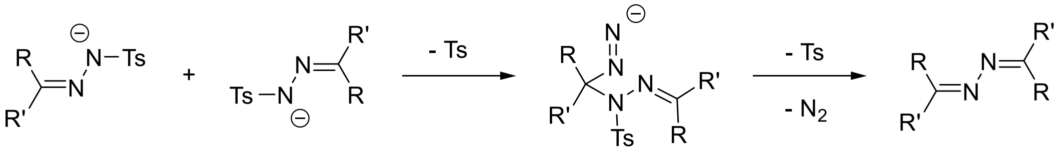


180 **181**

182 **183**

Scheme 3.5 - Other reactions from the base-induced cleavage of tosylhydrazones.

Two secondary competing reactions observed during the Bamford-Stevens reaction of tosylhydrazones are also observed during the dehydrogenation of non-substituted hydrazones and produce similar side products. One of these reaction pathways is the formation of azines by the coupling of two tosylhydrazone anions (Scheme 3.6).[218] The other is the decomposition of α-diketone bis(tosylhydrazones) to produce acetylenes, during which 1,5-cyclization to 1*H*-1,2,3-triazoles is also possible.[204]



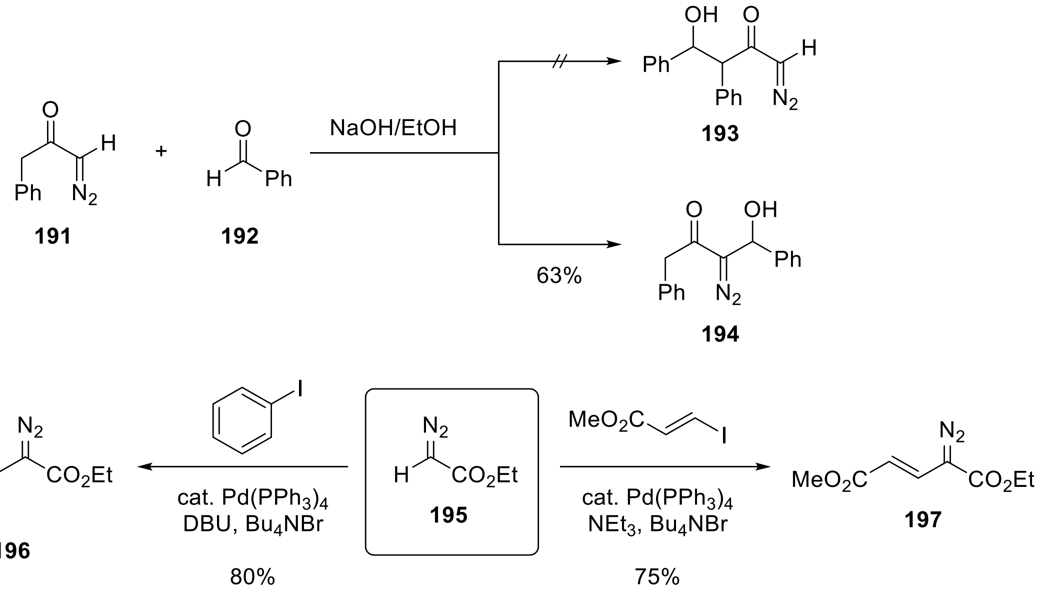
184 **185** **186** **187**

Scheme 3.6 - Secondary reactions of tosylhydrazones.

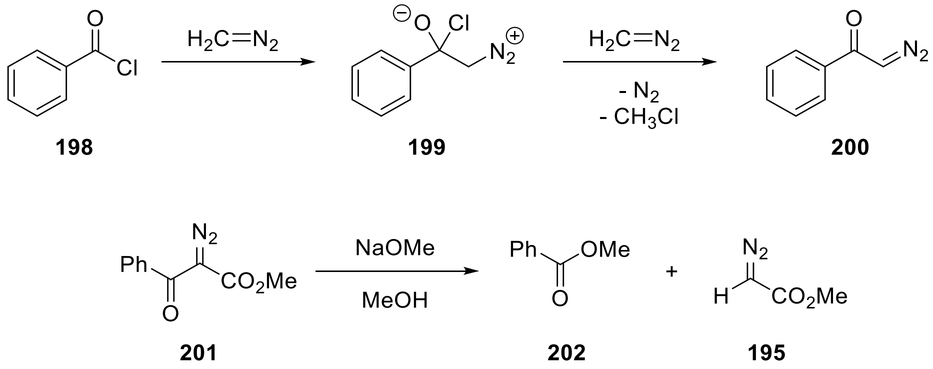
Due to the high reactivity of diazo groups, they are often introduced towards the end of targeted syntheses. However, there are also methods to perform manipulations after a diazo function has been installed while keeping intact the diazo group. Many of these procedures employ the nucleophilic nature of the azomethine carbon along with a removable substituent, for example a proton in diazomethyl compounds or an acyl group in disubstituted diazoalkanes. In many cases, this requires substituents such as a carbonyl or phosphoryl group to assist in stabilizing newly formed negative charges. In any case, diazo groups prove remarkably stable in these types of reactions which are important for creating synthetically useful diazoalkane reagents. In these processes, the diazoalkanes react as the nucleophile and reactions are fittingly referred to as electrophilic diazoalkane substitutions. The earliest methods date back over 90 years ago,[219] which now include metalation, transmetalation, alkylation, acylation, and other substitutions.[220] Despite this early history, the chemical modification of diazo compounds is mostly limited to stable diazomethane and diazocarbonyl compounds.

Metalation is the earliest known method for preparing diazo compounds for functionalization, ever since the mercuration of diazoacetates was discovered to form bis(ethyl diazoacetate) mercury.[219] Hydrogen/lithium exchange can also be performed on diazomethane using reagents such as methyl- or phenyl lithium.[221] These procedures require temperatures as low as -110 °C, as compounds such as ethyl lithiodiazoacetate decompose at temperatures higher than -50 °C due to their high CH-acidity. Examples using other metals are known but are rarely used nowadays considering more popular and robust methods for substitution. These mercury- and lithium-substituted diazo compounds can be used for alkylation of the azomethine carbon by electrophiles such as allyl cations and stable aromatic cations.

Alternatively, other possible reactions using diazoalkanes are alkylations of C=O, C=N, and C=C bonds. In these reactions, diazo carbons are added to the most electrophilic center of the double bond where the proton acidity of the diazomethyl hydrogens are known to be the driving force in these reactions. Towards aldehydes and ketones, aldol-like additions can be performed, even outperforming theoretically possible aldol reactions in some cases (Scheme 3.7, Top).[222] Furthermore, while aldol-type C-C couplings were traditionally used for electrophilic substitution at the diazo carbon atom, transition-metal-catalyzed C-C coupling chemistry has also emerged recently as a method for forming bonds with aryl and vinyl groups to construct more diverse diazoacetate derivatives (Scheme 3.7, Bottom).[223] Acylation reactions are also prominent in forming diazoketones and the most established method in this category is the Arndt-Eistert reaction (Scheme 3.8).[224] Diazomethane is most frequently used compound for this reaction and it is the method by which many diazocarbonyl compounds are formed. Conversely, α-diazo-β-dicarbonyl compounds are known to undergo acyl cleavage under alkaline conditions.[225]

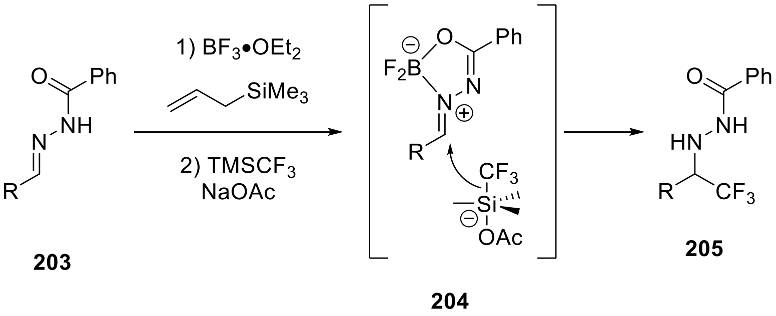


Scheme 3.7 – Top: Aldol-type additions using diazocarbonyl compounds. Bottom: palladium-catalyzed cross-coupling of ethyl diazoacetate.



Scheme 3.8 – Top: Acylation of diazomethane. Bottom: acyl cleavage of dicarbonyl-substituted diazo compounds.

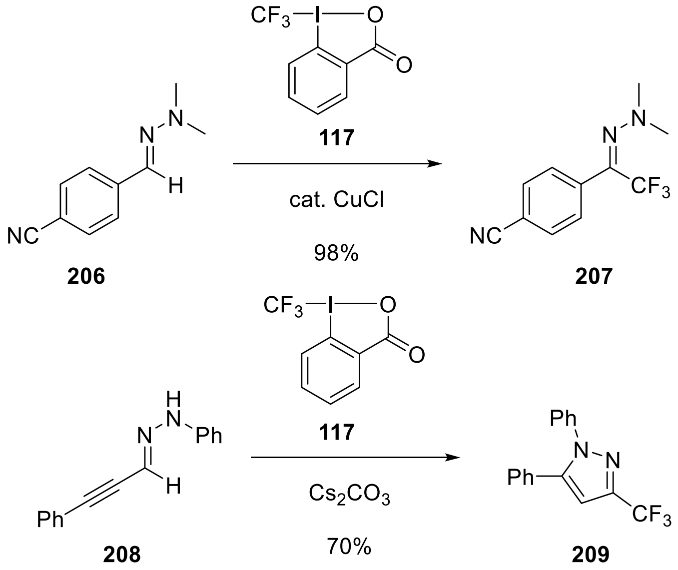
However, in these methods for diazo substitution, there is an absence of methods for trifluoromethylation at the azomethine carbon.[226] Since hydrazones and their substituted derivatives are efficient precursors to diazo compounds, a conceivable route towards the synthesis of trifluoromethylated diazo compounds would be the introduction of the trifluoromethyl functionality to hydrazone compounds prior to formation of the diazo group. The trifluoromethylation of hydrazones has seen interest mainly for the production of trifluoromethyl ketones as versatile synthetic building blocks for fluorinated molecules. As derivatives of carbonyl compounds, trifluoromethylation of nitrogen derivatives such as hydrazones and imines are seen as an alternative pathway to trifluoromethyl ketones, which they can form upon acidic hydrolysis. Accordingly, like conventional methods towards aldehydes, nucleophilic sources of CF_3 such as $TMSCF_3$ were used in the earliest attempts for the trifluoromethylation of hydrazones. However, due to the low electrophilicity of the azomethine fragment, methods were effective only for substrates that could be activated for increased electrophilicity, such as acyl-substituted hydrazones[227] and salicylaldehyde-derived hydrazones (Scheme 3.9).[228]



Scheme 3.9 - Lewis acid-activation of hydrazones for nucleophilic trifluoromethylation.

Since hydrazone compounds contain an electron-donating amino component, the azomethine carbon is activated towards electrophilic reagents, mainly acting as an umpolung carbonyl surrogates instead.[229] In this direction, the Togni reagent has seen considerable use as a formal electrophilic trifluoromethylating reagent for hydrazones (Scheme 3.10).[230] Moreover, the Togni reagent has been used for radical processes[231] alongside reports of other radical reagents like CF_3I,[232] CF_3SO_2Cl,[233] and

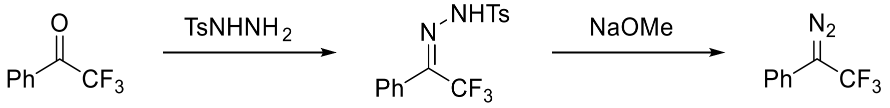
Langlois reagent (CF_3SO_2Na).[234] Unfortunately, the diversity of substituted hydrazones has been limited to *N,N*-dialkyl, -diaryl, or acyl substituted hydrazones, none of which are suitable diazo precursors. The trifluoromethylation of hydrazones with secondary amino groups in all of these examples were unsuccessful except in the case of *N*-phenyl alkynic hydrazones (Scheme 3.10, Bottom).[235] However, considering these hydrazones are also not suitable for diazotization, these derivatives undergo cyclization to the corresponding azole upon trifluoromethylation.



Scheme 3.10 - Examples of trifluoromethylations of hydrazone compounds.

3.4 Proposal

The inclusion of fluorine and CF_3 groups on compounds is an effective tool in modifying and improving the chemical properties for various applications. As the pharmaceutical industry continues to grow, so does need for effective late-stage trifluoromethylation methods in the synthesis of complex trifluoromethylated molecules and for the synthesis of fluorinated building blocks. Considering the various types of trifluoromethylation methods, expanding the depth of the methods for electrophilic trifluoromethylation would be important in allowing more flexible procedures and different angles for product synthesis. The hypervalent iodine-based Togni reagent is a recently developed tool that has already garnered attention for its flexible applications and easy handling. It is evident that methods are scarce for trifluoromethylating diazo compounds and there are only a few instances for applications in trifluoromethylating hydrazone compounds, none of which are suitable precursors for diazo compounds. Synthesis of diazo compounds containing CF_3 groups would be particularly advantageous as diazo groups are highly reactive compounds that can be used for a variety of applications and would be an adaptable synthetic building block. The opposite approach to synthesize trifluoromethylated diazo compounds can also be considered—installing the diazo moiety after a trifluoromethyl group is already present. This sequence of steps would also be particularly advantageous in targeted product syntheses where a reactive diazo group may not survive many stages of synthesis. Historically, the preparation of trifluoromethylated diazo compounds started from treatment of trifluoromethyl ketones with sulfonyl hydrazides and subsequent alkaline decomposition (Bamford-Stevens reaction) (Scheme 3.11).[236]



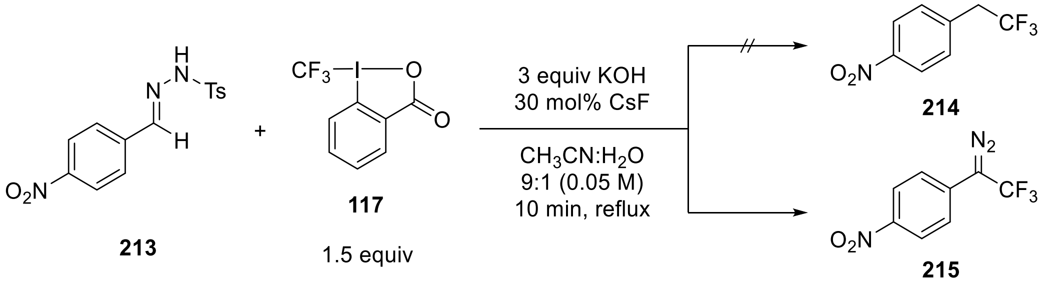
210 **211** **212**

Scheme 3.11 - Preparation of trifluoromethylated diazo compounds via the Bamford-Stevens reaction.

Upon consideration of the accessibility of the trifluoromethyl ketone compounds, the synthesis of the final trifluoromethylated diazo compound may necessitate many steps if the desired trifluoromethylated substrates are not initially available. It is evident that for some aryl substitutions, current procedures still require multiple steps in first synthesizing the trifluoromethylated ketone before diazo functionalization.[237] Therefore, after all considerations, it seems there is lack of synthetic methods towards trifluoromethylated diazo compounds and research towards these methods will allow easier access to complex molecules with useful properties due to CF_3 groups. It would be worthwhile to explore the trifluoromethylation of hydrazones and diazo compounds, ideally in relatively few steps from readily available compounds. As benzaldehyde compounds and their derivatives are easily accessible, using benzaldehyde-derived tosylhydrazones as precursors for diazo groups should prove to decrease expenses towards synthesis of these products. Given that both diazoalkanes and hydrazones are nucleophilic at the azomethine carbon, electrophilic trifluoromethylating reagents such as Togni reagent would provide the highest chance of success. The use of HVI reagents will also allow easy handling and safe procedures towards the synthesis of these products as well. A smooth and efficient procedure for the production of trifluoromethylated diazo compounds will be attractive in providing highly reactive and versatile functionalities towards the further synthesis of complex trifluoromethylated molecules.

3.5 Synthesis of Aryl(trifluoromethyl)diazomethanes

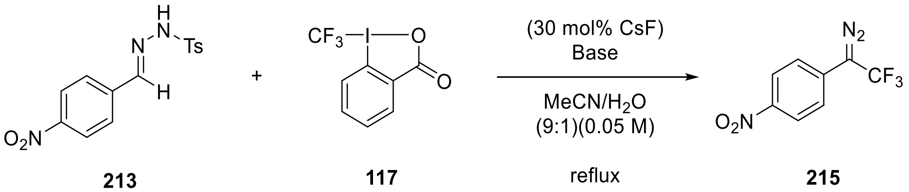
In recent work by Dr. Zhensheng Zhao, a former postdoctoral research fellow of the Murphy group, a Wolff-Kishner-based reduction of benzaldehyde hydrazones using Togni reagent was developed to produce trifluoroethylarene compounds such as **214** in up to 95% yield (Scheme 3.12).[238] During a control reaction in this method development, diazo product **215** was formed from the tosylhydrazone compound, presumably through a base-induced Bamford-Stevens reaction. This was a surprising result considering that in previous investigations in the Murphy lab, tosylhydrazones were found to be interchangeable with unsubstituted hydrazones in other HVI-mediated denitrogenative reactions.[154,239]



Scheme 3.12 - Synthesis of trifluoromethylated diazo compound **215** instead of the denitrogenated ethylbenzene compound **214**.

Studies towards the synthesis of this diazo compound began by replicating the standard conditions reported for the reduction method. Considering that electron-withdrawing groups increase stability of the diazo compounds, a nitro substituent was chosen as diazo compounds with other groups were known to have lower stability at room temperature. Therefore, *p*-nitrobenzaldehyde tosylhydrazone **213** was chosen as the model substrate due its ease of synthesis, high yield from available benzaldehydes, and stability of derived diazo product **215**. Short reaction times were also implemented to minimize thermal decomposition of the desired diazo compound. From the available information from Dr. Zhao and the published article,[238] it was gathered that precise addition order of the reagents was important for the solubility of the starting hydrazone and Togni reagent, however, minimal solubility issues were personally observed.

Initial results were promising, showing a 21% NMR yield and small amounts of the denitrogenated product **214**. However, the reaction was noted to be sensitive in some regards as heating of the reaction mixture prior to addition of CsF and KOH proved detrimental (Table 3.1, entry 2). Nevertheless, comparable yields were attained between one and three equivalents of base and also without the addition of CsF. The amount of Togni reagent used was also varied from 1.1 equivalents up to 3 equivalents with no observable change in product yield or reaction time. Following this, a screening of bases was performed and both organic and inorganic bases were found to be viable to a lesser degree. As per the established reaction conditions,[238] the addition of CsF improved yields considerably (Table 3.1, entry 6, 12), although the reason for this is currently unknown. After these experiments, both 1 and 3 equivalents of base were tested for viability in the future.



213
1 equiv

117
1.5 equiv

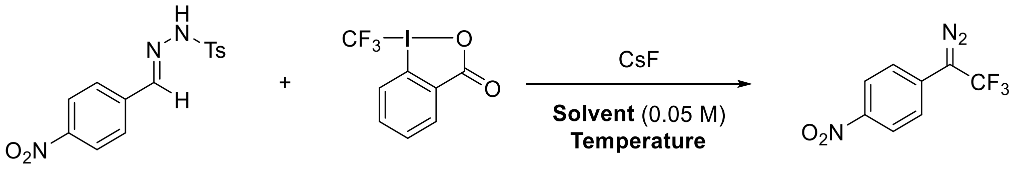
215

Entry	CsF equiv	Base equiv	Base[a]	Solvent	Time (min)	NMR Yield 215 (%)[b]
1	0.3	3	KOH	MeCN/H_2O	15	21
2[c]	0.3	3	KOH	MeCN/H_2O	15	11
3	0.3	1	KOH	MeCN/H_2O	15	23
4	0	3	KOH	MeCN/H_2O	15	19
5	0	1	K_2CO_3	MeCN/H_2O	60	14
6	0.3	1	K_2CO_3	MeCN/H_2O	20	22
7	0	1	KOAc	MeCN/H_2O	60	16
8	0	1	$NaHCO_3$	MeCN/H_2O	60	4
9	0	1	NEt_3	MeCN/H_2O	60	12
10	0	1	2,6-Lutidine	MeCN/H_2O	60	12
11	0	1	DBU	MeCN/H_2O	60	11
12	0.3	1	DBU	MeCN/H_2O	20	20
13	0	1	Pyridine	MeCN/H_2O	60	8

[a] Inorganic bases were added as a solution in 50 µL H_2O. [b] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm). [c] Procedure: Tosylhydrazone and Togni reagent were heated in solvent prior to addition of CsF then KOH.

Table 3.1 - Initial testing using established reaction conditions.

It was observed in these experiments that upon addition of CsF, the reaction mixture turned to an orange colour, an indication of diazo formation. Thus, stoichiometric quantities of CsF were applied and achieved similar yields. The addition of KOH after 15 minutes also had no further effect, demonstrating cesium fluoride's efficacy as a base (Table 3.2, entry 2). Following this, since diazo compounds are thermolabile, lower temperatures were briefly investigated to minimize decomposition of the diazo product, but at 0 °C and room temperature the reactions were found to be ineffective, necessitating higher reaction temperatures. This result was consistent with the unproductive result using dichloromethane (DCM) because of its lower reflux temperature (42 °C). DCM tested as a relatively more inert solvent than acetonitrile, so it is also plausible that the Lewis basicity of MeCN is necessary instead. Following these sets of experiments, the solvent was adjusted to purely acetonitrile in future experiments for simplicity as CsF was already added as an aqueous solution and the inclusion of water in the reaction did not seem detrimental.



213 1 equiv; **117** 1.5 equiv; **215**

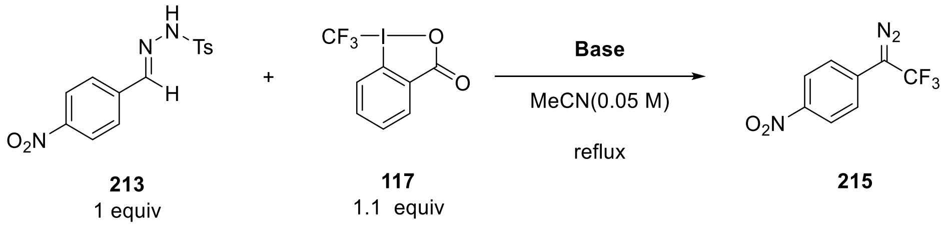
Entry	CsF equiv	Solvent	Temperature	Time (min)	NMR Yield 215 (%)[a]
1	1	MeCN/H_2O	reflux	60	20
2[b]	1	MeCN/H_2O	reflux	15	21
3	3	MeCN/H_2O	reflux	15	20
4	1	MeCN/H_2O	rt	20 h	0
5	1	MeCN/H_2O	0 °C	3 h	0
6	1	MeCN	reflux	15	23
7[c]	1	MeCN	reflux	15	19
8	1	DCM	reflux	15	0

[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm).

[b] 3 equivalents of KOH added after 15 min. [c] NMR yield taken without any work-up.

Table 3.2 - Application of CsF as a base.

Tetrabutylammonium fluoride (TBAF) and tetrabutylammonium iodide (TBAI) were also tested as bases with 14 and 7% NMR yields (Table 3.3). Since TBAI was productive in a small degree, it is speculated that one possible pathway this reaction undergoes is a radical mechanism since TBAI is known to be an initiator for electron catalyzed radical-chain reactions.[231] The use of TBAI also suppressed the residual peak of Togni reagent in ^{19}F NMR often seen in the crude NMR spectra, possibly indicating its decomposition by TBAI. When using TBAF, traces of the trifluoromethylated tosylhydrazone were isolated despite not being observed in the crude NMR spectrum and this phenomenon was briefly investigated. Considering that flash column chromatography led to the appearance of this compound from the crude product, crude mixtures were subjected to silica plugs and addition of silica gel to the reaction mixtures was also attempted. The trifluoromethylated tosylhydrazone compound was observed only occasionally, in addition to slight decomposition to the corresponding diazo product upon flash column chromatography. It was also noted that the addition of excess silica turned the reaction mixture brown, possibly signifying decomposition, despite the presence of diazo product in the crude mixture (Table 3.3, entry 5). Ultimately, the investigations were collectively inconclusive, and no further studies were done in this area and with these sets of reagents. However, these results did indicate that tosylhydrazone **213** could be trifluoromethylated under these reaction conditions along with some reaction to diazo product **215**.

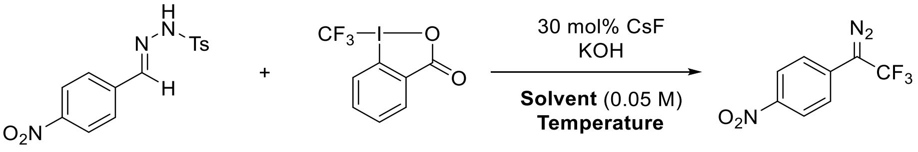


Entry	Base equiv	Base	Time (min)	NMR Yield 215 (%)[a]
1	1	CsF	15	23
2	1	TBAF	15	14
3	1	TBAI	15	7
4	3	TBAF	15	9
5[b]	3	TBAF	15	trace
6[c]	3	TBAF	15	12
7[d]	3	TBAF	15	0

[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm).
[b] The trifluoromethylated tosylhydrazone was isolated as a side product. [c] Silica gel (5 mL) was added to the mixture. [d] Silica gel (96 mg, 3 equiv) was added to the mixture.

Table 3.3 - Investigation into TBAF as a base for the synthesis of trifluoromethylated hydrazones.

Following this, other conditions were investigated such as solvents and addition orders. Solvents that could be heated close to acetonitrile's boiling point were used, such dimethylsulfoxide (DMSO), dimethylformamide (DMF), and dichloroethane (DCE). Both DMSO and DCE achieved comparable yields to MeCN, while DMF was inefficient as a solvent (Table 3.4). Although the reason for DMF's lack of productivity is unknown, it is noted that the positive result using DCE signified that it was the higher temperature that was an important factor in this reaction, not the Lewis basicity of MeCN, since the similar DCM solvent at lower temperatures was ineffective (Table 3.2, entry 8). Afterwards, different addition orders and procedures were tested to investigate if there was the formation of any necessary intermediates. When surveying the different addition orders and procedures, lower concentrations and equivalents of base were employed to minimize possible issues. Unfortunately, both the reverse addition of the tosylhydrazone **213** to a mixture of Togni reagent and base, and the slow addition of base to the reaction mixtures failed to improve outcomes.



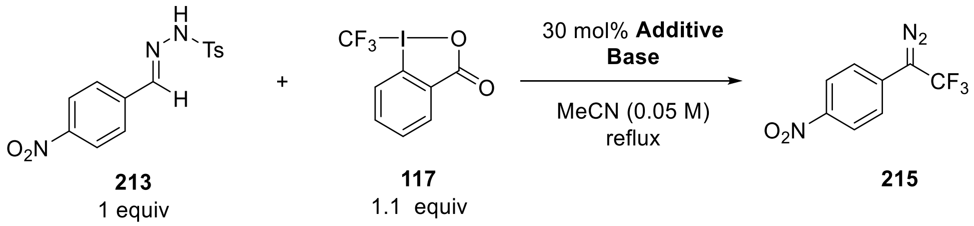
213 1 equiv **117** 1.1 equiv **215**

Entry	KOH equiv	Solvent	Temperature	Time (min)	NMR Yield 215 (%)[a]
1	3	MeCN	reflux	15	22
2	3	DMSO	90 °C	15	20
3	3	DMF	90 °C	15	0
4	3	DCE	reflux	15	24
5[b]	3	MeCN	reflux	15	13
6[c]	1	MeCN	reflux	30	15
7[d]	1	MeCN	reflux	15	11

[a]NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm). [b]Togni reagent and CsF was heated to reflux before adding tosylhydrazone then KOH. [c]KOH solution was slowly added over 15 min. [d]Solution of tosylhydrazone was slowly added over 15 min to solution of Togni reagent & CsF in MeCN.

Table 3.4 - Investigation of solvents and addition order of reagents.

Next, considering the positive results by inclusion of CsF, other counter ions for the additives were tested (Table 3.5). The other metal counter ions for fluoride were tested, with lithium, sodium, and potassium all producing approximately the same yields, despite the low solubility of lithium fluoride in water for its addition as a reagent. Looking towards other fluoride sources, when TBAF was used as the additive there was a relatively lower yield of 14%. While the inclusion of water did not compromise previous experiments with cesium fluoride, it was postulated that this was a possibility with TBAF considering it is sold commercially as a solution in tetrahydrofuran (THF). Thus, upon use of triethylamine instead of an aqueous KOH solution, yields increased back to ~20%. Subsequently, NEt_3*3HF, TBAI, and higher amounts of TBAF were tested and similar positive results were observed.

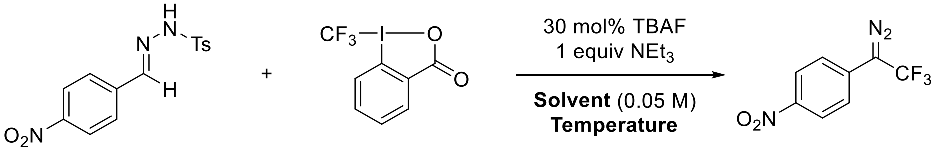


Entry	Additive equiv	Additive	Base equiv	Base	Time (min)	NMR Yield 215 (%)[a]
1	0.3	CsF	3	KOH	15	22
2	0.3	LiF	3	KOH	15	17
3	0.3	NaF	3	KOH	15	17
4	0.3	KF	3	KOH	15	20
5	0.3	TBAF	3	KOH	15	14
6	0.3	TBAF	1	KOH	15	13
7	0.3	TBAF	1	NEt_3	15	23
8	0.3	TBAF	3	NEt_3	15	17
9	0.3	NEt_3*3HF	1	NEt_3	15	18
10	0.3	TBAI	1	NEt_3	15	19

[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm).

Table 3.5 - Investigation into metal fluorides and other additives.

Thereafter, since the conditions of TBAF and NEt_3 gave comparable yields to the typical CsF and KOH, the water-free reagents was screened briefly for other temperature and solvent conditions to minimize the effect of water (Table 3.6). For temperature, the reaction was found to perform equally well at all temperatures above 50 °C, in agreement with previous unproductive results at room temperature and using the low boiling point DCM as a solvent. Since yields were equal across the various higher temperatures tested, this pointed to an unnecessary control of precise reaction temperatures and future experiments were conducted at reflux temperatures for procedural simplicity. However, it should be noted that the Bamford-Stevens reaction of tosylhydrazones has been reported to occur at room temperature to form similar aryldiazoacetates compounds *in situ*.[240] In regard to solvents while using the water-free reagents, the reaction was found to be unsuccessful with all types of solvents, with only trace amounts up to 9% yield of the diazo compound detected by NMR. Although the negative results of the lower boiling point solvents were expected, the large array of unproductive solvents was surprising considering that solvents such as DCE had previously given positive results using CsF and KOH. Considering these outcomes and lack of any improved yields, water-free conditions were not pursued any further.



213 1 equiv

117 1.1 equiv

215

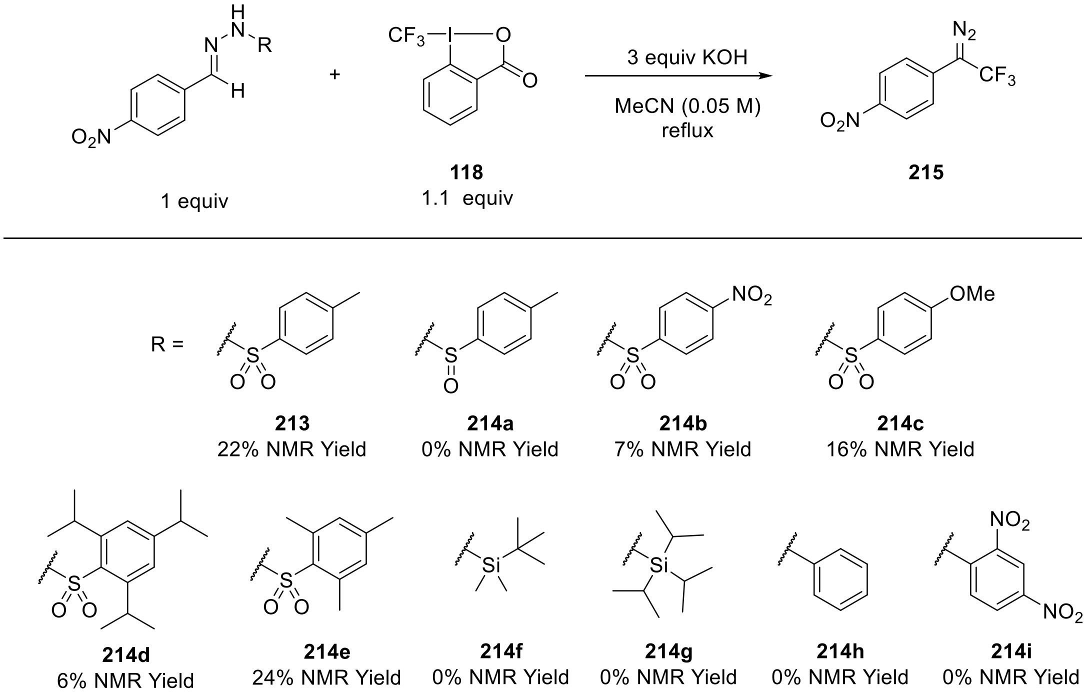
Entry	Solvent	Temperature (°C)	Time (min)	NMR Yield 215 (%)[a]
1	MeCN	82	15	23
2	MeCN	rt	15 h	0
3	MeCN	40	30	trace
4	MeCN	50	20	19
5	MeCN	60	15	22
6	MeCN	70	15	20
7	Et_2O	35	15	trace
8	DCM	40	15	7
9	Acetone	56	15	trace
10	$CHCl_3$	61	15	9
11	THF	65	15	trace
12	MeOH	65	15	trace
13	Hexanes	69	15	trace
14	EtOAc	77	15	trace
15	DCE	84	15	7
16	Toluene	110	15	trace

[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm).

Table 3.6 - Temperature and solvent screening under water-free conditions.

Drawing inspiration from the Bamford-Stevens reaction mechanism, hydrazones containing other *N*-substitutions were investigated to explore how leaving group ability might affect this reaction (Scheme 3.13). Firstly, in testing similar sulfonylhydrazones, the change from methyl group to electron-donating (**214b**) and electron-withdrawing (**214c**) groups both yielded positive but low results. Thus, it was unclear how the electronics of the leaving group affected the reaction since both increasing or decreasing the electron density of the aryl ring proved detrimental. Next, the steric substitutions of the sulfonylaryl ring were adjusted. The trimethyl substitution (**214e**) had little effect and yielded similar amounts of product, yet the triisopropyl (trisyl) substitution (**214d**) showed a much lower yield. Considering that the trisyl group is known to be a better leaving group than tosyl group,[241] one rationale for this is that increasing leaving group ability increases the rate of the plain diazomethane formation, and subsequent trifluoromethylation becomes unlikely. Alternatively, the isopropyl substitutions may have an effect in blocking the coordination of the Togni reagent to the hydrazone to prevent trifluoromethylation.

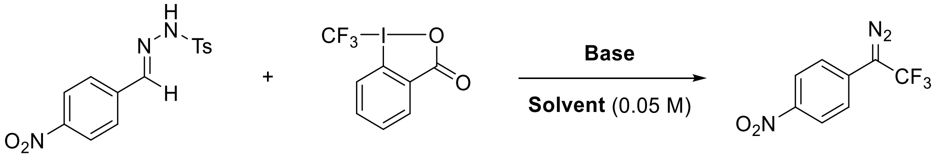
Silyl-substituted hydrazones (**214f, 214g**) were tested as they are known precursors for diazo compounds,[203b,242] however, this modification was also unsuccessful. Further, addition of a simple arene groups in place of a leaving group were explored. Given the poor leaving group ability of a phenyl anion, these reactions were not expected to produce any products. Curiously, the trifluoromethylation of phenylhydrazone **214h** was observed in a relatively high ^{19}F NMR yield of 40%. This result hints at the reaction mechanism since it demonstrates that trifluoromethylation of the hydrazones is readily occurring under these reaction conditions. However, it is unclear whether this trifluoromethylation step is successful due to the lack of the competing Bamford-Stevens reaction. Lastly, other substitutions such as toluenesulfinyl (**214b**), 2,4-dinitrophenyl (**214g**), and triisopropylsilyl (**214i**) groups were also attempted, but due to difficulties in the synthesis and purification of these corresponding hydrazones, crude residues were used for these experiments. As such, the results of these experiments remain inconclusive. Overall, the hydrazone with tosyl substitution was continued with due to a lack of any significant increase in yields with other N-substitutions.



Scheme 3.13 - Reactions with other hydrazone substitutions to investigate leaving group ability.

Finally, after the exploration of many conditions and reagents, it seemed pertinent to return to simpler conditions. Following along the avenues of known literature, *tert*-butoxides as bases in 1,4-dioxane solvent were tested as these conditions had previously been successful in base-catalysed diazotization of tosylhydrazones.[243] Alas, applications of the bases potassium and sodium *t*-butoxide were ineffective. Upon advice from the May laboratory, silanolate bases were also attempted due to the suggestion that these could deprotonate tosylhydrazones without the immediate formation of the corresponding diazo products. Under the reported conditions with dioxane, potassium trimethylsilanolate ($KOSiMe_3$) was unsuccessful (Table 3.7). Fortunately, upon the change to acetonitrile as a solvent with previous success, reactions using $KOSiMe_3$ proceeded in equal or better yields compared to all previous results, up to 30% NMR yield. This was the case only in stoichiometric quantities, as excess equivalents of $KOSiMe_3$ led to trace amounts of diazo product **215**, possibly due to decomposition of tosylhydrazone **213** to the plain diazomethane compound. Furthermore, since the solid base was added to the reaction flask portionwise, water was used one time to aid in its addition, and this small amount of water proved disastrous despite the tolerance of water in previous experiments. In light of this, moisture- and oxygen-free conditions were employed in hopes of minimizing decomposition, but no further improvement in yield was observed. The use of the sodium trimethylsilanolate ($NaOSiMe_3$), the base originally reported by May *et al.*, also achieved positive results to a lesser degree, possibly indicating some effect by the differing counter ions when used as a solid reagent. Intriguingly, the use of $KOSiMe_3$ at room temperature produced the denitrogenated ethylarene product **214** in 16% yield, possibly signifying the decomposition of the tosylhydrazone to the hydrazone or diazo form during this reaction, although the mechanism towards this is unclear.

The search for a suitable base continued with NEt_3*3HF and sodium hydride but both were unproductive. Continuing, tetramethylguanidine (TMG) was reported by Lévesque *et al.* as the best base candidate for sulfonylhydrazone decomposition for the *in situ* formation of aryldiazomethanes.[244] The more obtainable diphenyl guanidine (DPG) was initially used and gave the diazo compound in 8% yield. Later when available, TMG was tested in duplicate and the highest yield to date of 36% was achieved. Although untested, it is suspected that superstoichiometric amounts of TMG would be detrimental to the reaction such as in the results using DPG and $KOSiMe_3$. Regardless, these results were promising and further investigation with TMG in this direction could prove worthwhile.



213
1 equiv

117
1.1 equiv

215

Entry	Base equiv	Base	Solvent	Temperature	Time (min)	NMR Yield 215 (%)[a]
1	1	KOtBu	dioxane	reflux	15	0
2	1	NaOtBu	dioxane	reflux	15	0
3	1	$KOSiMe_3$	dioxane	reflux	15	0
4	1	$KOSiMe_3$	MeCN	reflux	15	30
5[b]	1	$KOSiMe_3$	MeCN	reflux	15	29
6	3	$KOSiMe_3$	MeCN	reflux	15	5
7[c]	1	$KOSiMe_3$	MeCN	reflux	15	0
8	1	$NaOSiMe_3$	MeCN	reflux	15	18
9	1	$KOSiMe_3$	MeCN	rt	15	0[d]
10	3	NEt_3*3HF	MeCN	reflux	15	0
11	3	NaH	MeCN	reflux	15	0
12	6	NaH	MeCN	reflux	15	0
13	3	DPG[e]	MeCN	reflux	15	8
14	1	TMG[f]	MeCN	reflux	15	36

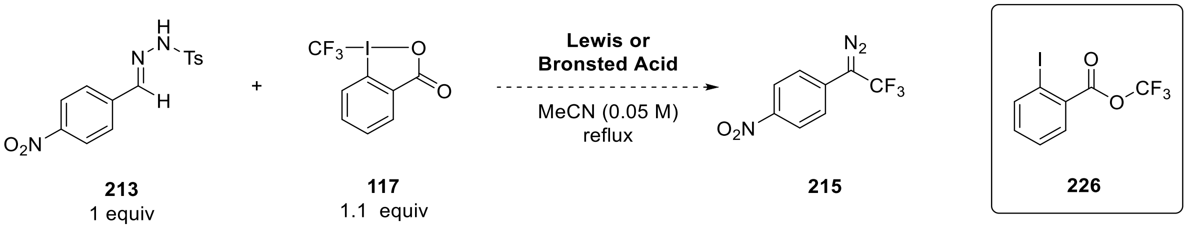
[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm). [b] Performed under oxygen and moisture free conditions. [c] A few drops of water were added to the reaction mixture. [d] The denitrogenated trifluoroethylbenzene product could be isolated in 16% yield. [e] DPG = Diphenylguanidine. [f] TMG = Tetramethylguanidine.

Table 3.7 - Final screening of bases.

3.6 Other Side Products

During many of the previous experiments, total mass balance was difficult to achieve and numerous ^{19}F NMR peaks were observed that could not be assigned to any isolated or identifiable compounds. This indicated the generation of many side products and even appropriate side products like the benzoate of the Togni reagent were difficult to locate and identify in significant quantities. The consumption of starting tosylhydrazone compound **213** was thought to produce traces of the toluenesulfinate leaving group upon tosylhydrazone decomposition which could plausibly be trifluoromethylated by the Togni reagent as a side reaction. However, arylsulfinate compounds were not found from any of the isolated mixtures with observable ^{19}F NMR peaks, and this was not unexpected as reports of these trifluoromethylated compounds are rare.[245]

Since Lewis and Brønsted acids are known to activate the Togni reagents, these were also explored towards the synthesis of the trifluoromethylated diazo compounds. In all instances using Lewis acids (BF_3, $AlCl_3$, and diphenyleneiodonium triflate) and Brønsted acids (TsOH and TfOH), the diazo compound was not observed (Table 3.8). Although the ^{19}F NMR spectra of the crude reaction mixtures of some experiments were initially thought to have signs of diazo product **215**, duplication of these results was not possible. Upon further examination, it was hypothesized that these peaks were likely that of the trifluoromethylated ester compound **226** (-57.1 to -57.4 ppm), frustratingly close to the aryl(trifluoromethyl)diazomethane **215** product peaks (-57.4 to -57.6 ppm). Although scarcely reported, **226** is noted to form by strong Lewis or Brønsted acid activation of the Togni reagent.[178,246] In our experiments, trace amounts of this uncyclized product were observed in impure mixtures by NMR spectroscopy during some experiments, including control experiments of heating mixtures of tosylhydrazones or aryldiazomethanes with Togni reagent **117** without the addition of other reagents. Interestingly, considering that these trifluoromethylated ester compounds form in acidic environments, this points towards the acidic nature of the tosylhydrazone and aryldiazomethane compounds. This interaction may also be the cause of many side reactions, including decomposition of the Togni reagent. Despite this, increasing the equivalents of Togni reagent to account for its decomposition was previously explored, but achieved similar yields. It is probable that these interactions are minimized by the presence of excess base in solution.



213 1 equiv

117 1.1 equiv

215

226

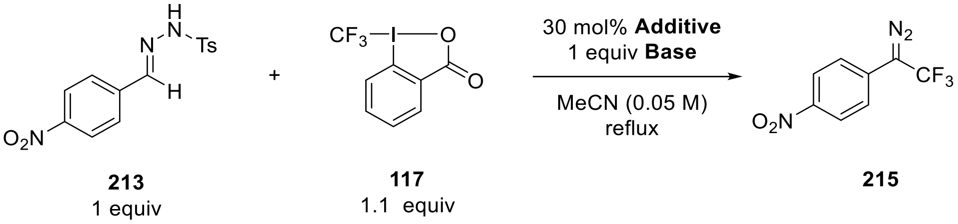
Entry	Equiv	Lewis or Brønsted Acid	Time (min)	NMR Yield 215 (%)[a]
1	1	BF_3	15	0
2	0.3	$AlCl_3$	15	0
3	1	$AlCl_3$	24 h	0
4	1	DPIT[b]	24 h	0
5	1	TsOH	15	0
6	1	TfOH	15	0

[a]NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm).

[b]DPIT = Diphenyleneiodonium Triflate.

Table 3.8 - Lewis and Bronsted acid-mediated reactions.

The formation of benzaldehydes was also frequently observed in crude reaction mixtures and initially thought to be the product of acid- or base-catalyzed hydrolysis. Upon further consideration, it was hypothesized to be from Lewis acid activation, since it was previously reported by the Murphy group that HVI reagents could be activated by the borosilicate glass of typical reaction flasks.[247] Furthermore, it was found that oxygen atoms from borosilicate glass could actually be incorporated into reaction mixtures, forming benzaldehydes from the hydrazone derivatives. Thus, to minimize these effects on tosylhydrazone **213** and possible degradation of the Togni reagent, several experiments were performed in both perfluoroalkoxy alkane (PFA) and silanized vials (Table 3.9) and the intended effect in reducing the amount of benzaldehyde side products was achieved. However, the yields of the diazo product were also lowered and thus this method was not explored further.

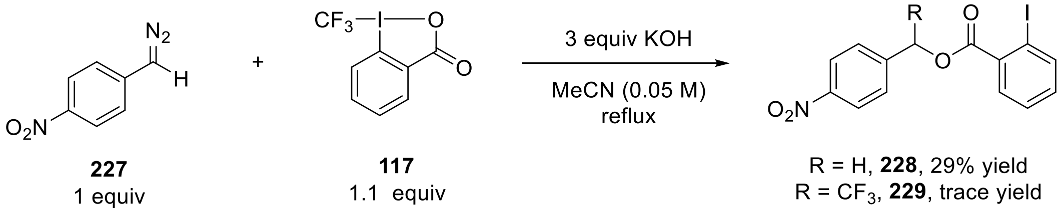


Entry	Vessel	Additive	Base	Solvent	Time (min)	NMR Yield 215 (%)[a]
1	RB Flask	CsF	KOH	MeCN	15	22
2	PFA vial[b]	CsF	KOH	MeCN	15	12
3	PFA vial[b]	TBAF	NEt_3	MeCN	15	12
4	Silanized vial	CsF	KOH	MeCN	15	13
5	Silanized vial	TBAF	NEt_3	MeCN	15	15

[a]NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm). [b]PFA = PerFluoroalkoxy Alkane.

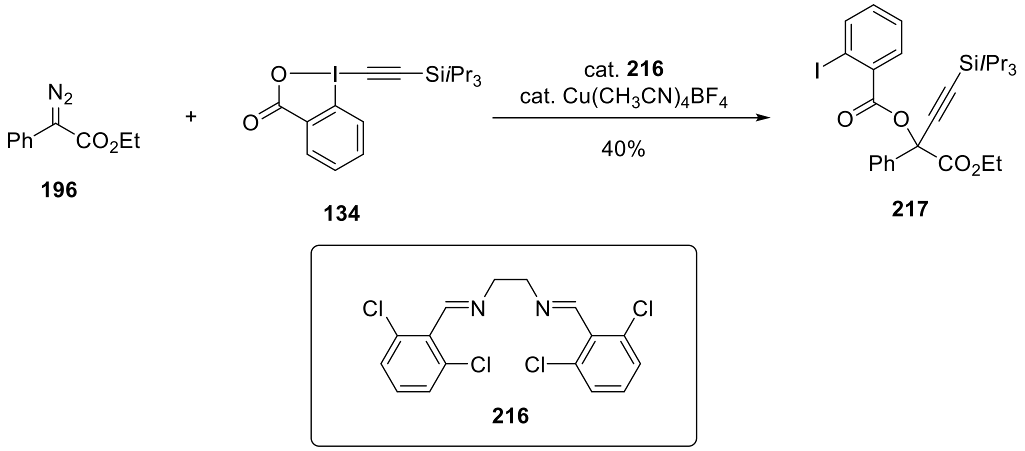
Table 3.9 - Reactions in PFA and silanized vials.

The formation of many side products was suspected to be the cause of the low yield of the desired trifluoromethylated diazo compound and the reaction pathways were questioned. In regard to other identifiable side products, the crude mixtures of many experiments were collected together in attempts to isolate some of these compounds. The previously mentioned trifluoromethyl ester (**226**) was identified along with 4-nitrobenzyl 2-iodobenzoate (**228**) and its trifluoromethylated derivative (**229**). It was hypothesized that these benzyl benzoate compounds originated from the reaction of the benzoates leftover from reaction using the Togni reagent and aryldiazomethane compounds. Since these diazo compounds could be the products of base-induced Bamford-Stevens reaction of the starting tosylhydrazones, aryldiazomethane compound **227** was synthesized directly according to known procedures and subjected to the standard reaction conditions with Togni reagent. Although some experiments displayed a complex mixture of compounds, benzyl benzoate **228** was detected in 58% NMR yield and was isolated in 29% yield, along with many other unidentifiable products observed in the crude NMR spectrum (Scheme 3.14). This provided some insight into one of the many reaction pathways in the difunctionalization reaction and suggested that the decomposition of starting tosylhydrazone **213** was occurring. It also indicated the plausible decomposition of the desired trifluoromethyl diazo product **215** to the trifluoromethylated benzyl benzoate **229**. Following this, the synthesis of deuterated diazomethane and tosylhydrazone were also attempted in order to further explore the mechanism towards these benzyl benzoate compounds, but difficulties in synthesis and purification limited further work.



Scheme 3.14 - Formation of benzyl benzoate side products.

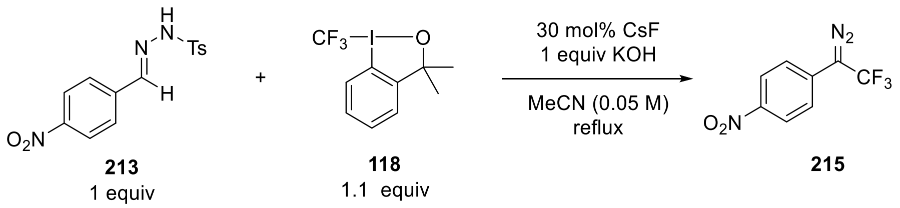
It is known that diazo compounds and HVI reagents can be react in this manner.[248] Towards the incomplete incorporation of the Togni reagent, Szabó and coworkers reported geminal oxytrifluoromethylation reactions of diazo compounds.[249] Additionally, complete incorporation of benziodoxole reagents is also possible, where Waser and Hari devised of a method of incorporating both the alkyne and iodine functionalities of the ethynylbenziodoxolone (EBX) reagent to a diazo compound (Scheme 3.15),[250] where the incorporated groups can be exploited for further functionalization.



Scheme 3.15 - Geminal additions to diazo compounds using benziodoxole reagents.

After isolation and identification of the benzyl benzoate compounds, it was then postulated that a more basic reagent would hinder the protonation of the diazoalkanes that was necessary to form the side products. Thus, it was speculated that using the dimethyl derivative of the Togni reagent, upon release of the CF_3 unit, would render a more basic alkoxide than the carboxylate of the carbonyl derivative. Although the synthesis proved challenging, the final crystalline reagent of **118** was used and resulted in the same yield as the carbonyl Togni derivative (Table 3.10). This signified that the basicity of the resulting alkoxide and carboxylate does not play a significant role in this reaction.

However, during initial syntheses of **118**, one batch of product with gummy consistency produced one high yielding result, prompting further exploration. The reagents and side products during the synthesis of the dimethyl Togni reagent **118** were added to the reaction in one experiment (Table 3.10, entry 4), and while the diazo product could be formed in 12% yield, the exceptional result could not be replicated. In another experiment, basic alumina was also added to the flask because the synthesis of **118** required filtration through alumina by which the gummy reagent was produced. However, this also did not replicate the high yielding result and no further work was done in this direction.



Entry	Togni reagent equiv	Solvent	Time (min)	NMR Yield 215 (%)[a]
1[b]	1.5	MeCN	15	23
2	1.2	MeCN	15	22
3	1.5	MeCN	15	22
4[c]	1.5	MeCN	15	12
5[d]	1.5	MeCN	15	23

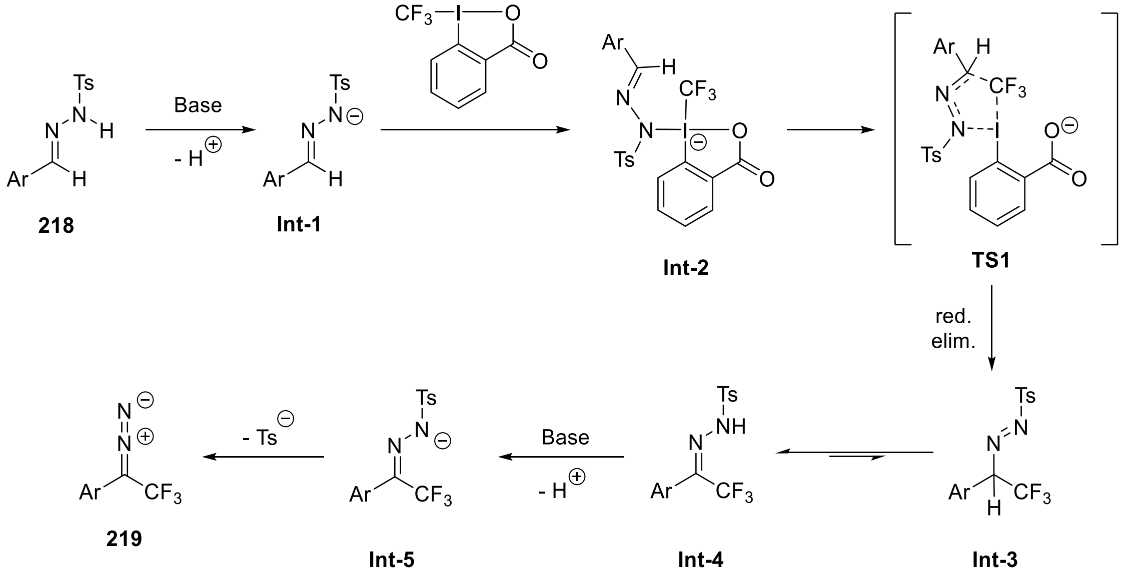
[a] NMR yields determined using trifluorotoluene as internal standard (-63.0 ppm). [b] Carbonyl Togni reagent 117 used, for comparison. [c] KF (1 equiv) and $TMSCF_3$ (1 equiv) also added to the mixture. [d] Basic alumina (33 mg, 3 equiv) also added to the mixture.

Table 3.10 - Application of the dimethyl derivative of the Togni reagent.

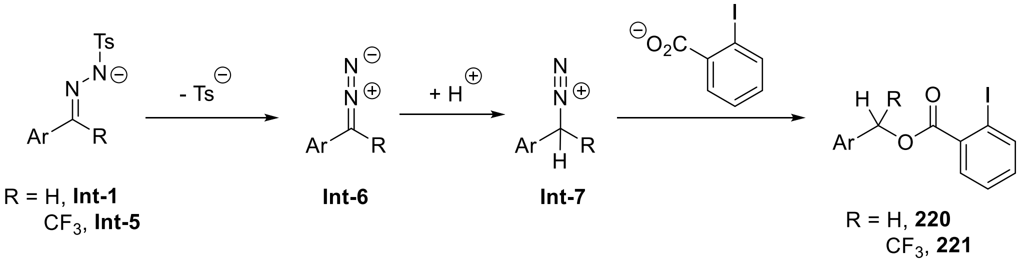
3.7 Discussion

It was found regularly that this reaction was difficult to navigate, as many positive results could often not be duplicated or were simply misconstrued due to other side products. In addition, many compound peaks were often observed by NMR of the crude product mixtures but were not possible to isolate for identification. As such, it is evident that this reaction is sensitive to many conditions and reagents and special care must be taken to document and replicate experimental procedures. However, the isolation of some key side products has provided hints to a few of the many pathways in this system. The mechanism towards the trifluoromethylation and diazotization of tosylhydrazones is proposed below in Scheme 3.16 with considerations taken from the computational studies performed for the parallel hydrazone reduction.[238] Beginning from the tosylhydrazone, deprotonation by base forms the first intermediate **Int-1**. Subsequently, this forms **Int-2** upon coordination with the Togni reagent at the nitrogen atom, which is calculated to be more favoured than coordination at the azomethine carbon of the plain hydrazone. Through a 5-membered ring transition state and subsequent reductive elimination, the azomethine carbon is then trifluoromethylated to form **Int-3**. It is noted that computational calculations could not be converged for the 1,2-elimination for trifluoromethylation at the nitrogen atom, nor the analogous 1,2-elimination at the carbon atom. Continuing, upon isomerization and deprotonation at the nitrogen atom again, the Bamford-Stevens reaction affords the trifluoromethylated diazo compound **219**.

Possible evidence for this mechanistic pathway is the identification and isolation of trifluoromethylated tosylhydrazone **Int-4**. Furthermore, the parallel trifluoromethylated derivative of phenylhydrazone **214h** was also identified in substantial NMR yields. This signifies the possibility of the trifluoromethylation portion of the pathway with Togni reagent under these basic conditions, with poor leaving group ability preventing the final diazotizing step from occurring. Additionally, it was found earlier that the substitutions of bulky 2,4,6-triisopropylbenzene sulfonyl and *tert*-butyldimethylsilyl (TBS) groups produced low yields, and this could be rationalized by consideration of the formation of **Int-2**. It is plausible that steric hindrance would limit coordination of the hydrazone with Togni reagent, and the alternative pathway towards direct diazomethane formation would be less difficult and decomposition of the starting tosylhydrazones is more likely. Moreover, **Int-1** and **Int-5** are prime candidates for the Bamford-Stevens reaction to form diazoalkanes **Int-6** (Scheme 3.17), which upon protonation can form both of the identified and isolated benzyl benzoate side products. Lastly, as traces of the denitrogenated trifluoroethylarenes were found, it is plausible that these compounds this could originate from **Int-3** upon removal of the tosylate and subsequent denitrogenation.



Scheme 3.16 - Proposed mechanistic pathway for the difunctionalization of tosylhydrazones.

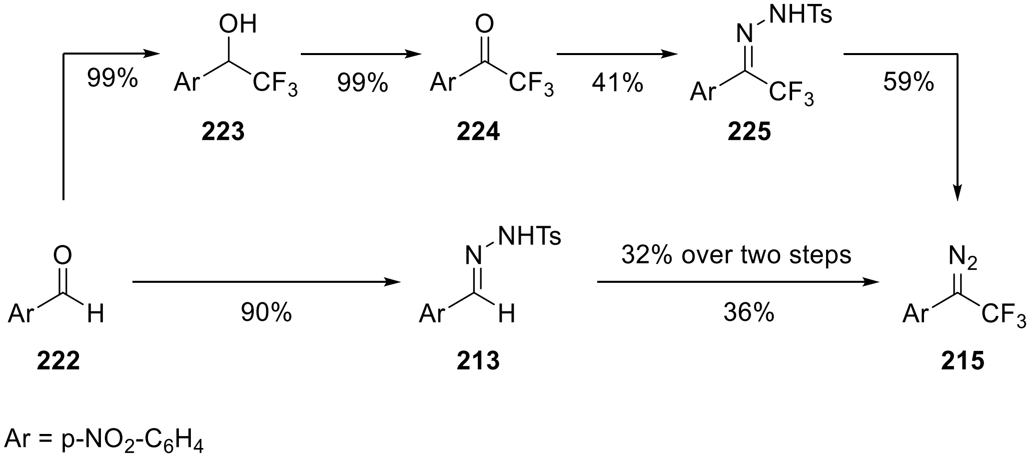


Scheme 3.17 - Bamford-Stevens reaction and subsequent formation of benzyl benzoates.

When discussing the viability of this proposed and explored synthesis route toward trifluoromethylated aryldiazomethane compounds from benzaldehydes, the overall yields can be compared to conventional multi-step syntheses. Considering our model substrate by starting from *p*-

nitrobenzaldehyde **222** in the known literature, two quantitative steps towards the trifluoromethylketone compound (**224**)[251] and two less-effective steps for the addition of the diazo group (**215**)[237] displays a 24% overall yield over four steps for conventional routes (Scheme 3.18, Top). Comparing to our synthetic route, a single step towards the *p*-nitrobenzaldehyde tosylhydrazone (**213**)[252] and then the currently highest 36% yield for the difunctionalization reaction provides an overall 32% yield over two steps (Scheme 3.18, Bottom). These comparable yields demonstrate the potential strength of this synthetic route and refinement of this procedure will prove beneficial towards the synthesis of these trifluoromethylated diazo compounds.

However, when considering the diazotization of derivatives using donating groups, there is a low 4% overall yield over two steps from the *p*-methoxytrifluoromethylketone.[237] This is an agreement with the many negative tests during our investigations where the methoxy-substituted diazo product **215a** was never detected. Furthermore, preliminary tests for the difunctionalization for *p*-bromo derivatives **215b** achieved a 11 and 14% yield using KOH and TMG, respectively (overall 11% yield over two steps), proving low when compared to the conventional methods in the literature (40% yield over four steps).[237,251] Therefore, it is evident that significant development of this difunctionalization procedure is still required.



Scheme 3.18 - The proposed route (Bottom) compared to conventional routes (Top) to synthesize aryl(trifluoromethyl)diazomethanes.

3.8 Conclusions and Future Work

Starting upon the odd result of a control reaction during previous method development in the Murphy lab,[238] it was discovered that starting from the benzaldehyde tosylhydrazone **213**, the respective trifluoromethylated diazo compound **215** could be afforded by use of Togni reagent **117**, and an appropriate base. The reaction required elevated temperatures, short reaction times and displayed ~20% NMR yield at first. Initial experiments consisted of testing the order of addition of reagents and heating, as well as screenings of organic and inorganic bases. It was noticed early that CsF, initially used as an additive to increase yields, could also be solely used as the base to similar yields, even in catalytic amounts. Aiding the use of KOH as base, additives such as metal fluorides and TBAF were then tested, with a small foray into using water-free conditions that also performed equally well. Temperature screening using these conditions showed that elevated temperatures above 50 °C were required, and reflux temperatures were subsequently used for operational ease. While choice of solvent was important, only a few were efficacious and there was no discernable pattern to their effectiveness. In investigating other *N*-substitutions of the hydrazone, it was found that sulfonylarene groups were moderately effective while other hydrazone groups were difficult to synthesize and remained untested. Further, more bases were screened, and it was found that $KOSiMe_3$ and tetramethylguanidine afforded the highest yields thus far, encouraging their future use in development of these procedures.

Catalysis using Lewis or Brønsted acids was also unfruitful, as the trifluoromethyl ester **226** originating from the Togni reagent was a frequent side product. The respective aryldiazomethane **227** was able to react with Togni reagent under established conditions and this produced benzyl benzoate side products **228** and **229** that had been observed and isolated in trace amounts during many collective reactions. This type of reactivity has been observed regarding diazo compounds and other hypervalent iodine reagents.[250] Following this, the dimethyl variant of the Togni reagent was synthesized and used in an attempt to minimize the formation of these side products, but to minimal success.

Possible future endeavors include the *in situ* generation of the trifluoromethylated diazo compounds from the benzaldehyde tosylhydrazones that can act as intermediates in reactions to minimize thermal decomposition. Although initial attempts were unfruitful when using styrene and metal catalysts, formation of metallocarbenes using diazo compounds is a well explored field of chemistry and the likelihood of success is high. Finally, while some comparisons of the proposed synthetic pathways to conventional routes are unfavourable, other substrates such as nitro-substituted substrates can achieve comparable to better yields and development into these procedures is sure to be successful.

3.9 Experimental and Spectral Data

3.9.1 General Experimental Details

Reactions were carried out in oven-dried glassware with magnetic stirring under open atmosphere, unless otherwise stated. PFA vials (4 mL, 14 x 52 mm) were purchased from Elemental Scientific. All reagents and solvents were purchased from Sigma-Aldrich or Oakwood Chemical and used without further purification, unless otherwise stated. Solvents were dried and purified using a JC Meyer solvent purification system or purified according to the Purification of Laboratory Chemicals handbook. Transfer of anhydrous solvents and reagents was accomplished with oven-dried needles. Reactions were monitored by thin-layer chromatography (TLC) on glass plates pre-coated with commercial silica 0.25 mm Kieselgel 60 F254 (Silicycle) and viewed by UV lamp (254 nm). Flash chromatography was performed using 60 Å (230-400 mesh) silica gel (Silicycle) using eluent systems described for each experiment. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrum Two with ATR Two. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. All NMR spectra are reported in chemical shifts (δ) in parts per million (ppm) relative to reference compounds and/or residual undeuterated solvent peaks. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br. s = broad singlet. Proton NMR spectra (^{1}H NMR) were recorded at 300 or 500 MHz and are reported relative to the residual chloroform peak (7.26 ppm) and coupling constants (J) are reported in hertz (Hz). Carbon NMR spectra (^{13}C NMR) were recorded at 125 or 75 MHz and are relative to the center line of the triplet from $CDCl_3$ (77.11 ppm). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 or 470 MHz and are reported relative to the peak of trifluoroacetic acid (-76.53 ppm).

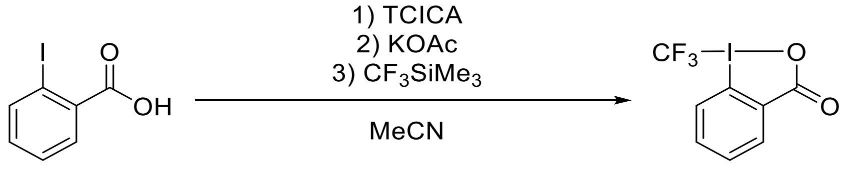
Important Safety Note:

Diazo compounds are presumed to be toxic and potentially explosive.[253] These materials should only be handled with care and in a well-ventilated fumehood. Gloves must be worn at all times when handling diazoalkane solutions and vessels. No incidents occurred handling diazoalkanes during the preparation of this thesis, yet the reader should be aware of the carcinogenicity and explosiveness of the herein described diazo compounds and general safety precautions should always be followed.

Purification of Acetonitrile:

Residual acidic impurities were removed from solvent by treatment with freshly dried K_2CO_3 as follows: Stir MeCN (500 mL) over flame dried K_2CO_3 (20 g) for 24 h under nitrogen gas, filter into a dry round-bottom flask containing activated 3 Å molecular sieves. Sparge with nitrogen gas for 15 min and seal with a septum.

3.9.1.1 Synthesis of (Trifluoromethyl)-1,2- benziodoxol-3(1H)-one (117)



143 **117**

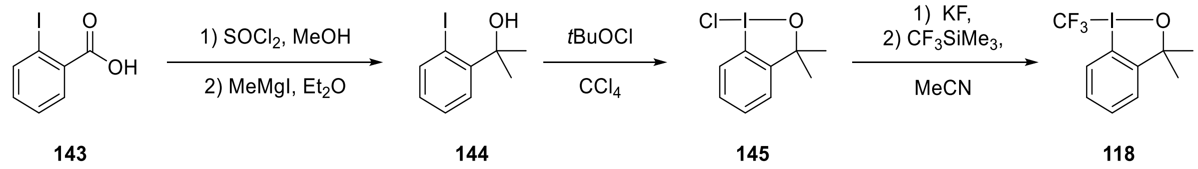
Procedure followed from known literature procedures.[171a]

Starting from 2-iodobenzoic acid **143** (3.525 g, 13.9 mmol, 1 equiv), Togni reagent **117** was prepared as a white solid (3.13 g, 71% yield). Spectral data is consistent with literature values.[171a]

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.46 (d, J = 7.0, 1H), 7.78 (m, 3H).

^{19}F NMR (471 MHz; $CDCl_3$): δ -34.3.

3.9.1.2 Synthesis of Trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benzodioxole (118)



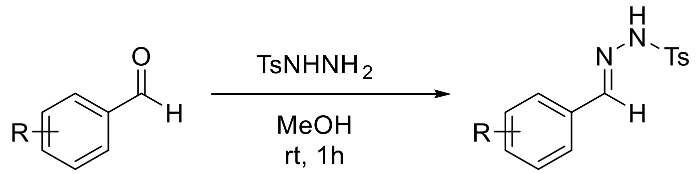
Procedure followed from known literature procedures.[156]

Starting from 2-iodobenzoic acid **143** (3 g, 12.1 mmol), the methyl ester was synthesized as a pale yellow liquid (3.009 g, 95% yield). Upon transformation to alcohol **144**, the crude brown liquid was subjected to tert-butylhypochlorite to afford the chloroiodane **145** as a yellow solid (1.2116 g, 62% yield). Following other known literature procedures,*[171a]* the final ligand exchanges gave benziodoxole **118** as a white solid (0.700 g, 35% yield) Spectral data is consistent with literature values.[101]

^{1}H NMR (300 MHz; CDCl$_3$): δ 7.52 (m, 2H), 7.41 (m, 2H), 1.47 (s, 6H).

^{19}F NMR (471 MHz; CDCl$_3$): δ -40.4.

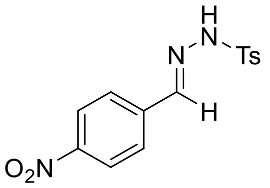
3.9.2 General Procedure A: Synthesis of Tosylhydrazones



Procedure adapted from known literature procedures.[252]

The aldehyde (1.0 equiv) was added dropwise/portionwise to a suspension of tosylhydrazide (1.0 equiv) in MeOH (1.0 M). A mildly exothermic reaction ensued, and the hydrazide dissolved. The reaction mixture then was stirred at room temperature until complete conversion was observed by TLC. The solvent was removed by rotary evaporation and the crude solid was dissolved in dichloromethane and filtered by vacuum filtration to remove residual aldehyde. The solution was concentrated under reduced pressure to give the tosylhydrazone compound.

3.9.2.1 Synthesis of 4-Nitrophenylbenzaldehyde Tosylhydrazone (213)

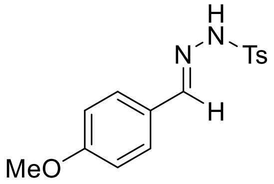


4-Nitrophenylbenzaldehyde **222** (1.5 g, 10 mmol, 1 equiv) was subjected to General Procedure A to yield tosylhydrazone **213** as a pale yellow solid (2.826 g, 90% yield). Spectral data is consistent with literature values.[252]

R_f: 0.30 (40% EtOAc in hexanes, UV Active).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.26 (s, 1H), 8.20 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 8.5 Hz, 2H), 7.80 (s, 1H), 7.72 (m, J = 8.5 Hz, 2H), 7.36-7.33 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H).

3.9.2.2 Synthesis of 4-Methoxyphenylbenzaldehyde Tosylhydrazone (213a)

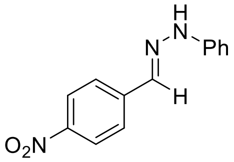


4-Methoxyphenylbenzaldehyde (0.242 mL, 2 mmol, 1 equiv) was subjected to General Procedure A to yield tosylhydrazone **213a** as an orange solid (0.304 g, 50% yield). Spectral data is consistent with literature values.[252]

R_f: 0.43 (40% EtOAc in hexanes, UV Active).

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.85 (d, J = 8.3 Hz, 2H), 7.71 (s, 1H), 7.58 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.81 (s, 3H), 2.40 (s, 3H).

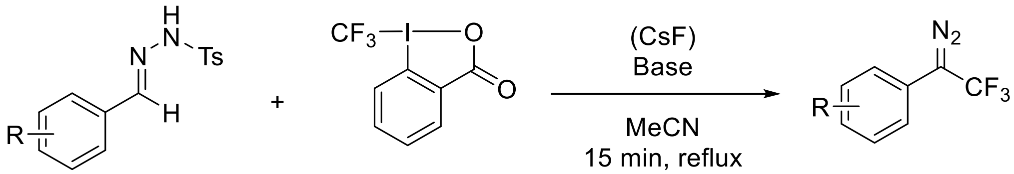
3.9.2.3 Synthesis of (E)-1-(4-nitrobenzylidene)-2-phenylhydrazine (214f)



4-Nitrobenzaldehyde **222** (0.302 g, 2 mmol, 1 equiv) was added to a solution of phenylhydrazine (0.196 mL, 2 mmol, 1 equiv) in EtOH (1.0 M) and stirred under reflux for 3 hours. Upon cooling, the crude solid was filtered by vacuum filtration, washed with EtOH, and dried *in vacuo* to yield **214f** as a dark red solid (0.433 g, 90% yield) Spectral data is consistent with literature values.[254]

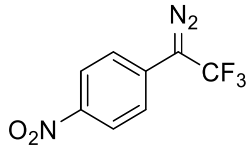
^{1}H NMR (300 MHz; $CDCl_3$): δ 8.22 (d, J = 8.8 Hz, 2H), 7.96 (br. s, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.70 (s, 1H), 7.31 (t, J = 7.8 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 6.97-6.92 (t, J = 7.0 Hz, 1H).

3.9.3 General Procedure B: Synthesis of Aryl(trifluoromethyl)diazomethanes



To an oven dried flask with a magnetic stir bar was charged arylaldehyde tosylhydrazone (1.0 equiv), Togni reagent **117** (1.1 equiv), and acetonitrile (0.05 M). If necessary, the additive (30 mol%) was added, and in quick succession, the base (3 equiv) was added in one portion. The reaction mixture was stirred in an appropriate heating oil bath while monitoring by TLC analysis for the consumption of the tosylhydrazone (within 15 min). The reaction mixture was diluted with CH_2Cl_2 and water. The aqueous phase was extracted three times with CH_2Cl_2 , and the combined organic extracts were washed with a saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product mixture subjected was to ^{19}F NMR analysis, where the NMR yield was determined using trifluorotoluene as an internal standard.

3.9.3.1 Synthesis of 1-(1-Diazo-2,2,2-trifluoroethyl)-4-nitrobenzene (215)



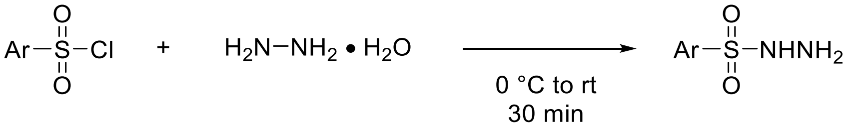
4-nitrophenylbenzaldehyde tosylhydrazone **213** (0.032 g, 0.1 mmol) was subjected to General Procedure B and purified via column chromatography (gradient elution 0 to 20% EtOAc/hexanes) to isolate **215** as an orange liquid (0.002 g, 8% yield). Spectral data is consistent with literature values.[237]

R_f: 0.80 (40% EtOAc in hexanes, UV Active).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.28 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H).

^{19}F NMR (471 MHz; CDC13): δ -57.3.

3.9.4 General Procedure C: Synthesis of Substituted Hydrazides

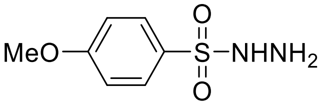


$$Ar-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-Cl \quad + \quad H_2N-NH_2 \bullet H_2O \xrightarrow[\substack{0\ °C\ \text{to rt} \\ 30\ \text{min}}]{} Ar-\overset{O}{\underset{O}{\overset{\|}{\underset{\|}{S}}}}-NHNH_2$$

Procedure adapted from Backes *et al.*.[255]

Hydrazine hydrate (5 equiv) was diluted in H_2O (30 mL) and cooled to 0 °C. The arylsulfonyl chloride (1 equiv) was dissolved in THF (5 mL) and added dropwise to the hydrazine solution, and the mixture was stirred for 30 min slowly warming to room temperature. The solvent was removed by rotary evaporation and re-dissolved in Et_2O, washed with H_2O then sat. NaCl, and dried *in vacuo* to yield the arylsulfonyl hydrazide.

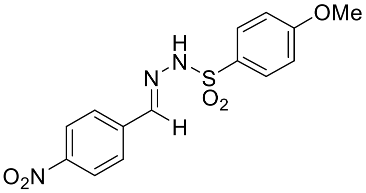
3.9.4.1 Synthesis of 4-Methoxybenzenesulfonohydrazide



4-Methoxybenzenesulfonyl chloride (1.01 g, 5 mmol, 1 equiv) was subjected to General Procedure C to yield 4-methoxybenzenesulfonohydrazide as a white solid (0.53 g, 51% yield). Spectral data is consistent with literature values.[256]

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.84 (d, J = 8.5 Hz, 2H), 7.01 (d, J = 8.5 Hz, 2H), 5.43 (br. s, 1H), 3.88 (s, 3H), 3.57 (s, 2H).

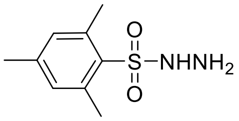
3.9.4.2 Synthesis of (E)-4-Methoxy-N'-(4-nitrobenzylidene)benzenesulfonohydrazide (214b)



4-Nitrobenzaldehyde **222** (0.151 g, 1 mmol, 1 equiv) was subjected to General Procedure A to yield **214b** as a white solid (0.327 g, 98% yield).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.25-8.22 (m, 2H), 8.07 (s, 1H), 7.97-7.94 (m, 2H), 7.81 (s, 1H), 7.77-7.74 (m, 2H), 7.04-7.01 (m, 2H), 3.88 (s, 3H).

3.9.4.3 Synthesis of 2,4,6-Trimethylbenzenesulfonohydrazide

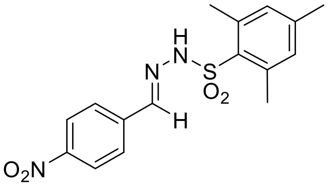


Alternate procedure from Levesque *et al.*.[244]

Mesitylsulfonyl chloride (1.093 g, 5 mmol, 1 equiv) was subjected to General Procedure C to yield 2,4,6-trimethylbenzenesulfonohydrazide as a white solid (0.719 g, 67% yield). Spectral data is consistent with literature values.[257]

^{1}H NMR (300 MHz; $CDCl_3$): δ 6.98 (s, 2H), 5.58 (br. s, 1H), 3.58 (s, 2H), 2.64 (s, 6H), 2.31 (s, 3H).

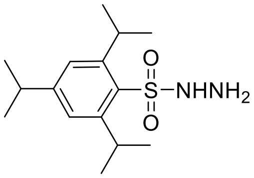
3.9.4.4 Synthesis of (E)-2,4,6-Trimethyl-N'-(4-nitrobenzylidene)benzenesulfonohydrazide (214e)



4-Nitrobenzaldehyde **222** (0.151 g, 1 mmol) was subjected to General Procedure A to yield **214e** as a white solid (0.260 g, 75% yield).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.59 (br. s, 1H), 8.21 (d, J = 9.0 Hz, 2H), 7.82 (s, 1H), 7.67 (d, J = 8.8 Hz, 2H), 7.03 (s, 2H), 2.76 (s, 6H), 2.33 (s, 3H).

3.9.4.5 Synthesis of 2,4,6-Triisopropylbenzenesulfonohydrazide

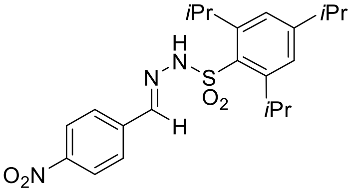


Procedure followed from known literature procedures.[258]

2,4,6-Triisopropylbenzenesulfonyl chloride (1.514 g, 5 mmol, 1 equiv) was dissolved in THF (10 mL, 0.5 M) and cooled to 0 °C. Hydrazine (1.215 mL, 25 mmol, 5 equiv) was added dropwise over 5 min and the mixture was stirred at 0 °C for 30 minutes. After which H_2O and Et_2O were added and the organic phase was washed with sat. NaCl (x 3), dried with Na_2SO_4, and the solvent was removed by rotary evaporation to yield 2,4,6-triisopropylbenzenesulfonohydrazide as a yellow solid (0.597 g, 40% yield). Spectral data is consistent with literature values.[258]

^{1}H NMR (300 MHz; $CDCl_3$): δ 7.19 (s, 2H), 5.43 (br. s, 1H), 4.20-4.07 (m, 3H), 2.97-2.84 (m, 2H), 1.27-1.25 (m, 18H).

3.9.4.6 Synthesis of (E)-2,4,6-Triisopropyl-N'-(4-nitrobenzylidene)benzenesulfonohydrazide (214d)



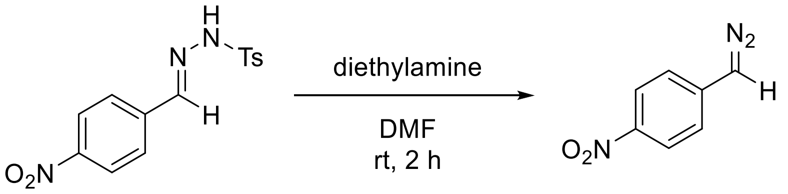
Alternate procedure from Knezz *et al.*.[258]

4-Nitrobenzaldehyde **222** (0.15 g, 1 mmol, 1 equiv) was added to a suspension of 2,4,6-triisopropylbenzenesulfonohydrazide (0.3 g, 1 mmol, 1 equiv) in MeOH (6 mL, 1.0 M) and stirred overnight. The solvent was removed by rotary evaporation and the crude residue was re-dissolved in acetone. Upon vacuum filtration, the filtrate was concentrated under reduce pressure and purification via silica plug (30% EtOAc in hexanes) gave trisylhydrazone **214d** as a beige solid (0.374 g, 87% yield). Spectral data is consistent with literature values.[259]

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.20 (d, J = 8.6 Hz, 2H), 8.05 (br. s, 1H), 7.78 (s, 1H), 7.70 (d, J = 8.6 Hz, 2H), 7.19 (s, 2H), 4.23 (sept, J = 6.7 Hz, 2H), 2.90 (sept, J = 6.9 Hz, 1H), 1.31 (d, J = 6.8 Hz, 12H), 1.24 (d, J = 6.9 Hz, 6H).

3.9.5 Miscellaneous

3.9.5.1 Synthesis of 4-Nitrophenyldiazomethane (227)



213 **227**

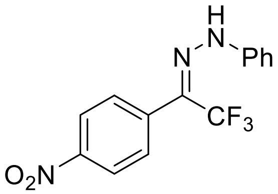
Procedure adapted from Davies and Schwarz.[260]

4-Nitrophenylbenzaldehyde tosylhydrazone **213** (2 g, 6.27 mmol, 1 equiv) was dissolved in DMF (20 mL, 0.3 M). Diethylamine (2 mL, 19.4 mmol, 3.1 equiv) was added and the solution was stirred at room temperature for 2 h. The dark red mixture was transferred to a 500 mL Erlenmeyer flask and the crude product precipitated upon addition of water (100 mL) and cooling to 0 °C. The residue was collected by vacuum filtration, dissolved in CH_2Cl_2, washed by water, brine, dried with Na_2SO_4, filtered, concentrated under reduced pressure to yield diazoalkane **227** as an orange solid (0.306 g, 30% yield). Spectral data is consistent with literature values.[261]

R_f: 0.23 (40% EtOAc in hexanes, UV Active).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.16 (d, J = 8.9 Hz, 2H), 7.00 (d, J = 8.9 Hz, 2H), 5.16 (s, 1H).

3.9.5.2 Synthesis of (Z)-1-Phenyl-2-(2,2,2-trifluoro-1-(4-nitrophenyl)ethylidene)hydrazine



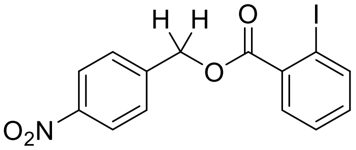
4-Nitrobenzaldehyde phenylhydrazone **214f** (0.024 g, 0.1 mmol) was subjected to General Procedure A with no additives. Upon addition of KOH, the mixture turned dark red and after 15 minutes of heating, the mixture turned black. Dichloromethane was added to the mixture and washed with H_2O. Purification by flash column chromatography yielded (Z)-1-phenyl-2-(2,2,2-trifluoro-1-(4-nitrophenyl)ethylidene)hydrazine as a dark orange liquid (0.002 g, 6% yield)

R_f: 0.60 (10% EtOAc in hexanes, UV Active).

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.27 (d, J = 9.3 Hz, 2H), 7.88 (d, J = 7.3, 2H), 7.61-7.56 (m, 5H).

^{19}F NMR (282 MHz; $CDCl_3$): δ -66.9.

3.9.5.3 Synthesis of 4-Nitrobenzyl 2-iodobenzoate (228)



In a PFA vial, 4-nitrophenyl diazomethane **227** (0.078 g, 0.5 mmol, 1 equiv) and Togni reagent **117** (0.160 g, 0.5 mmol, 1 equiv) were dissolved in MeCN. The mixture was heated to reflux and stirred while adding a solution of KOH (0.25 mL, 6.0 M in H_2O, 3 equiv). The reaction was stirred for 10 minutes, after which the solution turned orange and there was no further discernable change in TLC. The reaction continued to be stirred at reflux for a total of 1.5 hours, after which the solvent was removed by rotary evaporation. The crude reside was re-dissolved in Et_2O, and washed with H_2O, sat.

NH_4Cl, sat. NaCl, dried with Na_2SO_4, filtered, and concentrated under reduce pressure to give **228** as a yellow solid (0.054 g, 28% yield).

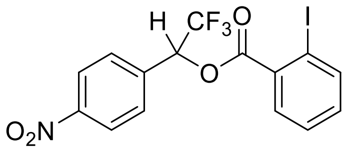
R_f: 0.66 (40% EtOAc in hexanes, UV Active).

IR (ATR) 3083, 2984, 1750, 1607, 1522, 1345, 1262, 1238, 1188, 1083, 844, 732, 712 cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.25 (d, *J* = 8.7 Hz, 2H), 8.02 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.44 (td, *J* = 7.6, 0.9 Hz, 1H), 7.19 (td, *J* = 7.7, 1.6 Hz, 1H), 5.47 (s, 2H).

^{13}C NMR (76 MHz; $CDCl_3$): δ 165.9, 147.8, 142.7, 141.5, 134.3, 133.1, 131.1, 128.7, 128.1, 123.9, 94.3, 65.8.

3.9.5.4 Synthesis of 2,2,2-Trifluoro-1-(4-nitrophenyl)ethyl 2-iodobenzoate (229)



From a collection of crude mixtures from multiple experiments following General Procedure A, separation via flash column chromatography (eluent gradient of 0 to 30% EtOAc in hexanes) yielded **229** as a yellow solid.

R_f: 0.73 (40% EtOAc in hexanes, UV Active).

IR (ATR) 3083, 2984, 1750, 1607, 1522, 1345, 1262, 1238, 1188, 1083, 844, 732, 712 cm^{-1}.

^{1}H NMR (300 MHz; $CDCl_3$): δ 8.35-8.31 (app. dt, 2H), 8.10 (dd, J = 8.0, 1.0 Hz, 1H), 8.00 (dd, J = 7.8, 1.7 Hz, 1H), 7.79 (d, J = 8.9 Hz, 2H), 7.52 (td, J = 7.6, 1.2 Hz, 1H), 7.31-7.25 (td, J = 7.5, 1.7 Hz, 1H), 6.46 (q, J = 6.6 Hz, 1H).

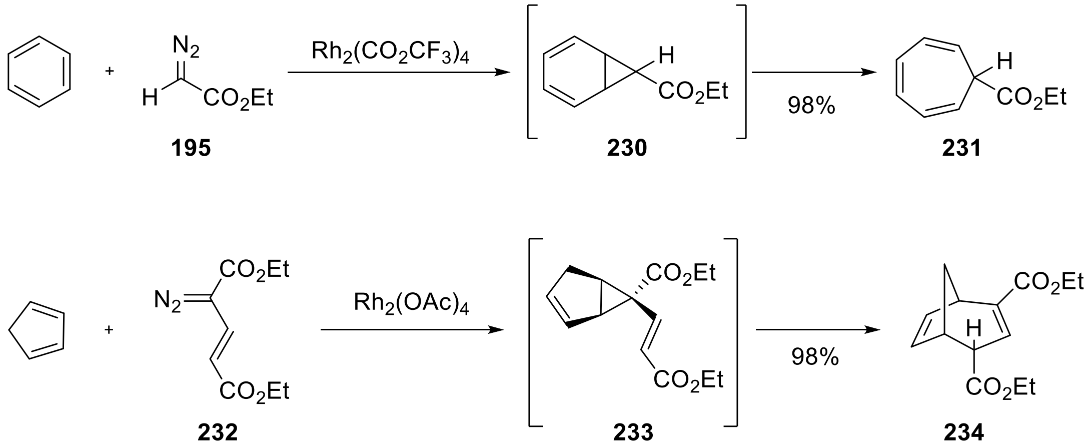
^{19}F NMR (283 MHz; $CDCl_3$): δ -75.1.

Chapter 4: Blue-light-mediated Cyclopropanation

4.1 Background

Cyclopropanes are 3-membered cycloalkanes that have applications in diverse areas of organic chemistry. They are prone to ring opening reactions due to the inherent ring strain of the C-C bonds, where the release of this strain is the driving force behind their high reactivity. Interest in these strained ring compounds has grown due to their high potential as synthetic intermediates.[262] The most well-known subclass of cyclopropanes are the donor-acceptor cyclopropanes, which contain vicinal EDG and EWG substitutions which weakens the joining C-C bond and activates the cyclopropane towards reactions with electrophiles, nucleophiles, and dipolarophiles. These doubly activated cyclopropanes are important synthetic motifs that can be used for a large array of reactions including annulations or cycloadditions (including pericyclic reactions) to form (hetero)cyclic compounds. They have also been the subject of frequent reviews throughout the past two decades.[263] Cyclopropanes have been found to occur as structural subunits in a number of natural products including many biologically active compounds.[264]

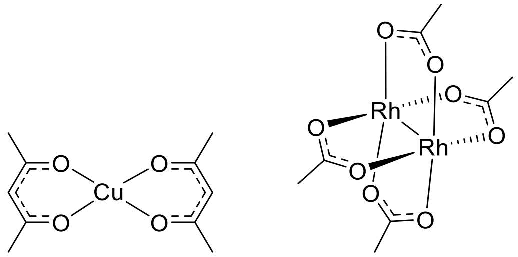
Although diazo compounds are known for their role as carbene precursors for reactions such as X-H insertions (X = N, O, C, S, etc.), an interesting application of carbenes is for the synthesis of 3-membered rings, most notably cyclopropane compounds. The use of diazo compounds towards the synthesis of cyclopropanes has seen considerable attention and thus has been a consistently reviewed topic.[226b,265] The applications of diazo compounds for cyclopropanation include reactions of diazocarbonyl derivatives with aromatic rings for Buchner ring expansions (Scheme 4.1, Top)[266] and formal [3+4] and [3+2] cycloadditions via sigmatropic rearrangements like the Cope rearrangement and vinylcyclopropane-cyclopentene rearrangement (Scheme 4.1, Bottom).[267]



Scheme 4.1 - Top: Buchner ring expansion with ethyl diazoacetate.
Bottom: Formal [3+4] cycloadditions with vinyldiazoacetate derivatives.

Historically, cyclopropanation using diazo compounds extends back to 1906.[268] However, this methodology evolved very slowly until the 1960s when metal catalysis grew popular with the advent of new catalysts. From then on, development accelerated and eventually blossomed in the 1990s when a large breadth of intermolecular, intramolecular, and asymmetric methods had been established and the methodology was further extended to cyclopropene-forming reactions from the respective alkynes. The most prevalent method for carbene formation and cyclopropanation is via metal catalysis, with palladium, copper, and rhodium being the most commonly utilized (Figure 4.1), whereas the use of ruthenium and cobalt are only recently gaining traction.[226b] The attractiveness of catalytic methods for diazo decomposition is due not only to the economy of the chemical catalysis, but also the high levels of selectivity achieved in the addition reactions.[226b,265c]

Intermolecular cyclopropanation of alkenes by catalytic addition of carbenes can have diastereo- and regioselectivity dictated by many factors such as the carbene substituents and the metal ligands. Selectivity stems from the carbene substituents where more polar substituents determine the predominant stereochemistry, and stronger electron-withdrawing groups decrease nucleophilic reactivity. Metal ligands also have a significant influence where among the carboxylate and carboxamidate ligands for rhodium, greater acid strength of the ligands' conjugate acid results in higher reactivity of catalyst and lower selectivity.[269] However, cyclopropanation by these methods is remarkably insensitive to structural influences because of the inherently high electrophilic reactivity of the intermediate metal carbene. This is due to the fact that bond formation with the alkenes occurs at distances sufficiently removed from the center which limits steric interaction between carbene and alkene substituents.[265b]

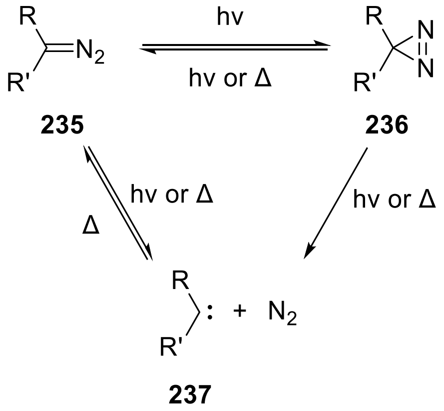


238 **239**

Figure 4.1 - Copper (II) acetylacetonate and rhodium (II) acetate, the two most popular metal catalysts for diazo decomposition.

For diazomethane decomposition, palladium is the most used metal, as copper and rhodium often leads to polymethylene and carbene dimer formation.[270] In particular, palladium (II) acetate ($Pd_2(OAc)_4$) is the most commonly used because Pd (II) coordinates well to alkenes for the electrophilic addition by the metal olefin complex onto diazomethane.[271] Conversely, for diazocarbonyl compounds, copper and rhodium are the most often used reagents. The oldest used reagents were copper bronze and copper (II) sulfate, both of which were insoluble in suitable diazo reaction mediums. Thus, copper (I) chloride and copper (II) acetylacetonate ($Cu(acac)_2$) were developed in the 1960s as soluble catalyst alternatives.[272] Copper (II) complexes were initially favored because of their stability and general ease of preparation and handling compared to air-sensitive copper(I). Also in the 1960s, dirhodium tetraacetate ($Rh(OAc)_4$) was first prepared and characterized and the Teyssie group introduced their use for diazo decomposition in 1973.[273] It has since become the single most widely used catalyst for metal carbene transformations. Dirhodium (II) catalysts have grown in popularity as the most effective and versatile catalysts for diazo decomposition. The advantages of these air-stable compounds include a wide variety of bridging carboxylate or carboxamide ligands that provide a degree of control and selectivity not evident in copper or palladium.

The photochemistry of diazo compounds also has a deep history and the formation of carbenes by photocatalysis has been known since 1942 when Meerwein *et al.* reported the UV photolysis of diazomethane for the C-H functionalization of diethyl ether.[274] Since then, it has been established that irradiation of diazo compounds can proceeds with two pathways—either the reversible isomerization to diazirines, or the irreversible nitrogen elimination for carbene formation and the Wolff rearrangement of α-diazocarbonyl compounds. In general, longer wavelengths are used for the photosyntheses of diazirines as diazo compounds irradiated with shorter wavelength light mainly form carbenes, although carbene formation is often inevitable as both the diazo compound and diazirine are carbene precursors (Scheme 4.2).

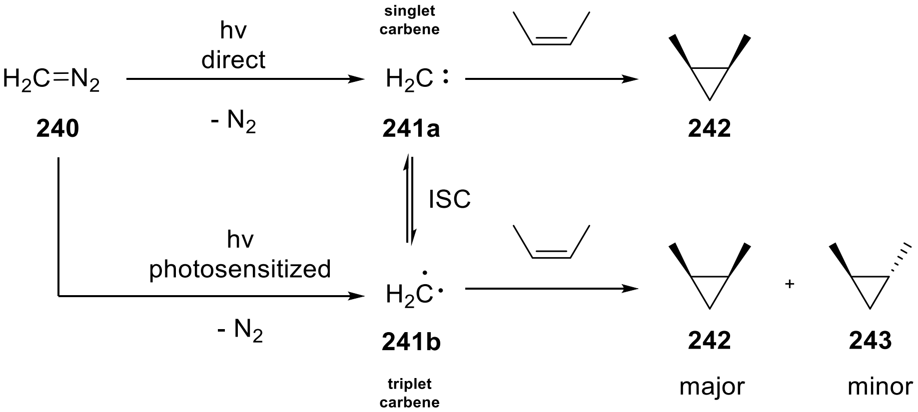


Scheme 4.2 - The known interconversions between diazoalkanes, diazirines, and carbenes.

Diazo groups are known to absorb in two regions: one intense absorption maximum at 250-320 nm and a weaker maximum at 350-500 nm, with the latter usually interpreted as the forbidden $n \rightarrow \pi^*$ or $\pi \rightarrow \sigma^*$ excitation.[188] Furthermore, conjugation with functionalities such as carbonyl groups causes a redshift of the shortwave absorption and a blueshift of the longwave absorption, such that the weaker longwave absorption may occasionally only appear as a shoulder to the main band or completely overlap. Naturally, selective excitation of such compounds is difficult or may be impossible.

The main interest in the photolysis of diazo compounds is for the generation of highly reactive carbenes, similar to metal catalysis. For the photodecomposition of diazo compounds to generate carbenes, methods have been developed both with and without the use of a photosensitizer over the past few decades. It is commonly accepted that singlet carbenes are formed from direct UV-irradiation when no photocatalyst is applied, whereas the triplet state carbenes can be selectively populated by the inclusion of triplet sensitizers. Photolysis in the presence of sensitizers (e.g. benzophenone, Michler's ketone, xanthone) or unreactive compounds (e.g. perfluorinated hydrocarbons) leads to an increased population of the triplet state.

It is also important to note that carbenes can interconvert between states in a process known as intersystem crossing (ISC), depending on reaction conditions. The influence of temperature affects the equilibrium between singlet/triplet states and also the activation energies of their competing reactions (Scheme 4.3). Thus, adjustment of the temperature can direct the selectivity of the carbenes for the suppression or formation of some stereoisomers or Wolff rearrangement products. In addition, although the triplet state carbene is often more stable, ISC in both directions is possible since the energy levels of the triplet state could be higher or degenerate with the singlet state. The spin states of carbenes can be determined in the gas phase or at low temperature in inert matrices by either electron paramagnetic resonance spectroscopy or flash photolysis techniques. However, the spin state of a carbene in reaction is not always at ground state and thus product distributions are used as a method to rationalize spin states. These explanations are based on the widely accepted assumption that singlet and triplet carbenes engage in distinctly different chemical reactivity, selectivity, and stereospecificity.



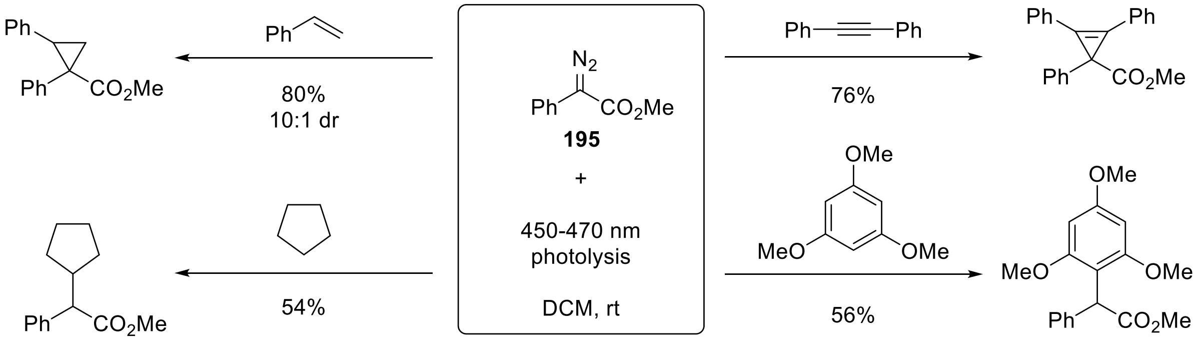
Scheme 4.3 - The formation of carbenes from diazomethane by photoexcitation and possible intersystem crossing (ISC).

Generally, it is thought that singlet carbenes in solution react with olefins in a concerted [2+1] process while triplet carbenes perform a two-step addition to generate 1,3-diradicals. Since spin inversion is slower than C-C bond rotation, this leads to the formation of a mixture of both cyclopropane stereoisomers (Scheme 4.3).[275] Alternatively, O-H insertions and Wolff rearrangements to ketocarbenes are linked to the singlet state. Additionally, during C-H insertions, singlet state carbenes react in a one-step 3-membered ring mechanism, while triplet state carbenes engage in radical pairing and the subsequent radical recombination can lead to many possible products. In summary, investigation into a reaction's product distribution allows for subsequent tuning of the equilibrium between the carbene states and consequently the output of the products.

4.2 Proposal

The intersection of photocatalysis and diazo chemistry began in the 1940s and continued for the next several decades. However, modern applications have been relatively scarce compared to thermal processes.[276] Historically, mercury (Hg) lamps were used to produce light in the UV range, but their higher energy light resulted in significant heating of reactions. In recent years, light-emitting diodes (LEDs) have emerged as new tools in the light-mediated reactions of organic compounds. The lower energy of 400-500 nm light irradiation could be achieved, enabling more convenient, practical, and selective generation of intermediates under mild conditions to produce fewer unwanted side reactions. In addition, this permits simpler setups and reactions are also often able to be performed in air without exclusion of moisture or oxygen, proving very user-friendly. Thus, due to these innovations, general interest in visible light chemistry has grown and photocatalysis has developed as a powerful strategy to initiate organic transformations that adheres to the core principles of green and sustainable chemistry.[277]

For the field of diazo chemistry, while most photochemical procedures in the past 20 years have been photocatalytic, there have been a few examples of direct photoexcitation for Wolff rearrangement reactions using visible light.[278] However, starting in 2018, seminal publications by Jurberg and Davies,[279] and the groups of He and Zhou[280] and Koenigs[281] have demonstrated a series of visible light-promoted carbene transfer reactions from aryldiazoacetate derivatives. Following this, photocatalytic reactions of diazo compounds were brought to the forefront and explored in many facets.[282] The class of aryldiazocarbonyls was noted to absorb light in the wavelength region of 400-500 nm to react with a variety of partners to perform cycloadditions, sigmatropic rearrangements of free ylides, and various X-H insertions (X = C, Si, N, O) (Scheme 4.4).



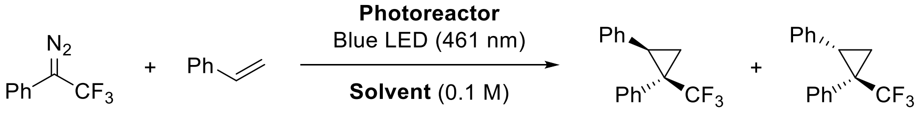
Scheme 4.4 - Visible light-mediated reactions of diazo compounds.

Despite these new breakthroughs, it seemed that approaches were limited to the donor-acceptor class of diazo compounds, with aryldiazocarbonyl compounds as the sole substrates capable of these reactions, compared to the monostabilized ethyl diazoacetate and destabilized dimethyl 2-diazomalonate derivatives which do not absorb in the blue light region. The similar aryl(trifluoromethyl)diazomethane compounds were also found to absorb light at a similar region, but were successful in only one instance.[281] However, there has also been one known example of using the trifluoromethylated aryldiazo compounds for cyclopropanation, although the use of UV light is surprising in this regard.[283] Noting that these compounds were unsuccessful in all other investigations by the Koenigs group,[284] effective applications using visible light on trifluoromethylated diazo compounds remain relatively unexplored. Therefore, inspired by this recent explosion in interest in visible light-mediated diazo chemistry and our synthesis of these aryl(trifluoromethyl)diazomethane products detailed earlier in Chapter 3, it seemed natural to explore the reactivity of these compounds with photochemistry. Starting from these donor-acceptor diazoalkanes, the synthesis of the trifluoromethylated cyclopropanes was anticipated to broaden this new growing field of chemistry.

4.3 Synthesis of Cyclopropanes from Diazo Compounds

Given the Murphy group's recent foray into visible light-mediated reactions on iodonium ylides for cyclopropanation,[285] it was opportune to gather the gained knowledge and apply the developed technology towards this new area of research. Hence, based on the reported reaction of iodonium ylides with alkene substrates, investigations commenced by applying similar procedures to styrene for possible cyclopropanation. Preliminary attempts on some samples with trace amounts of trifluoromethylated diazo product **215** were particularly encouraging and thus a bulk amount of a trifluoromethylated diazo compounds was required to continue the investigation. Phenyl(trifluoromethyl)diazomethane **209** was chosen as the model substrate due to the commercially availability of trifluoroacetophenone (**207**) and was synthesized in two steps upon condensation with tosyl hydrazide and subsequent base-catalyzed Bamford-Stevens reaction.

Employing the photoreactor (X2) used previously for the irradiation of iodonium ylides (see Chapter 4.5 for details and visual aids), diazo compound **209** was stirred with 2 equivalents of styrene as the alkene on top of the LED with 461 nm wavelength light as per the optimized conditions for cyclopropanation found previously.[285] DCM was used as an unreactive solvent to minimize the foreseen side reactions with formed carbenes. Gratifyingly, the expected NMR peaks were present in ~50% yield in the ^{1}H NMR and ^{19}F NMR spectra of the crude product mixture (Table 4.1). $CDCl_3$ was also tested as a solvent for its operational ease in being able to directly analyze the solution by NMR spectroscopy without rotary evaporation of the solvent. Due to its similar inertness, similar results were expected and subsequently achieved, enabling it as a choice for more efficient procedures in the future. When using photoreactor X1 with the same type of LEDs and wavelength (461 nm), the reaction times were twice as long and the yields were slightly lower. It was also determined that moisture-free conditions were not necessary, mirroring the established reaction conditions of other blue light-mediated reactions.[282] The photoreactor IJ with a different brand of LED with a lower wavelength light (449 nm) also achieved similarly low yields and extended reaction times. Although this result could be due to several factors, this reactor and these LEDs were simply unused due to the better results of the other LEDs and photoreactor. Thus, future experiments continued using either DCM or $CDCl_3$ as solvent, and photoreactor X1 was chosen due to its comparable yields with photoreactor X2.



209 1 equiv

244 2 equiv

245

246

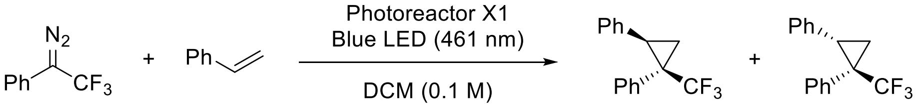
Entry	Photoreactor	Solvent	Time (h)	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	X2 (461 nm)	DCM	24	19	34	53
2	X2 (461 nm)	$CDCl_3$	24	18	38	56
3	X1 (461 nm)	DCM	48	15	26	41
4	X1 (461 nm)	DCM[b]	48	14	24	38
5	IJ (449 nm)	DCM[b]	66	15	29	44

[a]NMR yields determined using trifluorotoluene as internal standard. [b]Dry and purified DCM.

Table 4.1 - Initial experiments of visible light-mediated cyclopropanation.

Following the initial results, control reactions were performed by stirring diazoalkane **209** and styrene both in the dark and in ambient light. After 48 hours, no signs of any cyclopropane products were observed by NMR, although there was a lower amount of diazoalkane present in solution and the presence of other unidentified ^{19}F NMR peaks, signifying slow decomposition of the starting material. Next, it was postulated that a higher concentration of alkene in solution would improve yields and thus various equivalents of styrene were tested. It was found that increasing the equivalents of alkene would slightly increase yield and decrease reaction times (Table 4.2).

Puzzled by the longer reaction times of photoreactor X1 compared to X2 but with the same type of LEDs, several experiments were performed in parallel on both photoreactors and it was confirmed that longer reaction times were needed using photoreactor X1 despite yielding similar amounts of cyclopropane product (Table 4.3). Additionally, the standard was changed to ethyl trifluoroacetate to use an internal NMR standard whose peak was farther away from the peaks of the products and mixture of side reactions, while remaining close enough for yield determination without adjustment of the spectra baseline. At this time, the standard solvent of choice was also changed to $CDCl_3$ for ease of handling.



209
1 equiv

244

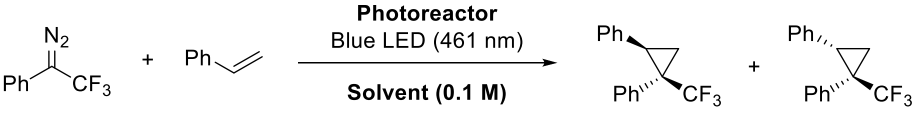
245

246

Entry	Styrene Equiv	Time (h)	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	2	48	15	26	41
2	1	48	4	7	11
3	5	48	20	37	57
4	10	40.5	21	46	67
5	0.2	48	8	13	21

[a] NMR yields determined using trifluorotoluene as internal standard.

Table 4.2 - Initial screening of styrene equivalents.



209
1 equiv

244

245

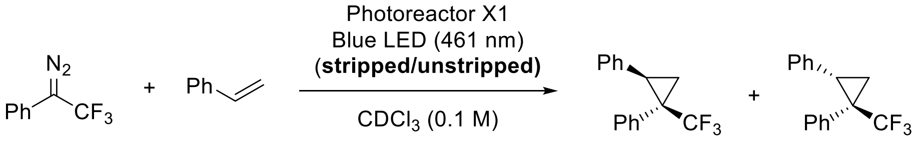
246

Entry	Photoreactor	Styrene Equiv	Solvent	Time (h)	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	X1	2	DCM	43	19	34	53
2	X1	5	DCM	43	29	59	88
3	X2	2	DCM	22	19	34	53
4	X2	5	DCM	20	26	53	79
5	X1	10	$CDCl_3$	21	19[b]	48[b]	67
6	X2	10	$CDCl_3$	12.5	19[b]	47[b]	66

[a] NMR yields determined using trifluorotoluene as internal standard. [b] Ethyl trifluoroacetate used as internal NMR standard.

Table 4.3 - Comparing photoreactors X1 and X2.

Following these experiments, it was observed that photoreactor X2's LEDs were qualitatively brighter due to the removal of the plastic coating regularly atop the LED strips, and it was hypothesized that this led to the difference in reaction times. Upon removal of the plastic coating from a few of photoreactor X1's LEDs, it was noticed that the lights were slightly brighter visually, although it was difficult to quantify. Reactions comparing the equivalents of styrene were once again performed to explore the outcome of the difference in brightness. It was found that yields did not increase above 5 equivalents of alkene and were comparable between the stripped/unstripped LEDs (Table 4.4). Reaction times were also lowered when using the stripped LEDs, mirroring the outcome of previously using photoreactor X2. Thus, the stripped LEDs were used for future experiments for faster reaction times. It should be highlighted that the higher total yields of cyclopropanes achieved here were presumed to be from the use of freshly prepared diazoalkanes, as it is known that these diazo compounds were prone to slowly degrade over time. Following this, future experiments were performed using freshly synthesized compounds.



209
1 equiv

244

245

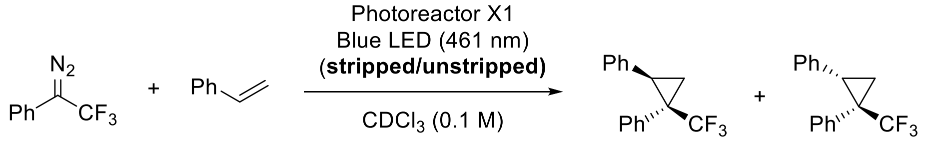
246

Entry	Photoreactor	Styrene Equiv	Time (h)	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	X1[b]	5	24	28	63	91
2	X1	5	30	27	63	90
3	X1[b]	10	24	29	72	101
4	X1	10	36	29	64	93

[a]NMR yields determined using ethyl trifluoroacetate as internal standard. [b]Outer plastic layer of the LED is removed.

Table 4.4 - Comparing the brightness of the LEDs.

Next, the concentration of alkenes in solution was systematically reinvestigated and it was observed that the total yield increased with the addition of increasing amounts of alkene up to 10 equivalents (Table 4.5). The diastereomeric ratio of the cyclopropane products was found during these experiments to be a clear 1:2 ratio between stereoisomers. Due to this unequal mixture of stereoisomer products, it was hypothesized that a portion of the formed carbenes were in the triplet state upon photoexcitation of the diazoalkane.[275] Oddly, a large excess of alkene (15 equiv) was found to be wholly detrimental to the reaction. The reason for this is currently unknown but it is speculated that since the large excess of styrene equates to a significant volume of the 1 mL reaction (170 µL of styrene), it may absorb a significant portion of light and cause side reactions. Additionally, due to the photoreactor set-up with the vial on top of the LED, the increased volume may limit amount of diazo compound absorbing light due to the small surface area. Continuing onwards, five equivalents of styrene were chosen to be used for future experiments for optimal yields and to minimize excess waste.



209
1 equiv

244

245

246

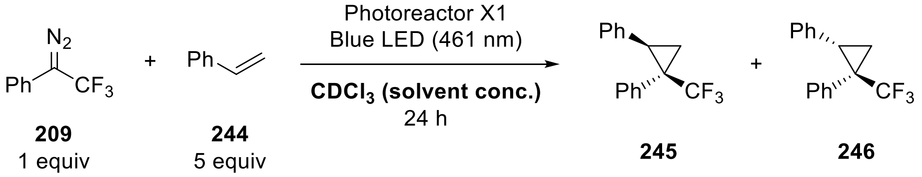
Entry	Photoreactor	Styrene Equiv	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	X1	1	14	28	42
2	X1	2	22	44	66
3	X1	3	25	52	77
4	X1	5	28	63	91
5	X1	10	29	72	101
6	X1[b]	15	8	16	24

[a]NMR yields determined using ethyl trifluoroacetate as internal standard. [b]Unstripped LED used.

Table 4.5 - Screening of equivalents of styrene.

Afterwards, solvent concentration was explored within the vial's limited 4 mL capacity. It was found that the original 0.1 mL volume with a 0.1 M concentration was already optimal, although the other concentrations achieved similar yields (Table 4.6). Additionally, it was noted that these results are in agreement with established procedures where photochemical reactions of this nature are conducted in the range of 0.05 to 0.4 M.[282] Thus, a concentration of 0.1 M was ideal for future experiments and optimizations, but unfortunately 2 mL of solvent (0.05 M) was used erroneously for

the following solvent screening. It was also at this time that one of photoreactor X1's uncovered LEDs broke, possibly because vials are held directly above the LED light which may be more detrimental to the electronics than initially thought. A new photoreactor KM was constructed to be used for the next set of experiments ylides (see Chapter 4.5 for details and visual aids). This allowed easy adjustment of the LED strip to minimize potential damage to the LEDs and the placement of the vials with LEDs was taken into careful consideration.



Entry[a]	Solvent	Solv. Conc.	NMR Yield 245 (%)[b]	NMR Yield 246 (%)[b]	Total Yield (%)
1	$CDCl_3$	0.1	28	63	91
2	$CDCl_3$	0.05	26	56	82
3	$CDCl_3$	0.2	24	61	85

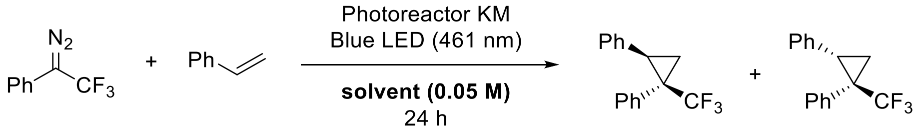
[a]Outer plastic layer of the LED is removed. [b]NMR yields determined using ethyl trifluoroacetate as internal standard.

Table 4.6 - Screening of solvent concentration.

With the new photoreactor KM, solvent screening experiments were performed using freshly prepared diazoalkane **209** (Table 4.7). It was found that ethereal solvents (THF and Et_2O), and polar aprotic solvents (acetone, MeCN, EtOAc, and DMF) all performed poorly, ranging from trace amounts to 11% NMR yield. This was rationalized by the fact that these polar solvents possess electron-donor functional groups which may undergo addition reactions to the electrophilic carbene intermediate. Following this, aliphatic solvents (hexanes and toluene) were found to be suitable to a slightly higher degree, with limited yields also attributed to possible C-H insertion reactions. Polar protic solvents like MeOH performed poorly as expected due to similar possible insertion reactions, but water as a solvent surprisingly returned a notable 35% yield. In addition to the possible side reactions, immiscibility between water and the two liquid reagents was assumed to disadvantageous, but the vigorous stirring employed in these procedures was evidently sufficient for the cyclopropanation reaction while somewhat minimizing side reactions with water. On the basis of this unexpected result, it was hypothesized that a reaction performed without solvent was possible, given the liquid nature of both reagents currently used. The reaction was performed neat in a conical vial to ensure proper mixing and was successful with 81% total NMR yield (Table 4.7, entry 16). However, significant amounts of other NMR peaks were observed, and reaction times were almost tripled with traces of the starting diazo compound still present after 48 hours. The reason for this is currently unknown as similar reactions performed in conical vials in $CDCl_3$ did not have similar outcomes and behaved normally (Table 4.7, entry 15). Thus, performing the reaction neat was not considered for the future.

Continuing, halogenated solvents (chloroform, dichloromethane, trifluorotoluene) unsurprisingly produced high yields, with trifluorotoluene appearing as the superior option. This particular solvent was used as the solvent of choice in the formation of diazo compounds *in situ* in similar cyclopropanations.[286] However, rationale was not given for this choice and the high diastereoselectivities and yields were simply stated to be generated by utilization of the solvent. It could speculated that the fluorinated solvent and fluorinated compound may have polar hydrophobic or weak H-bonding interactions that stabilize a carbene intermediate or polarized transition state.[20] Another theory is that fluorinated solvents in this reaction have a relatively higher inertness compared to chlorinated solvents, given the possible fluorine-fluorine interactions with the trifluoromethylated diazo compound. This could result in fluorous effects to avoid possible unfavoured interactions with the other elements of the reaction.[287]

The UV-Vis absorption spectrum of phenyl(trifluoromethyl)diazomethane **209** was taken and there was one strong shortwave maximum at 266 nm and one weaker longwave maximum at 459 nm (Figure 4.2), a minor deviation from the maximum of 467 nm reported by the Koenigs group.[281] However, these results match the properties expected of diazo compounds, with a bathochromic shift of the peak in the visible region compared to the maximum of 431 nm observed for aryldiazoacetate derivatives. In regard to the mechanism of this reaction, it is speculated that the uneven distribution of diastereomeric cyclopropanes indicates the formation of triplet state carbenes from the photoexcitation. This can be supported by the fact that the use of perfluorinated hydrocarbons further increased the overall yield, as it is known that unreactive mediums lead to an increased population of triplet state carbenes in some cyclopropanation reactions.[275] However, it has been observed by Zhang *et al.* that the triplet carbene of vinyldiazoacetates is only formed in minor quantities and that it is an unproductive pathway,[288] so further mechanistic studies will need to be performed.



209 1 equiv

244 5 equiv

245

246

Entry	Solvent	Time (h)	NMR Yield 245 (%)[a]	NMR Yield 246 (%)[a]	Total Yield (%)
1	Acetone	17	3	3	6
2	MeCN	17	4	7	11
3	$CHCl_3$	15.5	14	32	46
4	DCM	14	17	36	53
5	CF_3Ph	14	36	50	86
6	EtOAc	14	3	4	7
7	Et_2O	13	5	3	8
8	Hexanes	13	11	16	27
9	MeOH	13	1	1	2
10	THF	13	trace	trace	trace
11	Toluene	13	10	13	23
12	H_2O	15.5	9	26	35
13	DMF	15.5	trace	trace	trace
14	$CDCl_3$	12	24	54	78
15[b]	$CDCl_3$	18	13	31	44
16[b]	neat	36	28	54	81

[a]NMR yields determined using ethyl trifluoroacetate as internal standard. [b]Reaction performed in a conical vial.

Table 4.7 - Screening of solvents.

For the absorption of blue light by the diazo compound, one hypothesis stems from the results of previous investigations in visible light chemistry with iodonium ylides by the Murphy group.[285] It can be postulated that photoexcitation of the diazo compound occurs from the overlap of the blue light emission peak with the edge of the absorption peak in the UV region (266 nm maximum). However,

this was for single electron excitation in the iodonium ylide compounds and may not necessarily apply for the singlet free carbene formation for diazo compounds. It is then alternatively possible that photoexcitation is caused by the direct overlap of the blue light emission peak with the diazo compound's so-called forbidden absorption peak in the visible region (459 nm maximum).[188] It was noted in the work with iodonium ylides that a higher degree of overlap resulted in significant amounts of isomerization products. Given the longer reaction times needed when using photoreactor IJ with 449 nm light (Table 4.1, entry 5), it is speculated that this shorter wavelength light results in a slight increase in overlap (assuming overlap with the peak in the UV region) and causes an increased isomerization of the diazoalkane to the diazirine form or increased intersystem crossing of the singlet carbene to the triplet carbene may be unproductive in either case.

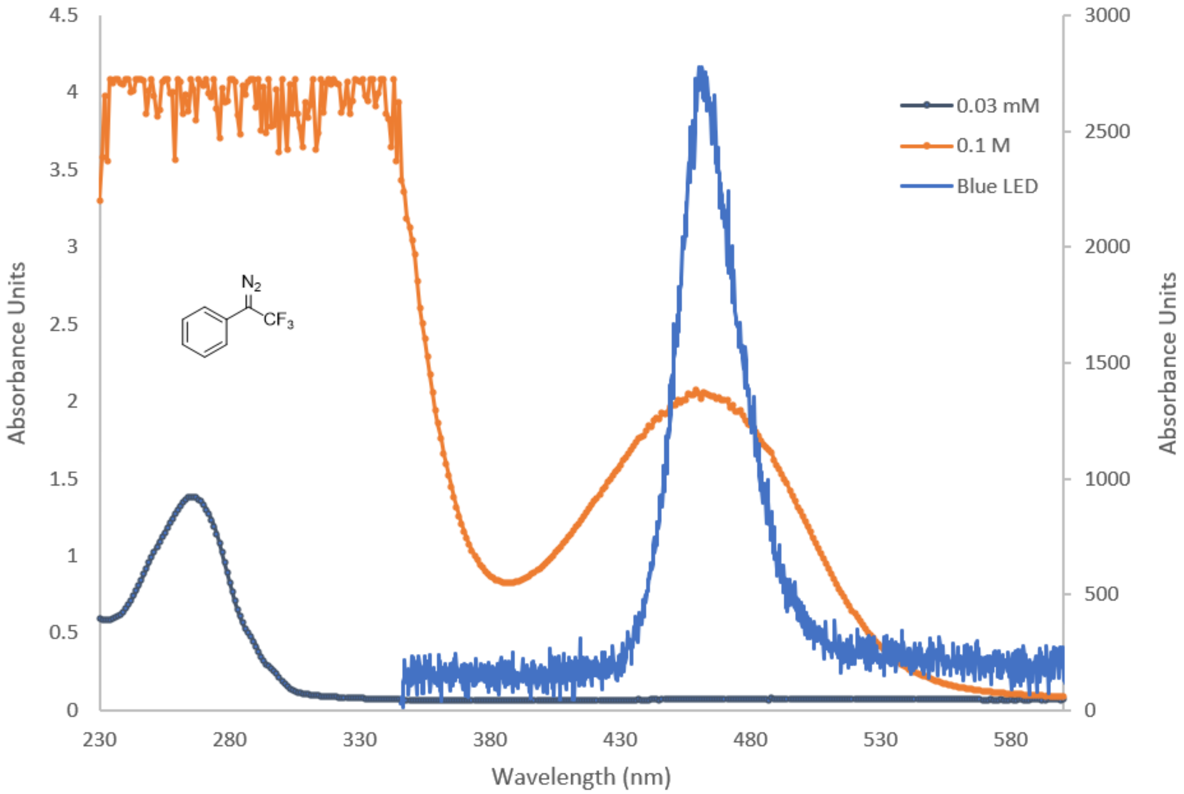


Figure 4.2 - UV-Vis spectra of phenyl(trifluoromethyl)diazomethane **219** at different concentrations overlayed with blue light emission.

4.4 Conclusion and Future Work

In conclusion, it was shown that the reaction of phenyl(trifluoromethyl)diazomethane with styrene under visible blue light conditions was effective for the synthesis of 1-aryl-1,2-diphenylcyclopropanes. Investigations were performed in regard to alkene equivalents, solvents, solvent concentration, and nature of the light. It was found that 5 equivalents of styrene was the most productive along with halogenated solvents to minimize side reactions. Qualitatively brighter also led to faster reaction times. These conditions must be further examined towards the re-optimization of the reaction conditions. In addition, a proper mechanistic study will need to be undertaken to explore the reactivity of this reaction.

A larger goal for this project would be a 1-pot reaction as it is known that diazo compounds are generally unstable and their generation *in situ* is ideal. Known reactions of this type include dehydrogenation of hydrazones for cyclopropanation using metal catalysts,[286a] and examples of Bamford-Stevens reactions of tosylhydrazones for pyrazole formation[253] or as carbene precursors.[212c] Previous reports of applications using trifluoromethylated diazo compounds in particular started from tosylhydrazones and required heating, the addition of base, and sometimes unreactive fluorinated solvents.[289] Recently, it has been shown that diazoacetates are able to be formed *in situ* from the corresponding tosylhydrazone by addition of base at room temperature, which could be used for blue light-mediated C-H insertion reactions.[240] Thus, the use of trifluoromethylated tosylhydrazones would be a high potential route for this research. An even larger goal would be to use the difunctionalization methods of the previous chapter for the generation of trifluoromethylated diazo compounds *in situ* starting from benzaldehyde tosylhydrazones. Unfortunately, preliminary work only resulted in small amounts of the trifluoromethylated diazo compound **215** with a complex mixture of products.

Future studies in substrate scope are to be conducted with various types of alkenes (e.g. aliphatic, aromatic, conjugated, sterically hindered styrenes derivatives). The aromatic substitution of the phenyl ring could also be explored. Preliminary tests using leftover samples of the diazoalkane **209** with allyl benzene and 4-fluorostyrene produced promising results with distinct ^{19}F NMR peaks and are expected to have positive outcomes. Further examination of the substrate scope would prove to be beneficial to expanding the scope of procedures for blue light-mediated reactions with compounds containing aryl and trifluoromethyl substituents, an area of research which is currently lacking.

Exploration into light-mediated techniques would provide alternatives to metal-free procedures,[286] and broaden the methods currently available for synthesizing these particular cyclopropane derivatives.[290] This is expected to expand the current breadth of trifluoromethylated materials used as building blocks in the synthesis of complex molecules and allow other options towards the improvement of metabolic properties of pharmaceutical compounds.

4.5 Experimental Procedures & Spectral Data

4.5.1 General Experimental Details

Reactions were carried out in oven-dried glassware with magnetic stirring under open atmosphere, unless otherwise stated. All reagents and solvents were purchased from Sigma-Aldrich or Oakwood Chemical and used without further purification, unless otherwise stated. Solvents were dried and purified using a JC Meyer solvent purification system or purified according to the Purification of Laboratory Chemicals handbook. Transfer of anhydrous solvents and reagents was accomplished with oven-dried needles. Reactions were monitored by thin-layer chromatography (TLC) on glass plates pre-coated with commercial silica 0.25 mm Kieselgel 60 F254 (Silicycle) and viewed by UV lamp (254 nm). Flash column chromatography was performed using 60 Å (230-400 mesh) silica gel (Silicycle) using eluent systems described for each experiment. All NMR spectra are reported in chemical shifts (δ) in parts per million (ppm) relative to reference compounds and/or residual undeuterated solvent peaks. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br. s = broad singlet, app. = apparent. Proton NMR spectra (^{1}H NMR) were recorded at 300 or 500 MHz and are reported relative to the residual chloroform peak (7.26 ppm) and coupling constants (J) are reported in hertz (Hz). Fluorine NMR spectra (^{19}F NMR) were recorded at 282 or 470 MHz and are reported relative to the peak of trifluoroacetic acid (-76.53 ppm).

Important Safety Note:

Diazo compounds are presumed to be toxic and potentially explosive.[253] These materials should be handled with care only in a well-ventilated fumehood. Gloves must be worn at all times when handling diazoalkane solutions and vessels. No incidents occurred handling diazoalkanes during the preparation of this thesis, yet the reader should be aware of the carcinogenicity and explosiveness of the herein described diazo compounds and general safety precautions should always be followed.

Photoreactor Set-up

The photoreactors used for photochemical reactions were constructed from Nalgene Unwire test tube racks interlaced with high density sapphire blue 5050 LED strips (www.creativelightings.com/ product: CL-FRS5050-12WP-12V). Suitable reaction vessels were 1 dram vials able to be held and suspended by the rack (Figure 4.3). The LED strips were secured to the notch spacing such that each individual vial could be placed directly above a single LED. This permits multiple simultaneous reactions at a minimal and standardized distance. The LEDs were secured either by pieces of plastic (Photoreactor X1) or elastic bands (Photoreactor KM). Multiple photoreactors with minor alterations were tested and photoreactor X1 was chosen as the main reactor for the majority of the experiments. Please see the Supporting Information document by Chidley[285] for visual aids and further information for the photoreactor set-up. For conical vials, an additional attachment can be clipped to photoreactor KM (Figure 4.3, Bottom) to properly suspend the conical vials at a suitable distance above the LEDs. It is also recommended to wear yellow-tinted safety glasses and to avoid looking directly at the LEDs when turned on as the light prolonged exposure may damage one's eyes and vision.

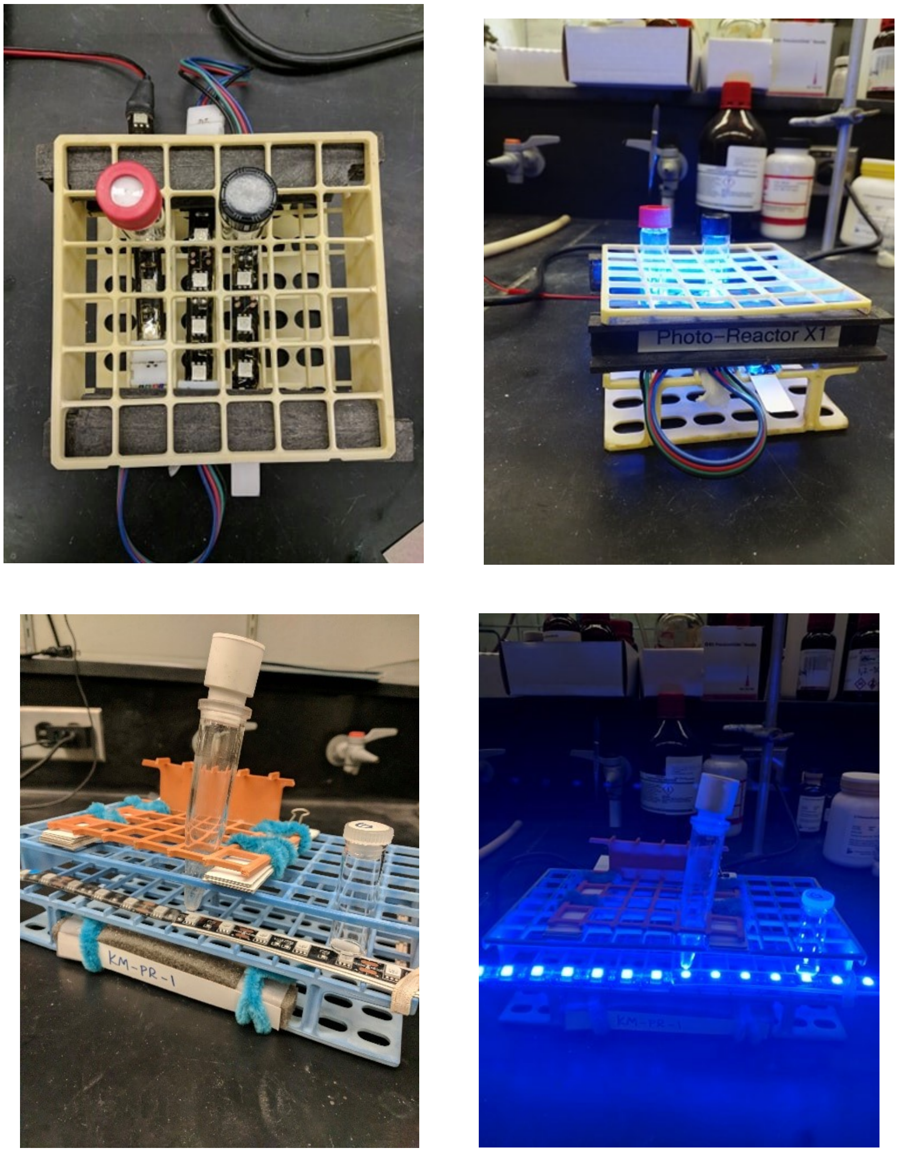
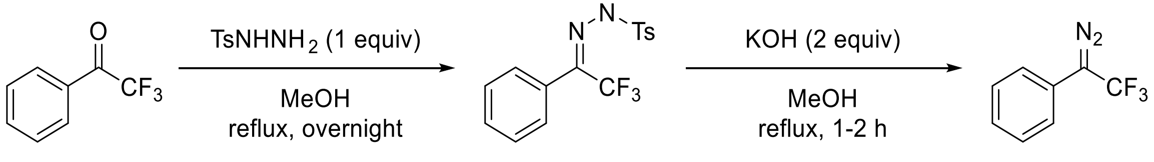


Figure 4.3 - Top: Photoreactor X1, used for the majority of experiments with blue light. Bottom: Photoreactor KM, made later with identical LEDs.

4.5.2 General Procedure D: Synthesis of Aryl(trifluoromethyl)diazomethanes

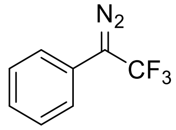


207 **208** **209**

Procedures adapted from known literature.[241,291]

To a round-bottom flask surmounted with a reflux condenser was added tosylhydrazide (1 equiv) and dissolved in MeOH at reflux (~1.5 M). The reaction was cooled to room temperature and trifluoroacetophenone **207** (1 equiv) was added in one portion. The reaction mixture was then stirred at reflux overnight. The solvent was removed under reduced pressure and used in subsequent steps without additional purification. The crude residue was re-dissolved in MeOH (~0.4 M) and a mixture of KOH (2.0 equiv) in MeOH (~1.0 M) was added. The reaction mixture was heated to reflux for ~1-2 h, until the colour of the solution no longer intensified. The reaction was cooled to room temperature and diluted with water. The crude product was extracted with hexanes (x3), washed with sat. NaHCO$_3$ (x1), brine (x1), dried with Na$_2$SO$_4$, filtered, and concentrated under reduced pressure, and purified by a silica plug.

4.5.2.1 Synthesis of Phenyl(trifluoromethyl)diazomethane (209)



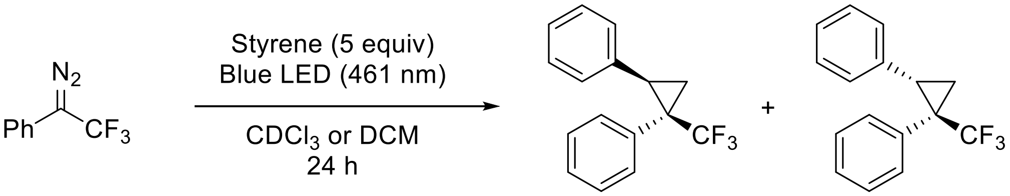
Trifluoroacetophenone (0.84 g, 6 mmol, 1 equiv) was subjected to General Procedure D. Purification via silica plug with hexanes gave **209** as a dark red liquid (0.334 mg, 30% yield over 2 steps). Spectral data is consistent with literature values.[237]

R$_f$: 0.65 (hexanes, UV Active).

^{1}H NMR (300 MHz; CDCl$_3$): δ 7.39 (t, J = 7.8 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H).

^{19}F NMR (282 MHz; CDCl$_3$): δ -57.6.

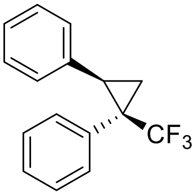
4.5.3 General Procedure E: Synthesis of 1-Trifluoromethyl-1,2-diphenylcyclopropanes



209 **245** **246**

In an oven-dried 1 dram vial containing solvent (1 mL, 0.1 M) was stirred diazoalkane **209** (0.019 mL, 0.10 mmol, 1 equiv) and styrene (0.057 mL, 0.5 mmol, 5 equiv) for ~1 min, giving a dark orange mixture. The vial was capped, and the LED light was turned on. The reaction mixture was stirred until the solution became clear and TLC analysis confirmed complete consumption of the diazoalkane. For mixtures not using CDCl$_3$ as solvent, the solvent and excess styrene were removed by rotary evaporation and *in vacuo*. The resulting crude product mixture was subjected to ^{19}F NMR analysis where the NMR yield was determined using trifluorotoluene (-63.0 ppm) or ethyl trifluoroacetate (-75.5 ppm) as an internal standard.

4.5.3.1 Synthesis of Racemic (1*R*,2*R*)-1-Trifluoromethyl-1,2-diphenylcyclopropane (245) and (1*R*,2*S*)-1-Trifluoromethyl-1,2-diphenylcyclopropane (246)



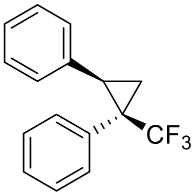
245

Diazoalkane **209** (0.019 mL, 0.10 mmol, 1 equiv) was subjected to General Procedure E. From a mixture of crude products of multiple experiments, purification via flash column chromatography (gradient elution of 0 to 10% EtOAc in hexanes) gave **245** as a clear liquid.

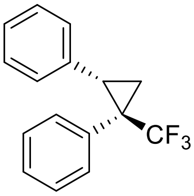
R$_f$: 0.20 (hexanes, UV Active)

^{1}H NMR (300 MHz; CDCl$_3$): δ 7.63-7.57 (m, 2H), 7.48-7.31 (m, 8H), 2.73 (t, J = 8.7 Hz, 1H), 1.95 (t, J = 6.2 Hz, 1H), 1.62-1.56 (m, 1H).

^{19}F NMR (282 MHz; CDCl$_3$): δ -64.0.



245



246

During the purification step, **246** was isolated as a diastereomeric mixture with **245** as a clear liquid. Comparing to the isolated spectrum peaks for **245**, the difference with the spectra for the mixture results in peaks for **246** which are consistent with literature values.[286]

^{1}H NMR (300 MHz; CDCl$_3$): δ 7.64-7.61 (m, 2H), 7.48-7.30 (m, 8H), 7.25-7.09 (m, 8H), 6.81-6.78 (m, 2H), 2.86 (dd, J = 9.4, 7.1 Hz, 1H), 2.76 (t, J = 8.3 Hz, 1H), 1.97 (t, J = 6.5 Hz, 1H), 1.90 (dd, J = 9.3, 6.0 Hz, 1H), 1.72-1.68 (m, 1H), 1.64-1.59 (m, 1H).

^{19}F NMR (282 MHz; CDCl$_3$): δ -63.9, -70.0.

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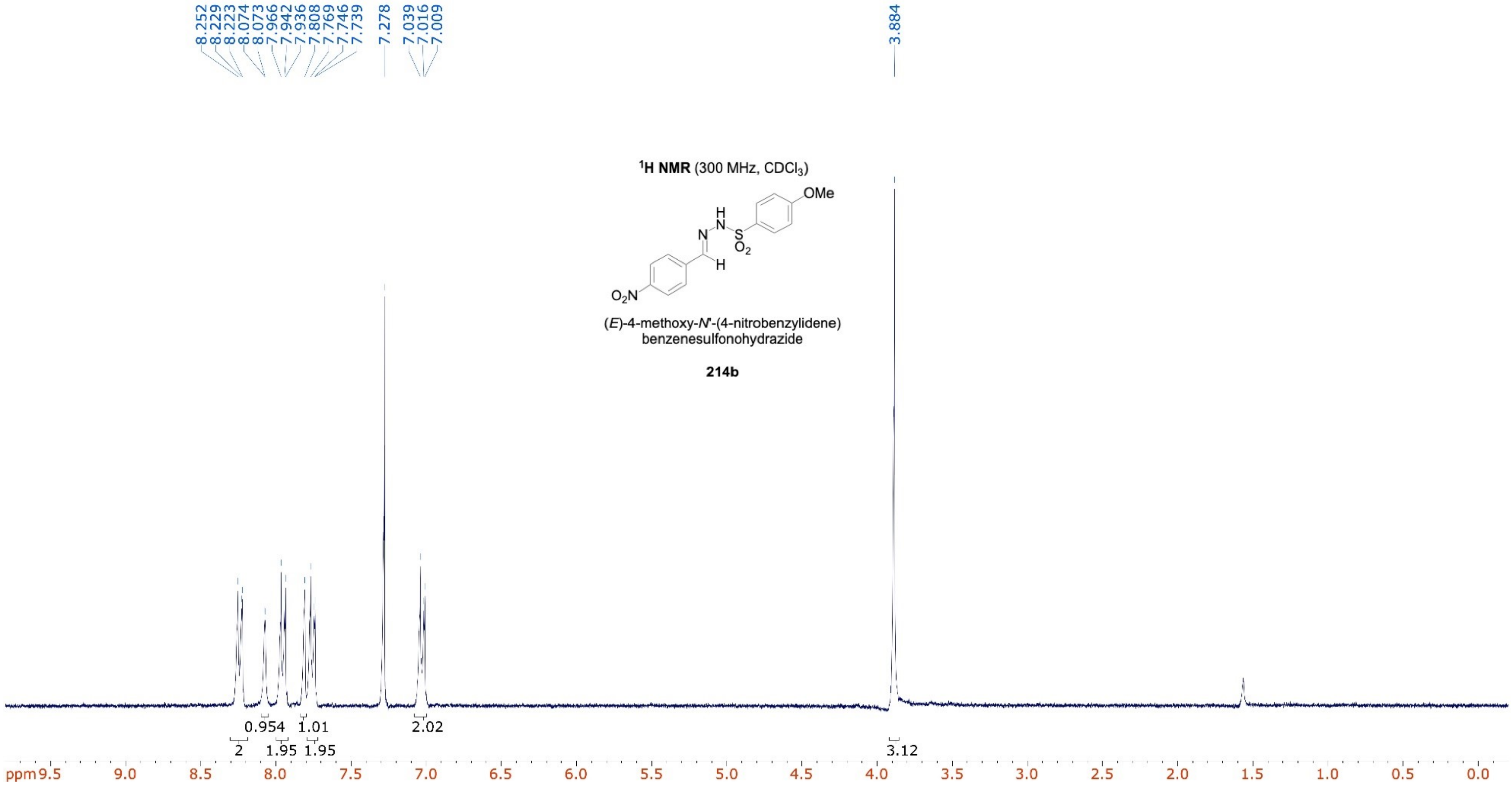
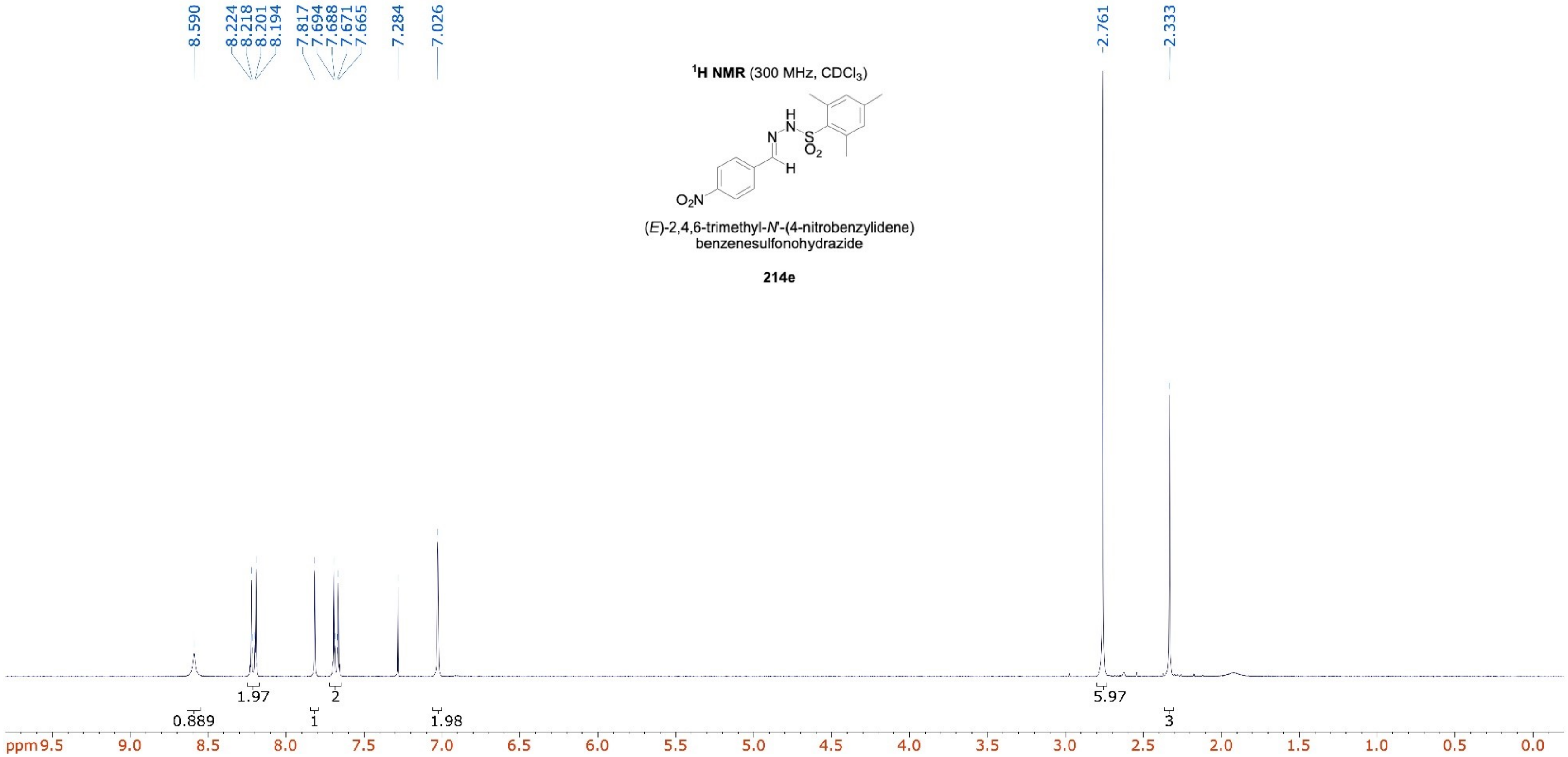
Appendix A: NMR Spectra



^{1}H NMR (300 MHz, $CDCl_3$)

(*E*)-4-methoxy-*N'*-(4-nitrobenzylidene)
benzenesulfonohydrazide

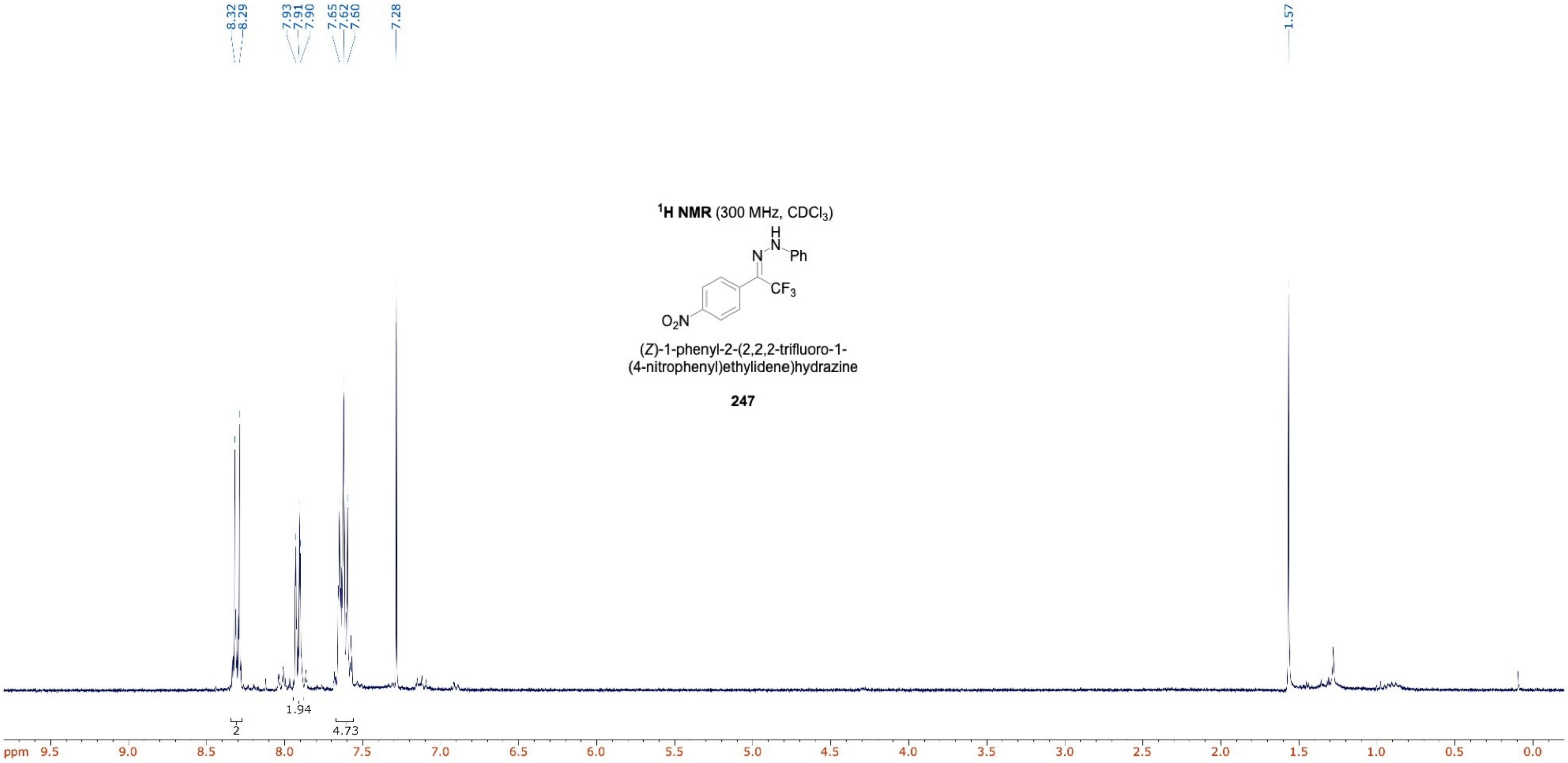
214b



^{1}H NMR (300 MHz, $CDCl_3$)

(*E*)-2,4,6-trimethyl-*N'*-(4-nitrobenzylidene)
benzenesulfonohydrazide

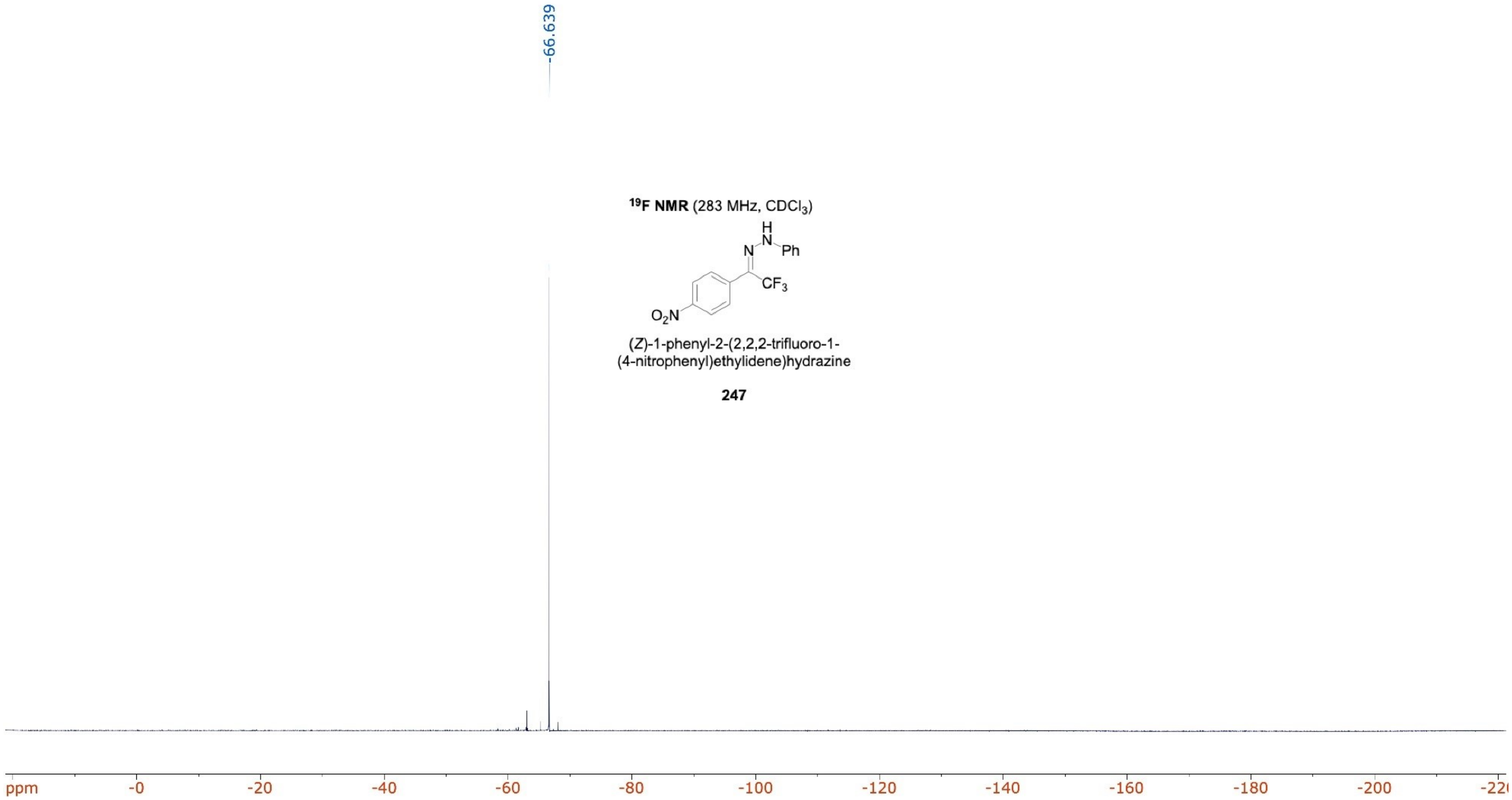
214e



^{1}H NMR (300 MHz, $CDCl_3$)

(*Z*)-1-phenyl-2-(2,2,2-trifluoro-1-(4-nitrophenyl)ethylidene)hydrazine

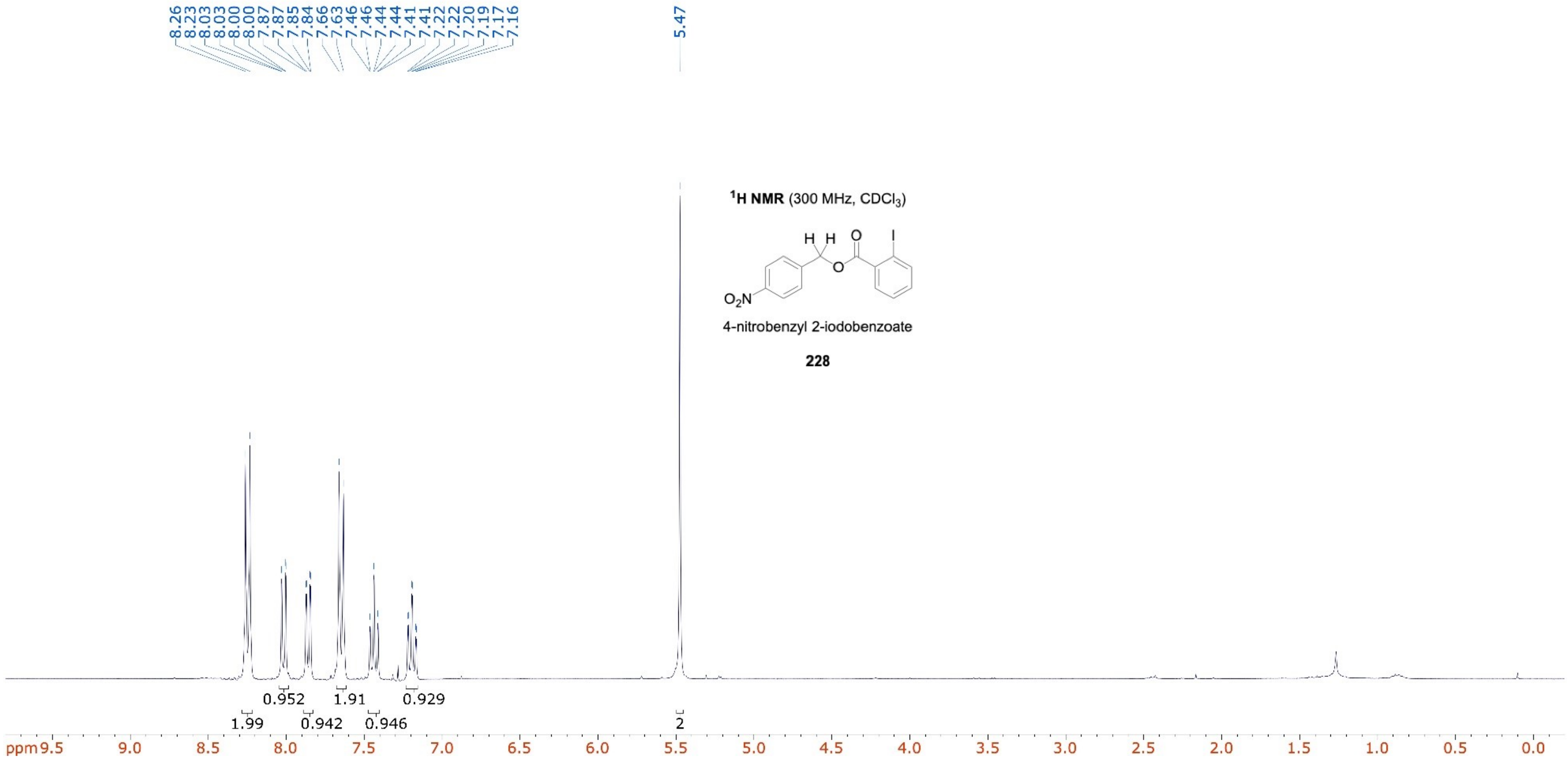
247



^{19}F NMR (283 MHz, $CDCl_3$)

(*Z*)-1-phenyl-2-(2,2,2-trifluoro-1-(4-nitrophenyl)ethylidene)hydrazine

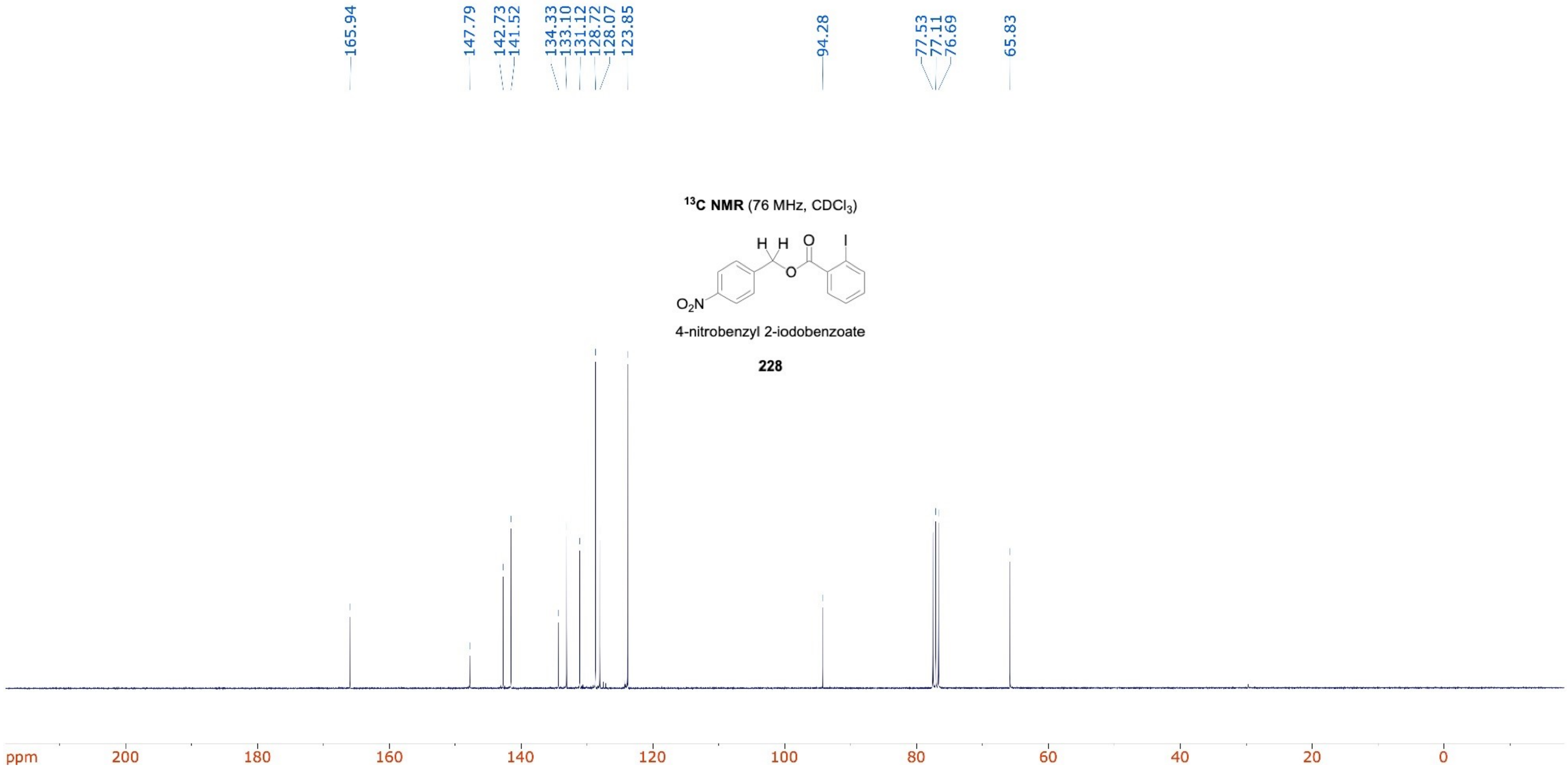
247



^{1}H NMR (300 MHz, $CDCl_3$)

4-nitrobenzyl 2-iodobenzoate

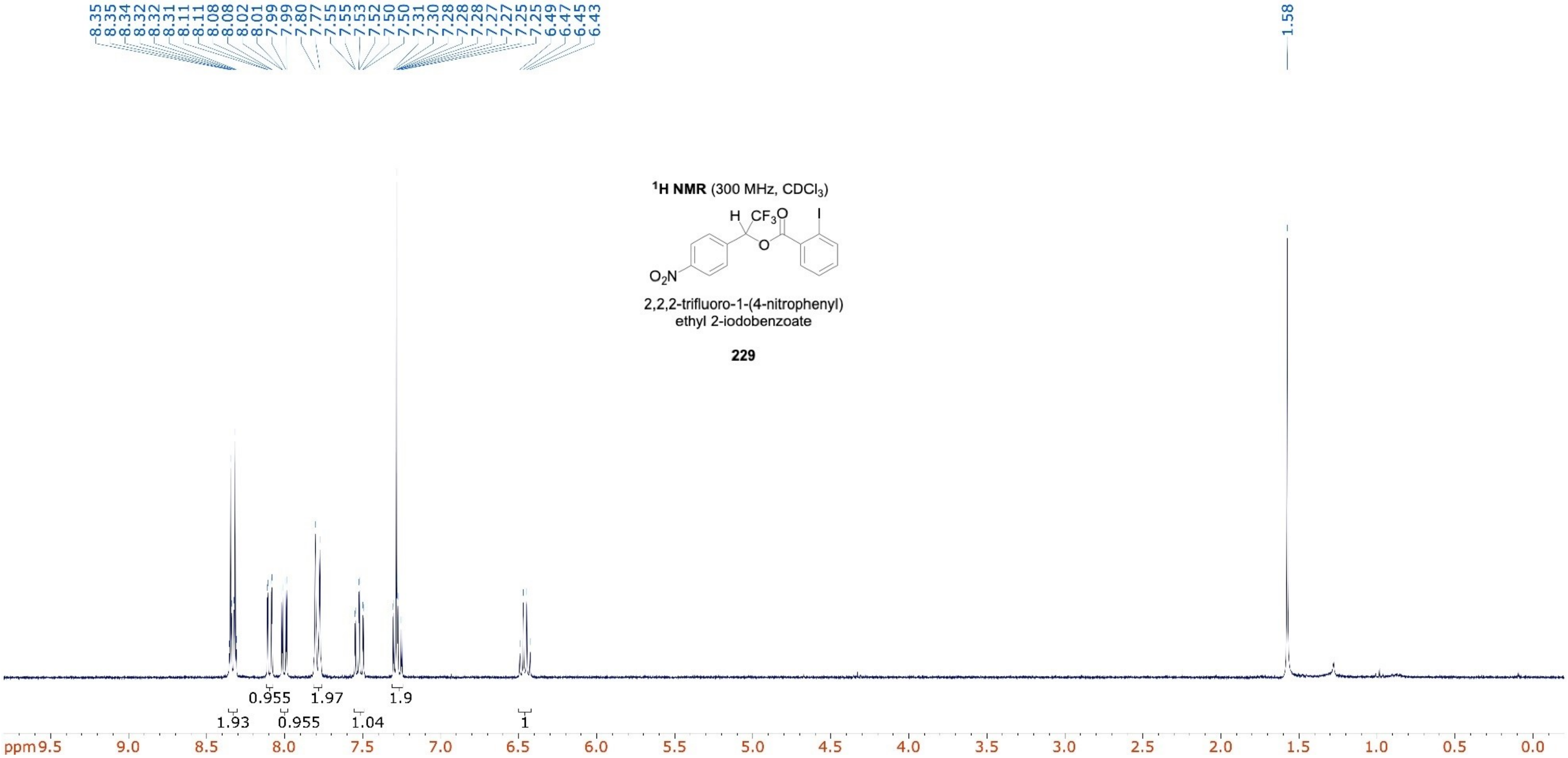
228



^{13}C NMR (76 MHz, $CDCl_3$)

4-nitrobenzyl 2-iodobenzoate

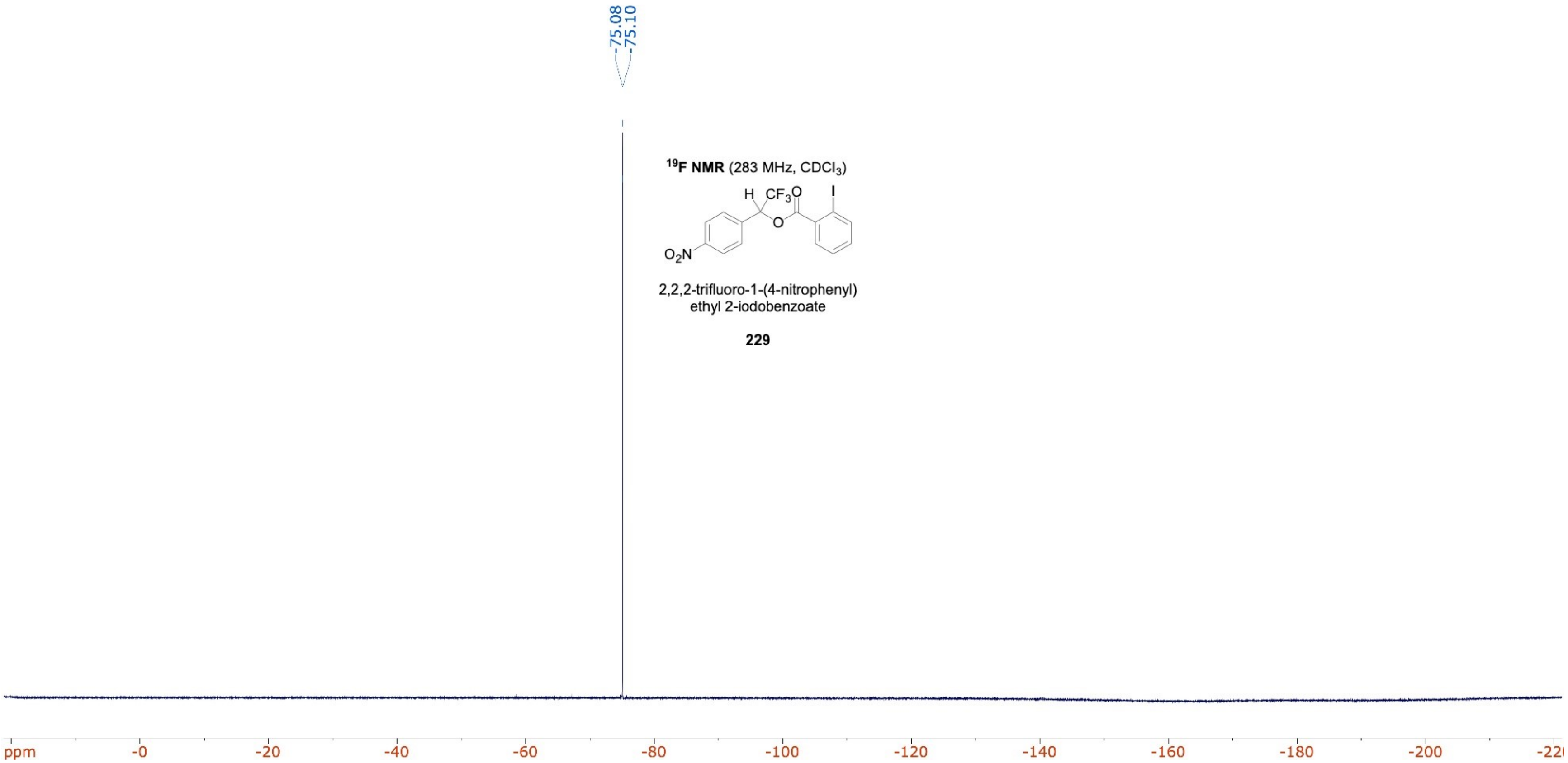
228



^{1}H NMR (300 MHz, $CDCl_3$)

2,2,2-trifluoro-1-(4-nitrophenyl)
ethyl 2-iodobenzoate

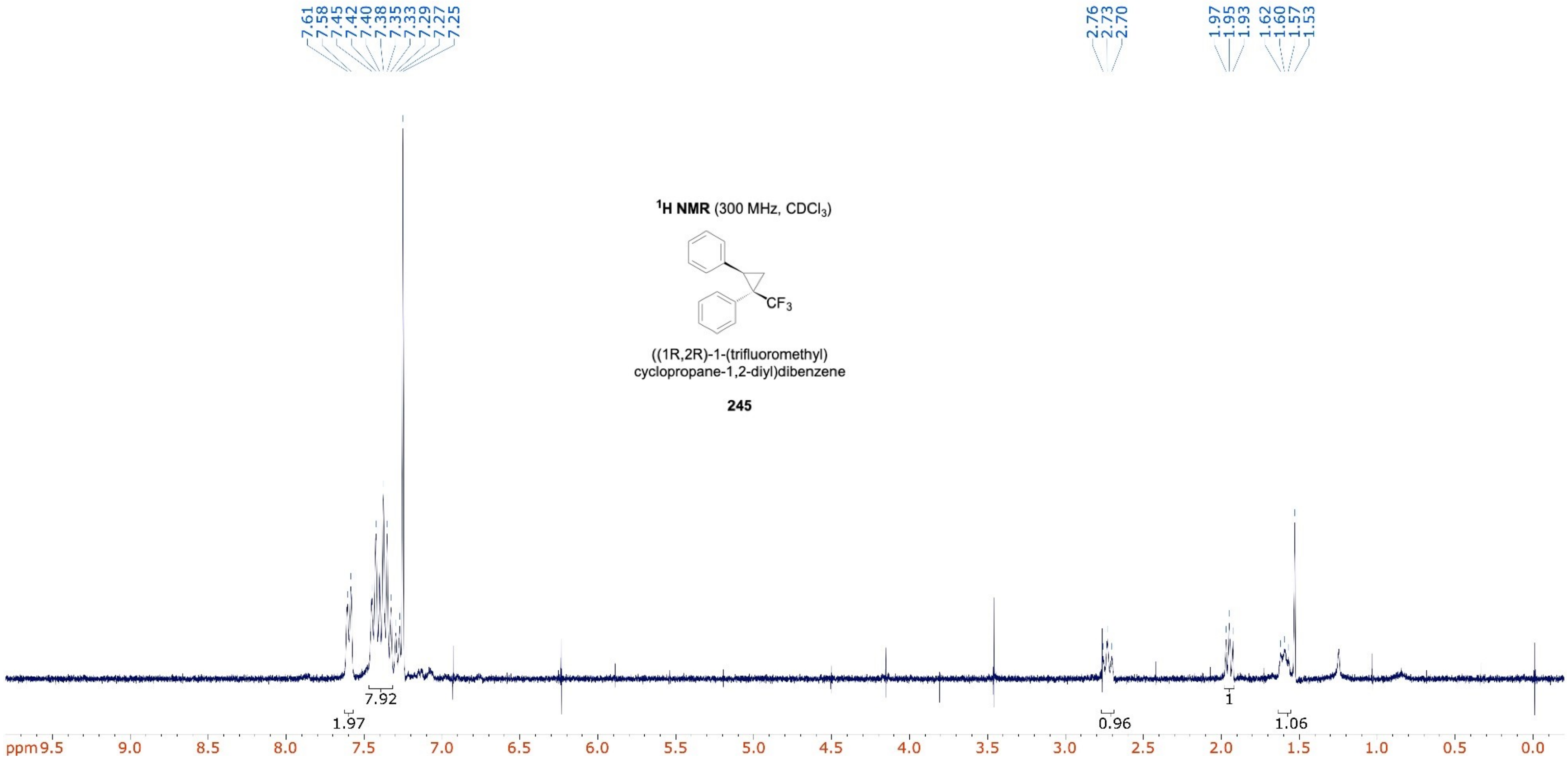
229



^{19}F NMR (283 MHz, CDCl$_3$)

2,2,2-trifluoro-1-(4-nitrophenyl)
ethyl 2-iodobenzoate

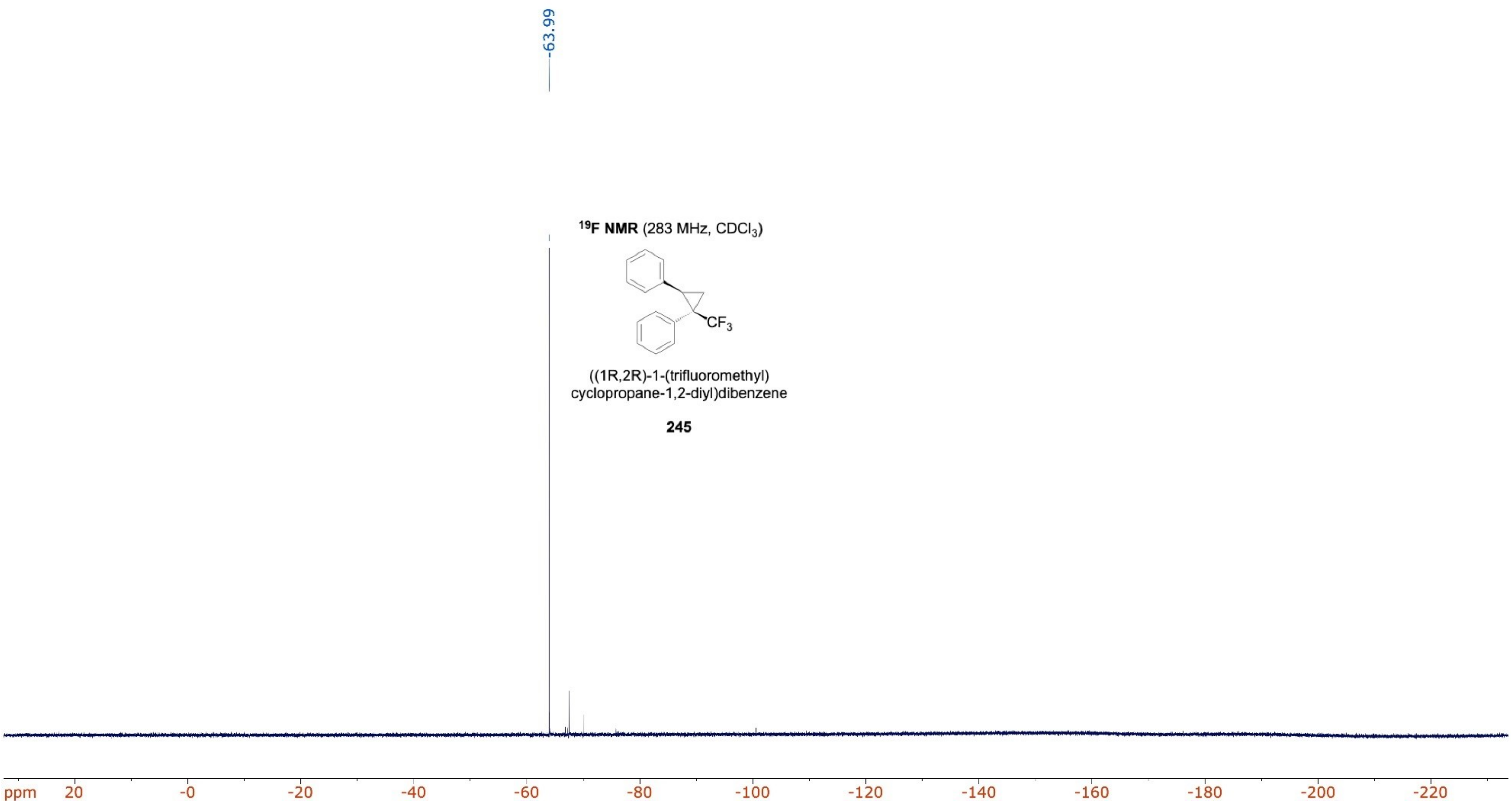
229



^{1}H NMR (300 MHz, $CDCl_3$)

((1R,2R)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

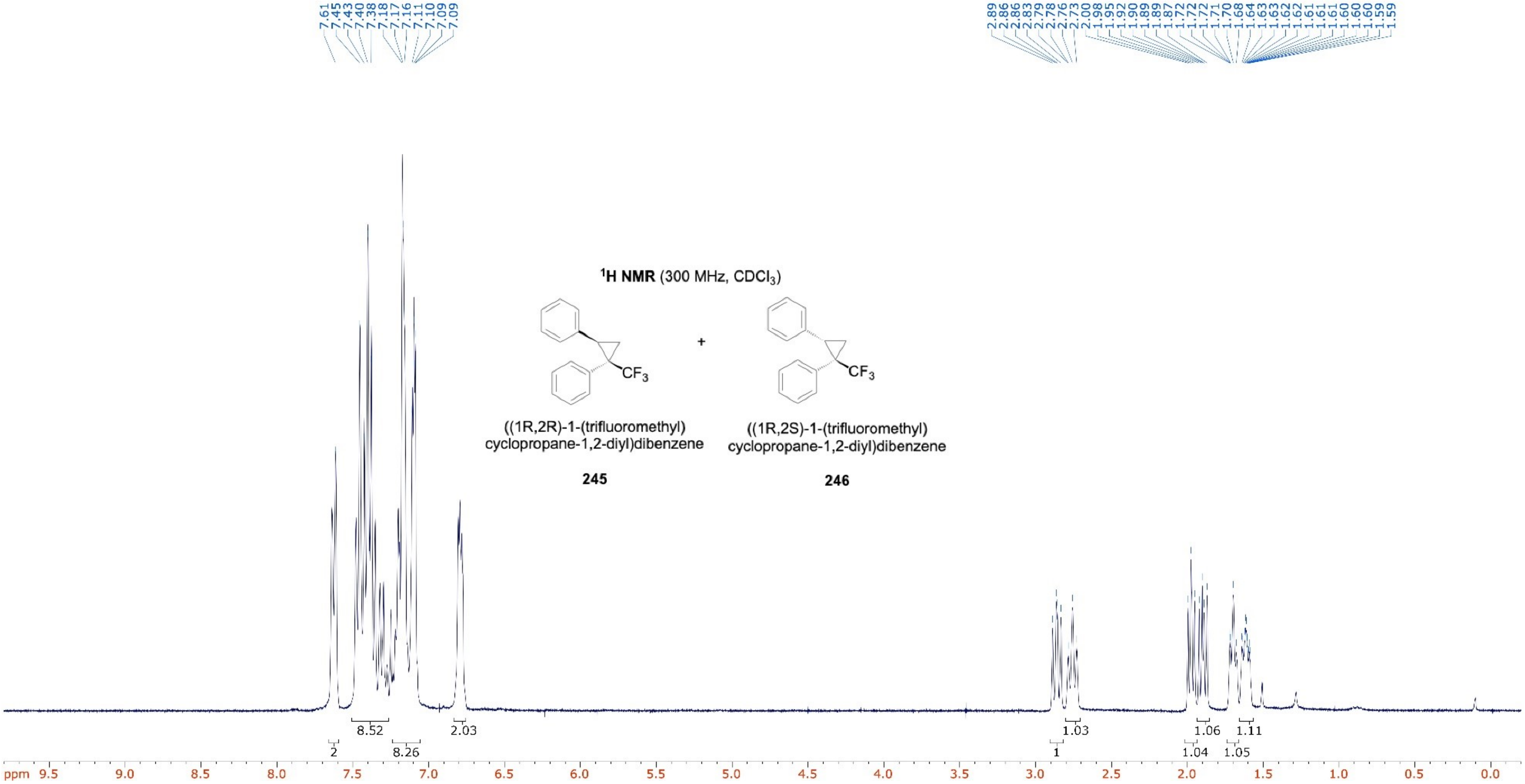
245



^{19}F NMR (283 MHz, $CDCl_3$)

((1R,2R)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

245



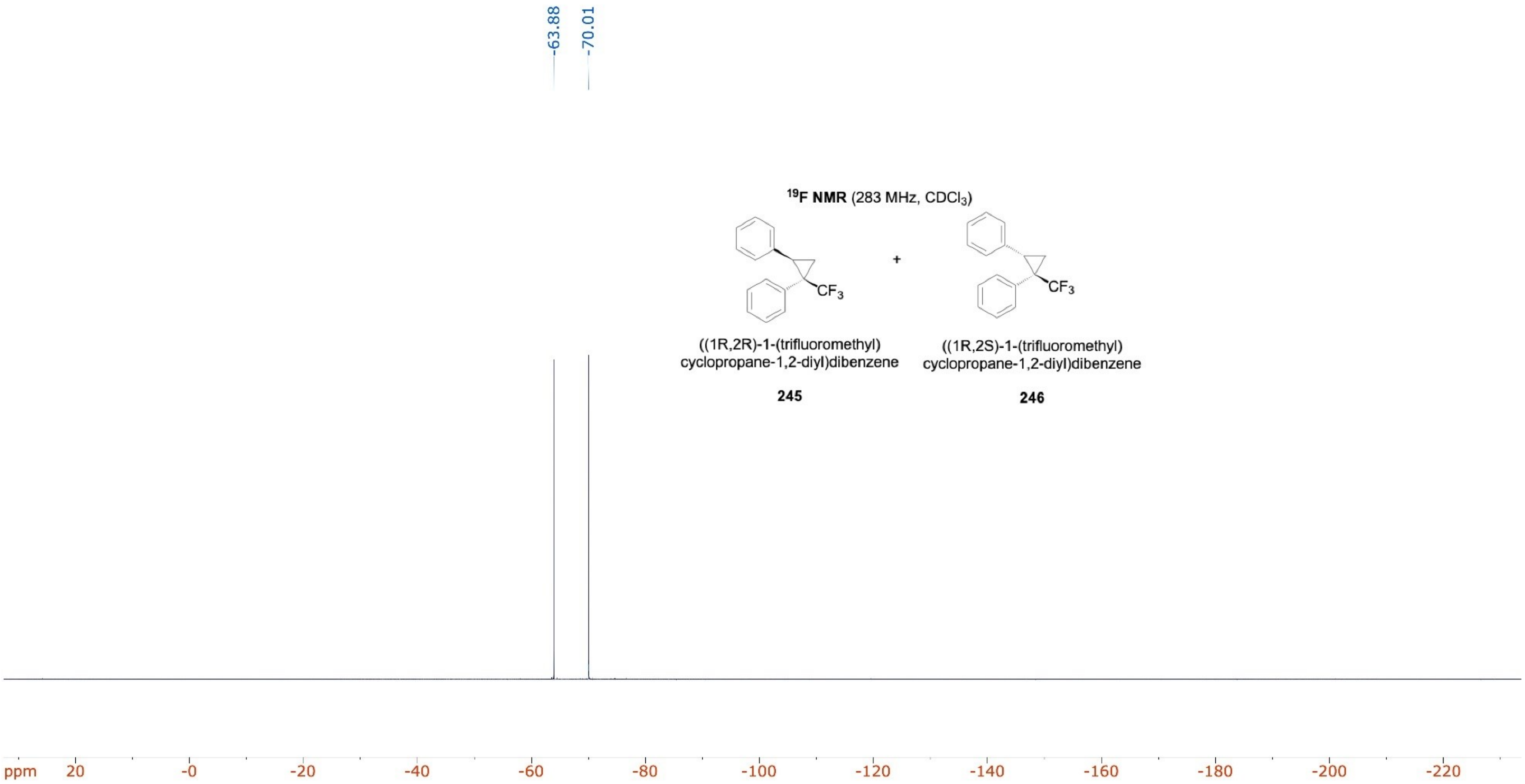
^{1}H NMR (300 MHz, $CDCl_3$)

((1R,2R)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

245

((1R,2S)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

246



^{19}F NMR (283 MHz, CDCl$_3$)

((1R,2R)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

245

((1R,2S)-1-(trifluoromethyl)
cyclopropane-1,2-diyl)dibenzene

246