# Generation and valorization of gases in organic synthesis

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During my stay at MIT (Cambridge, USA), I learned a second cow-based idiom: 'It's as if a cow is pissing on a flat rock'. Crazy, isn't it? Here, a big thanks to Prof. Timothy F. Jamison, Rachel Beingessner, M. Grace Russell, Jessica Weber, Grace Putka Ahlqvist and my two European buddies: Martin Bundgaard Johansen (read: Yow Handsome) and Martin Lahn Henriksen.

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Lastly, I would like to devote a small, but special paragraph to the love of my life, Simon Claeys. Thank you!

## Summary

Although industrial processes readily use reactive and dangerous gases as platform chemicals, a different picture is seen in lab-scale synthesis. The difficult-to-handle nature of gaseous reagents in combination with stringent safety requirements have posed a significant barrier for research scientists to conduct chemical reactions with gases on a regular basis.

In 2011, the Skrydstrup group launched the two-chamber reactor as a safe and user-friendly tool to employ gases in organic synthesis. In this device, a gas is released from a precursor molecule in one chamber, which subsequently diffuses to the adjacent chamber, where it is consumed in a chemical reaction. Consequently, the risk of direct contact between the operator and the gaseous reagent is completely eliminated.

In this thesis, we developed one of the most cost-efficient carbon monoxide (CO) generating systems to date, with formic acid as the CO source. In a follow-up project, this system was implemented in a two-chamber reactor for the synthesis of a novel heterocyclic scaffold *via* an unprecedented intramolecular carbonylative C-H activation of 1-(2-bromoaryl)-1,2,3-triazoles.

Moving away from carbon monoxide, precursor molecules for other useful gases were sought after. Due to the renewed interest in sulfuryl fluoride gas ($SO_2F_2$), we developed a straightforward protocol for its on-demand production in a two-chamber reactor to transform phenols into aryl fluorosulfates. This class of substrates is particularly interesting, either by merit of its leaving group ability or as a SuFEx click chemistry partner. Lastly, in collaboration with the Skrydstrup group, the field of CO and $SO_2F_2$ chemistry were merged to synthesize α,α-bis(trifluoromethyl) carbinols from aryl bromides and fluorosulfates.

# Samenvatting

Hoewel industriële processen vlot reactieve en gevaarlijke gassen gebruiken als platformchemicaliën, is dit bij synthese op laboratoriumschaal een ander verhaal. De moeilijk hanteerbare aard van gasvormige reagentia in combinatie met strenge veiligheidsvereisten hebben een belangrijke barrière gevormd voor wetenschappers om op geregelde basis chemische reacties met gassen uit te voeren.

In 2011 introduceerde de Skrydstrup groep de tweekamerreactor als een veilig en gebruiksvriendelijk systeem om gassen te hanteren in organische synthese. In dit toestel wordt een gas vrijgezet uit een precursormolecule in één kamer, dat vervolgens diffundeert naar de aangrenzende kamer, waar het wordt gebruikt in een chemische reactie. Bijgevolg is het gevaar op contact tussen de operator en het gasvormige reagens volledig weggenomen.

In dit proefschrift hebben we een van de meest kostenefficiënte koolmonoxide (CO) producerende systemen ontwikkeld, met mierenzuur als de CO-bron. In een vervolgproject werd dit systeem gebruikt in een tweekamerreactor voor de synthese van een nieuwe heterocyclische structuur via een ongekende intramoleculaire carbonylatieve C-H-activering van 1-(2-broomaryl)-1,2,3-triazolen.

Naast koolstofmonoxide, werden er ook surrogaten voor andere gassen onderzocht. Vanwege de hernieuwde interesse in sulfurylfluoride ($SO_2F_2$) hebben we een eenvoudig protocol ontwikkeld voor de productie van dit gas in een tweekamerreactor om fenolen om te zetten in arylfluorosulfaten. Deze klasse van substraten is bijzonder interessant, omdat de fluorosulfaatgroep enerzijds kan optreden als een vertrekkende groep en anderzijds als een SuFEx click reagens. Tenslotte werd in een samenwerking met de Skrydstrup groep de expertise in CO- en $SO_2F_2$-chemie gecombineerd om α,α-bis(trifluormethyl)carbinolen uit arylbromiden en fluorosulfaten te synthetiseren.

## List of abbreviations

| | |
|---|---|
| Δ | Heat |
| [Bmim]Cl | 1-Butyl-3-methylimidazolium chloride |
| AISF | [4-(Acetylamino)phenyl]imidodisulfuryl difluoride |
| Ap | Apparent |
| Ar | Aryl |
| b.p. | Boiling point |
| BINAP | (2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl) |
| BPR | Back pressure regulator |
| Brd | Broad signal |
| COD | 1,5-Cyclooctadiene |
| COgen | 9-Methyl-9*H*-fluorene-9-carbonyl chloride |
| COware | Commercialized two-chamber reactor |
| $C_p^*$ | Pentamethylcyclopentadienyl |
| CPME | Cyclopentyl methyl ether |
| CSA | Camphorsulfonic acid |
| CuAAC | Copper(I)-catalyzed alkyne-azide cycloaddition |
| DABCO | 1,4-Diazabicyclo[2.2.2]octane |
| DABSO | 1,4-Diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct |
| dba | Dibenzylideneacetone |
| DBU | 1,8-Diazabicyclo(5.4.0)undec-7-ene |
| DCM | Dichloromethane |
| DIPEA | *N,N*-Diisopropylethylamine (Hünig's base) |
| DMA | *N,N*-Dimethylacetamide |
| DMAP | 4-Dimethylaminopyridine |
| DMF | Dimethyl formamide |

| | |
|---|---|
| DMSO | Dimethyl sulfoxide |
| DPEPhos | Bis[(2-diphenylphosphino)phenyl]ether |
| dppb | 1,4-Bis(diphenylphosphino)butane |
| dppf | 1,1′-Ferrocenediyl-bis(diphenylphosphino) |
| dppp | 1,3-Bis(diphenylphosphino)propane |
| DSC | Differential scanning calorimetry |
| e.g. | Exempli gratia |
| FeTTP | Iron tetraphenylporphyrin |
| FT-IR | Fourier-transform infrared spectroscopy |
| HR-MS | High resolution mass-spectroscopy |
| JohnPhos | (2-Biphenyl)di-*tert*-butylphosphine |
| m.p. | Melting point |
| Mes | Mesitylene |
| MPLC | Medium pressure liquid chromatography |
| MsCl | Methanesulfonyl chloride |
| $M_W$ | Microwave |
| NIOSH | National Institute of Occupational Safety and Health (USA) |
| NMP | 1-Methyl-2-pyrrolidinone |
| NMR | Nuclear magnetic resonance |
| $PCy_3$ | Tricyclohexylphosphine |
| Ph | Phenyl |
| ppm | Parts per million |
| Py | Pyridine |
| RWGS | Reverse water-gas shift reaction |
| SDI | 1,1'-Sulfonyldiimidazole |
| SDS | Sodium dodecyl sulfate |

| | |
|---|---|
| SilaCOgen | Methyldiphenylsilanecarboxylic acid |
| SuFEx | Sulfur(VI) Fluoride Exchange |
| Syngas | Synthesis gas |
| $TBABF_4$ | Tetrabutylammonium tetrafluoroborate |
| $TESCF_3$ | Triethyl(trifluoromethyl)silane |
| TFA | Trifluoroacetic acid |
| TFE | 2,2,2-Trifluoroethanol |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMAF | Tetramethylammonium fluoride |
| TMEDA | *N*,*N*,*N'*,*N'*-Tetramethylethylenediamine |
| TMG | 1,1,3,3-Tetramethylguanidine |
| $TMSCF_3$ | Trifluoromethyltrimethylsilane |
| TPPTS | Triphenylphosphine-3,3′,3″-trisulfonic acid trisodium salt |
| Ts | Tosyl |
| Xantphos | 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene |

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# CHAPTER 1

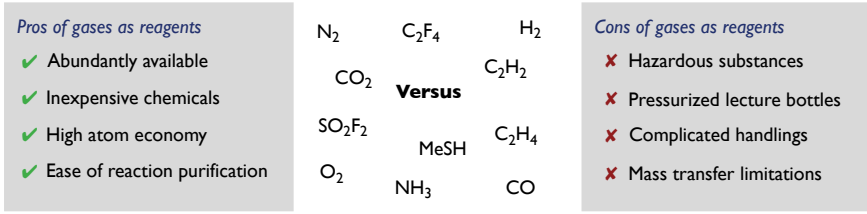
# A general introduction

## 1.1. Relevance of gases in organic chemistry

In many ways, gases are considered as ideal chemical building blocks. In industry for example, gases are regularly employed as feedstock for the production of value-added bulk and fine chemicals due to their abundant availability at low cost. In addition, the purification of chemical processes involving gaseous reagents is often straightforward since excess gas can simply be removed by venting the reaction vessel.

Notwithstanding these clear benefits, there are just as many reasons why gases tend to be avoided in lab-scale organic synthesis. One of these is the inherent hazardous properties of certain gases, especially when they are undetectable by human senses. Another issue is related to handling and storing of pressurized lecture bottles. This requires extensive training of the operator to meet all the safety requirements and to mitigate risks such as accidental exposure to hazardous or even lethal concentrations. Lastly, gas-liquid reactions are often impeded by mass transfer limitations due to the low interfacial area. Enhancing this thermodynamic parameter is a challenging task, particularly in a conventional batch setup.

Considering the current state of the art in industry as well as in academia, the advantages of gaseous reagents outweigh the disadvantages (scheme 1.1). This introductory chapter will comment on the industrial relevance of gases, followed by a brief discussion on the most commonly employed techniques to engage synthetic gases on lab-scale. In the second part of this chapter, gas releasing molecules will be introduced as a safe and user-friendly tool in small-scale synthesis.




**Scheme 1.1** Pros and cons of gases as building block in organic synthesis.

## 1.1.1. Gases in an industrial setting

In the chemical industry, some of the most used reagents for the construction of more advanced chemicals are gaseous at room temperature. The production plants relying on these reagents evidently require a robust and reliably supply chain. This is often accomplished by making use of pressurized cylinders or tank trailers. However, in certain cases, the demand can also be met with on-site production plants or by using an underground pipeline network. Recently, the chemical company Bayer AG in Germany had the intention to build a new pipeline for CO transport, but was forced to stop its installation due to public protest.[1] Hence, demonstrating that not only the physical and chemical properties of gases can hamper its exploitation, but also the increasing social pressure and environmental awareness.

Besides feedstock, gases are often employed to ensure safety (*e.g.* flushing reactors with nitrogen gas to prevent formation of an explosive atmosphere) and to lesser extent for industrial services (*e.g.* helium as carrier gas in analytical instruments). The following paragraphs will briefly touch upon the relevance of six commonly encountered industrial gases: nitrogen, oxygen, synthesis gas, hydrogen, carbon monoxide, and carbon dioxide.

### *1.1.1.1. Nitrogen*

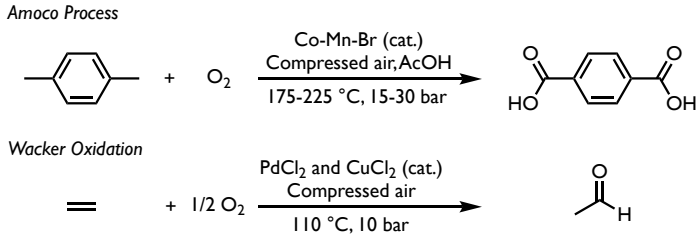
Since Earth's atmosphere is composed of approximately 78% nitrogen, it is a highly interesting gas to use as feedstock for chemical processes. However, its remarkable inertness makes this by no means an obvious task. A rare example where this is accomplished is the Haber-Bosch process for the production of ammonia from nitrogen and hydrogen gas.[2] In the food industry, this gas is mainly used to create a modified atmosphere to ensure product quality by preventing undesired oxidation reactions.[3]

### *1.1.1.2. Oxygen*

The remaining 22% of gases in the Earth's atmosphere consists roughly of 21% oxygen, 0.9% argon and traces of other gases, such as carbon dioxide, neon, helium, and methane. In an industrial context oxygen gas is a powerful oxidizing agent and is readily extracted from the atmosphere by

fractional distillation of liquified air.[4] Depending on the process, pure oxygen gas or a dilute mixture with nitrogen gas is used. Although the first one is much more effective, the latter is sometimes preferred to mitigate hazards, particularly when flammable and volatile fuels are oxidized.

Oxidative processes are often mediated by a catalyst. Two textbook examples of catalytic oxidation that employ compressed air as the oxidant are the Amoco process,[5] the synthesis of terephthalic acid from *para*-xylene in the presence of manganese and cobalt salts, and the Wacker oxidation of alkenes for the manufacture of carbonyl compounds promoted by palladium and copper chloride (scheme 1.2).[6]

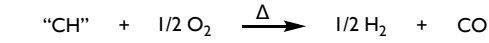



**Scheme 1.2** Catalytic oxidation of *p*-xylene to terephthalic acid (Amoco Process) and the conversion of ethylene into acetaldehyde (Wacker oxidation).[7-8]

### *1.1.1.3. Synthesis gas*

Synthesis gas or shortly syngas is a mixture of carbon monoxide and hydrogen gas and is mainly manufactured by heat-induced gasification of carbon-containing feeds or by steam reforming of hydrocarbons (*e.g.* natural gas).

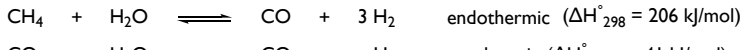
The first process is non-catalytic and relies on sub-stoichiometric amounts of molecular oxygen to suppress complete oxidation of the carbon feed.[9] The overall transformation is depicted in scheme 1.3.




**Scheme 1.3** Thermal oxidation of carbon-containing feedstock with sub-stoichiometric amounts of molecular oxygen for the production of synthesis gas.

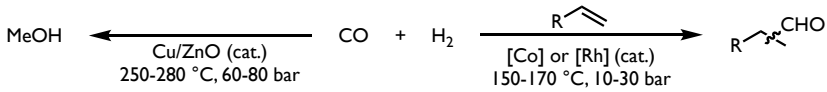
The second source of synthesis gas, steam reforming of hydrocarbons, consists of two key transformations (scheme 1.4).[9] First, the conversion of methane and other hydrocarbons in the presence of steam to produce hydrogen gas and carbon monoxide. This is an endothermic process and hence requires extreme temperatures (700-1100 °C). Then, the

exothermic water-gas shift reaction takes place. Here, carbon monoxide and water are converted into hydrogen gas and carbon dioxide. Interestingly, the produced $H_2$/CO ratio is dependent on the feedstock. The use of lighter hydrocarbons, such as methane typically affords higher $H_2$/CO ratios compared to heavier ones.[9]




**Scheme 1.4** Steam reforming of natural gas.[9]

Synthesis gas is key for the construction of a wide array of platform chemicals. Methanol, for example, can be produced from one CO molecule and two molecules of $H_2$ in the presence of copper and zinc oxides.[10] A related procedure is the Fischer-Tropsch synthesis of higher hydrocarbons from syngas.[11] More complex molecules, such as aldehydes, can also be obtained through a transition-metal-catalyzed hydroformylation of olefins (scheme 1.5).[12]




**Scheme 1.5** Synthesis gas as feedstock for the production of methanol (left arrow) and the hydroformylation of alkenes (right arrow).[10, 12]

Besides being a versatile reagent, synthesis gas is a valuable source for the production of pure $H_2$ and CO, which will be the topic of the next two sections.

### *1.1.1.4. Hydrogen gas*

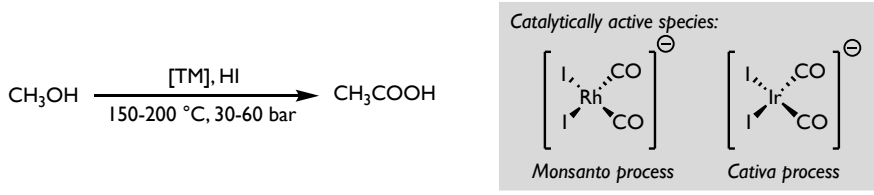
Since hydrogen gas is the smallest and lightest member in the gas family, its storage in a closed metal container is rather complicated. Hydrogen gas tends to diffuse into the metal, causing hydrogen embrittlement, which can eventually lead to cracks and leaks in the container.[13] In addition, $H_2$ gas is extremely flammable and may ignite spontaneously when it comes in contact with air.

Hydrogen gas is primarily sourced from steam reforming. The bulk of its production is intended for the synthesis of ammonia (Haber-Bosch process)[2] and as hydrogenation agent. Considering the relatively high stability of a hydrogen molecule, transition-metal catalysts are often needed

during hydrogenation processes to lower the activation barrier by dissociative adsorption of $H_2$ on the metal surface.[14] A few commonly encountered examples in industrial synthesis are the reduction of nitro compounds, olefins, aldehydes, carboxylic acids, esters, and nitriles.

*1.1.1.5. Carbon monoxide*

Similar to hydrogen gas, carbon monoxide is predominantly obtained by cryogenic distillation of synthesis gas. This diatomic reagent is extensively used for the installation of carbonyl moieties in commodity chemicals due to its high atom economy and low bulk cost. In the Koch synthesis, for example, tertiary carboxylic acids are generated from alcohols or alkenes and CO under strongly acidic condition.[15] Other examples are the synthesis of phosgene from CO and chlorine gas[16] and the oxidative carbonylation of methanol to dimethyl carbonate.[17] Since carbon monoxide is relatively inert, most industrial processes require a transition-metal catalyst for the *in situ* formation of a more reactive metal-carbonyl complex. As illustrated in Scheme 1.6, acetic acid is produced in bulk from methanol carbonylation mediated by a rhodium complex (Monsanto process)[18] or an iridium catalyst (Cativa process).[19] A closely related transformation is the Tennessee Eastman process.[20] Here, acetic anhydride is manufactured by a rhodium-catalyzed carbonylation of methyl acetate.

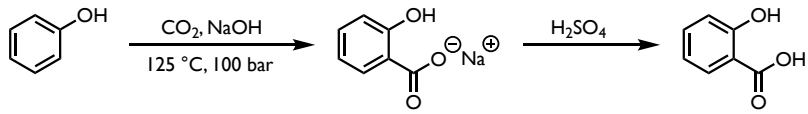



**Scheme 1.6** Catalytic carbonylation of methanol for the production of acetic acid.[18-19]

*1.1.1.6. Carbon Dioxide*

Carbon dioxide is generated as a waste product in numerous industrial processes. As a result, its recovery is currently the main route to acquire this gas on industrial-scale.[21] An alternative approach to obtain $CO_2$ could be *via* air separation. However, this is not economically viable because of the low $CO_2$ content in the atmosphere (approx. 400 ppm).

Carbon dioxide has found a wide variety of applications thanks to its interesting physical and chemical properties. For example, since carbon dioxide is a noncombustible gas with a density higher than air, it is often used as fire extinguishing agent. Another example can be found in the food sector, where $CO_2$ is commonly applied for the production of carbonated soft drinks. In the chemical industry, however, the use of carbon dioxide as reagent is rather limited. The two most relevant processes are the synthesis of urea[22] and sodium salicylate, the latter is known as the Kolbe-Schmitt reaction (scheme 1.7).[23-24]




**Scheme 1.7** Carboxylation of phenol with carbon dioxide and sodium hydroxide for the synthesis of sodium salicylate.[23]

## 1.1.2. Gases in an academic setting

Although industrial processes readily use reactive and dangerous gases as platform chemicals, a different picture is seen in lab-scale synthesis. The difficult-to-handle nature of gases in combination with stringent safety requirements have posed a significant barrier for research scientists to conduct chemical reactions with gases on a regular basis.

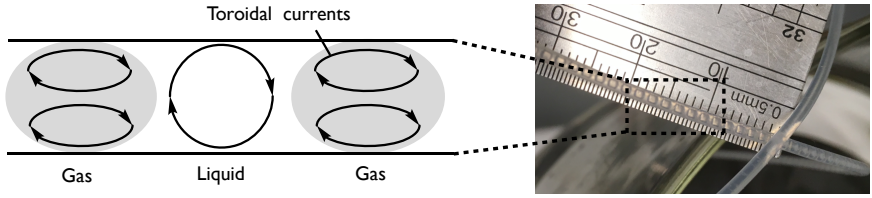
In academia, gaseous reagents are typically provided by using a balloon filled from a pressurized vessel or by relying on a stock solution. However, neither of these methods are ideal. The first approach is problematic in terms of safety and atom economy due to the presence of an unnecessary large excess of gas, whereas the latter is limited by the gas' solubility properties.[25] To give an example, the solubility of carbon monoxide in organic solvents ranges between 5 and 10 mmol per liter under standard conditions, thereby rendering it impracticable in use.[26] This is sometimes overcome by employing high pressure reactors such as Parr bombs and autoclaves.

The cumbersome handling of gaseous reagents has sparked researchers to explore new techniques to facilitate small-scale gas-liquid reactions. In the last decade, the launch of two new tools has expedited advances in this research area: the tube-in-tube reactor (section 1.1.2.1) and the two-chamber system (section 1.1.2.2).

*1.1.2.1. Microchannel and membrane reactors*

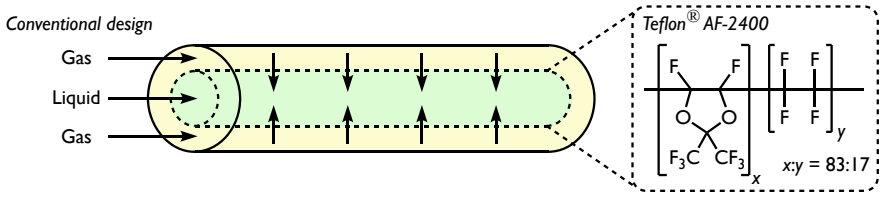
As mentioned earlier, the mass-transfer rate is one of the key parameters that governs chemical reactions with gases and depends largely on the interfacial area between the two phases. While this area is rather small in a traditional batch setup, a continuous flow process benefits from a more efficient degree of mixing, particularly when a microchannel reactor or membrane reactor is employed.[26]

In a microchannel reactor the gas and the liquid stream flow through the same microchannel, creating a segmented flow. As depicted in Scheme 1.8, the mass-transfer rate is not only enhanced by the increased interfacial area, but also by the improved mixing due to toroidal currents in the gas and liquid plugs.[27-28]




**Scheme 1.8** A schematic representation of toroidal currents in a segmented flow regime.

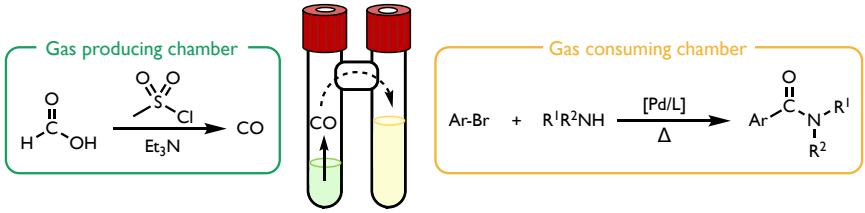
Recently, membrane reactor technology has emerged as an enabling tool for gas-liquid reactions.[29] The most commonly employed model is the tube-in-tube reactor developed by the Ley group.[30] This device consists of two concentric tubes, of which the inner tube is made of Teflon AF-2400, a gas permeable membrane (Scheme 1.9).[31] In the conventional design, the gas flows through the outer tube and causes microbubbles to migrate through the semipermeable barrier. These bubbles quickly dissolve into the inner liquid stream. In the reverse design, the streams have been swapped to ease additional heating of the liquid phase, which is less feasible in the conventional tube-in-tube reactor. The potential of these devices has been demonstrated with a plethora of gases, including carbon monoxide[32] and precursor molecules thereof,[33-34] carbon dioxide,[35] hydrogen gas,[36] synthesis gas,[37] ethylene,[38] oxygen,[39] ozone,[40] ammonia,[41] and diazomethane.[42]




**Scheme 1.9** Conventional tube-in-tube design. Gas flowing in the outer tube migrates through the semipermeable Teflon® AF-2400 membrane into the inner liquid stream.

### *1.1.2.2. Two-chamber system*

A second approach that paved the way to conduct gas chemistry on lab-scale is the on-demand generation of gases in a two-chamber reactor. This concept was introduced by the Skrydstrup group in 2011 and is illustrated in Scheme 1.10.[43] In one chamber, a gas is released from a precursor molecule (see section 1.2) which subsequently diffuses to the adjacent chamber, where it is consumed.[44] Hence, the operator benefits greatly from this approach as direct contact with the gaseous reagent is completely avoided. Since then, a variety of (do-it-yourself) two-chamber systems has been documented alongside the classical H-shaped device.[43, 45-48]




**Scheme 1.10** A schematic representation of a two-chamber system. Carbon monoxide is released from a precursor molecule in one chamber and subsequently consumed in the adjacent chamber.

Notwithstanding the apparent benefits this system creates, a note of warning is in order. Since gases are generated in a closed system, there is always a risk of explosion and the reaction should therefore be carried out behind a blast screen. The commercialized two-chamber reactor (COware)[49] is constructed of pyrex glass and even though it can endure up to 15 bar without failure, the recommended maximum pressure of 5 bar should never be exceeded. The safety concerns can be further alleviated by installing a pressure relief valve or by actively monitoring the pressure inside the vessel with a manometer.

Since the introduction of the two-chamber reactor, the field of gas releasing molecules has flourished tremendously. In the next section, more light will be shed on these so-called gas releasing molecules and how they can accommodate the current needs in this research area.

## 1.2. Gas releasing molecules in organic synthesis

The primary goal of gas releasing molecules is to render gases as safe and user-friendly tools for synthetic organic chemists, especially on lab-scale. There are typically two ways to implement these molecules in organic synthesis:

- *In situ* gas release: Both the gas producing reaction as well as the chemical transformation that requires the gas occur in the same vessel. Here, a cleverly designed molecule can be highly advantageous and fulfill a dual role as it might not only provide the desired gas, but also promote or catalyze the chemical reaction.
- *Ex situ* gas release: The gas generating reaction is physically separated from the gas consuming reaction. This is readily accomplished in a tube-in-tube reactor (continuous process) or a two-chamber system (batch process). Although more specialized equipment is needed, the *ex situ* approach is preferred when there are compatibility issues between both reactions.

The main advantage of gas releasing molecules, irrespective whether gas formation happens *in* or *ex situ*, is that the operator has the ability to precisely control the produced amount of gas by adding more or less precursor. Compared to conventional gas-liquid reactions, where usually a balloon filled with gas is used (see section 1.1.2), on-demand generation of gases is not only much safer to execute but often requires just stoichiometric amounts of gas. As a result, the use of gas releasing molecules opens new perspectives to access expensive isotope-labeled gases and expedites the search of novel volatile specialty reagents.

## 1.2.1. A clever design

During the development of a gas releasing molecule, one should try to adhere to the following guidelines.

(1) The gas releasing molecule is preferably a stable, non-toxic crystalline solid.

(2) It is an abundantly available commodity chemical or can easily be synthesized thereof.

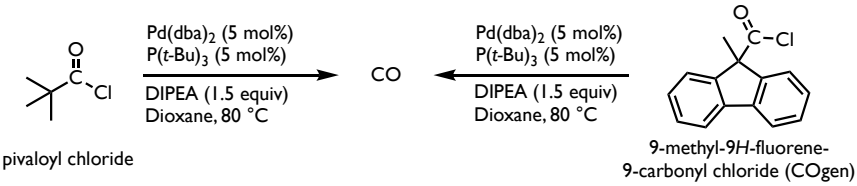
(3) The process is characterized by a high atom economy and a minimal waste disposal.

(4) Gas release occurs in a controlled manner under ambient conditions.

(5) Generated byproducts are non-invasive to prevent undesired side reactions.

(6) If applicable, the precursor molecule can readily be modified to produce isotope-labeled gas.

The importance of these guidelines will be exemplified by two precursor molecules that were originally investigated by the Skrydstrup group as CO releasing molecules: pivaloyl chloride and COgen (scheme 1.11).[43]




**Scheme 1.11** CO-release from pivaloyl chloride (left) and COgen (right).

Looking back at the six recommendations, guideline 2 and, to a lesser extent, guideline 3 are fulfilled for pivaloyl chloride. Since CO liberation readily occurs in the presence of a palladium complex at elevated temperatures, the use of a volatile liquid, such as pivaloyl chloride (b.p. 106 °C), as precursor molecule is not recommended (guideline 1). Aside from carbon monoxide, this molecule also generates an equivalent of isobutene gas. This is problematic as the olefin cannot only interfere in a transition-metal-catalyzed carbonylation reaction (*e.g.* carbonylative Heck

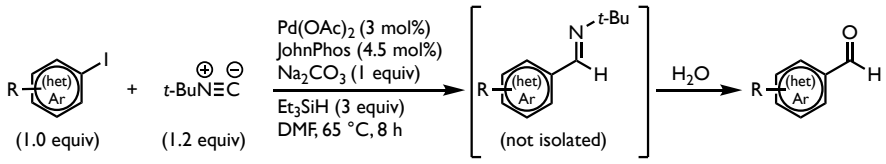
coupling), but also needlessly increases the overall pressure in the system (guideline 5).

These shortcomings prompted the Skrydstrup group to design a novel carbon monoxide releasing agent: 9-methyl-9*H*-fluorene-9-carbonyl chloride or shortly COgen (see section 1.2.3.7), which is an easy-to-handle and stable solid (m.p. 95 °C) (guideline 1).[43] Although its synthesis relies on a multiple step process, it is amenable to the production of the $^{13}C$-isotope-labeled variant. As a result, both have been marketed and are now commercially available (guideline 6). The gas release rate can be tuned by modifying the temperature and/or changing the solvent (guideline 4). However, one issue remains, the system suffers from a poor atom economy (guideline 3). This was partially addressed by demonstrating that the gas releasing molecule can be regenerated from its byproduct, albeit after multiple synthetic transformations. Nonetheless, COgen is still one of the most used CO surrogates, particularly if carbon isotope-labeling is required.[50]

## 1.2.2. Scope and limitations

In the rest of this chapter, a detailed overview will be given of the most commonly employed gas releasing molecules in organic synthesis. This section is subdivided into: (I) carbon monoxide precursors, which is the main focus; (II) synthesis- and hydrogen gas surrogates; (III) molecules liberating $C_2$ building blocks, such as ethylene, tetrafluoroethylene, and acetylene; (IV) formation of ammonia and hydrogen cyanide and lastly (V) S-containing gases: sulfur dioxide, sulfuryl fluoride, and methanethiol.

Due to the rich literature available, there will be a distinction between gas releasing molecules that formally liberate gases and reagents that deliver the same overall transformation, but do not produce these volatile substances. The latter one is exemplified in Scheme 1.12. Here, *tert*-butyl isocyanide operates as a CO equivalent and not as a CO source.[51] In some cases, these reagents will be mentioned or briefly addressed, but the main discussion will be on gas releasing molecules.




**Scheme 1.12** *Tert*-butyl isocyanide as a CO equivalent in the palladium-catalyzed formylation of (hetero)aryl iodides.[51]

## 1.2.3. Carbon monoxide

There exists a certain reluctance to work with carbon monoxide amongst researchers. This hesitation is understandable as CO is a flammable and highly toxic gas that cannot be detected by human senses. Every year, people die from carbon monoxide poisoning.[52] This is primarily due to the strong binding affinity of carbon monoxide to hemoglobin, which hampers the uptake of $O_2$ in the human body. In addition, the formed carboxyhemoglobin complex binds oxygen tighter in one of its three remaining subunits, causing a decreased oxygen release. This dual effect leads to oxygen deprivation and asphyxiation. Moreover, the symptoms of CO poisoning are often only visible at late-stage exposure, making it hard to act in time. Therefore, carbon monoxide rightfully earned the notorious nickname "the silent killer".

To mitigate these safety concerns, a myriad of carbon monoxide releasing molecules has been introduced to replace the use of CO in carbonylation chemistry. These advances have been reviewed extensively by Morimoto,[53] Larhed,[54] Manabe,[55] Beller,[56] Bhanage,[57] Skrydstrup,[44] and others.[58-59] Most of these contributions are personal accounts focusing on the applications of in-house developed CO surrogates, hence this section aims to provide a more complete picture of the carbon monoxide precursors currently reported in literature.

For this reason, it was opted to classify the precursor molecules based on their common chemical features. First, molecules containing a formyl C-H bond, such as formic acid, formate esters, formamides, and aldehydes will be discussed. Next, alcohols and polyols, followed by metal carbonyl complexes. Then, carbon dioxide and reagents that indirectly originate from $CO_2$. Finally, chloroform and other precursor molecules that don't fall into any of the aforementioned categories will be mentioned.

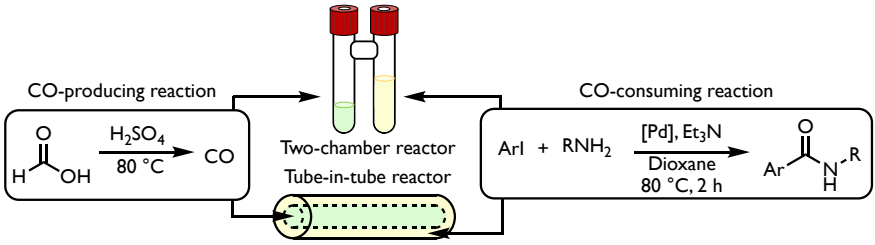
### *1.2.3.1. Formic acid*

Formic acid, the smallest carboxylic acid, is a preeminent C-1 building block. The annual production is estimated around 950 000 tons per year[60] and relies on carbon monoxide and methanol as building blocks. Future research to manufacture formic acid is directed towards hydrogenation of carbon dioxide[61] and oxidation of biomass.[62] This promising bio-renewable feedstock on its own also serves as an interesting carbon monoxide precursor.

*Morgan reaction*

One of the oldest ways to generate carbon monoxide from formic acid relies on the addition of a strong acid, typically fuming sulfuric acid, at elevated temperature (Morgan reaction).[63] Although this process is attractive in terms of cost-efficiency as both acids are low-cost commodity chemicals, it suffers from harsh and corrosive reaction conditions.

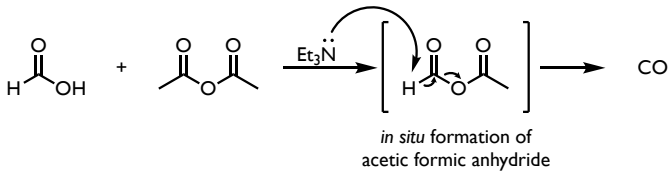
In an attempt to make the Morgan reaction more attractive for synthetic organic chemists, the Ryu group used modern techniques (*e.g.* a tube-in-tube reactor[40] (section 1.1.2.1) and a two-chamber reactor[44] (section 1.1.2.2)) to generate carbon monoxide.[33] In both setups, the CO-releasing and CO-consuming reaction are physically separated either by glass or by a semipermeable Teflon® AF-2400 membrane (Scheme 1.13). Losch and co-workers even took matters one step further and demonstrated that zeolites with the right acid site density and strength could catalyze the Morgan reaction, omitting the need of a corrosive acid.[64]




**Scheme 1.13** Modernized techniques in batch and flow employing formic acid as a CO source.[33]

*Mixed anhydrides*

Another strategy to dehydrate formic acid relies on the *in situ* formation of a mixed anhydride intermediate by the addition of an activator (e.g. anhydride[65-66] or carbodiimide[67-68]). In the presence of base or as result of thermal instability of the mixed anhydride under the reaction conditions, it decarbonylates and releases carbon monoxide (Scheme 1.14).[69] A similar outcome was observed when preformed acetic formic anhydride was used.[70]




**Scheme 1.14** Base-mediated dehydration of formic acid in the presence of acetic anhydride as an activator.[69]

Our research group also contributed to this field by developing a CO releasing system based on base-mediated decomposition of formic acid in the presence of a sulfonyl halide. This will be the topic of chapter 2.[71]

As a closing remark, it is important to note that formic acid can also decompose into hydrogen gas and carbon dioxide instead of water and carbon monoxide, depending on the energy provided and the catalytic system, if any. Section 1.2.4 regarding the on-demand production of syngas further explores this duality.

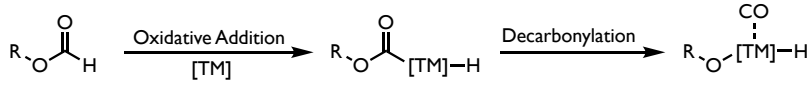
*1.2.3.2. Formate esters*

In the last few decades, formate esters were frequently exploited as a carbon monoxide source.[55] The associated decarbonylative mechanism has been rationalized by two pathways (scheme 1.15).

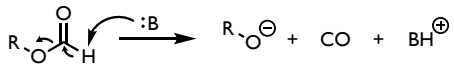
(i) Oxidative C-H bond activation of the formyl group by a transition metal complex, followed by decarbonylation, generating an organometal-carbonyl species.[72-73]

(ii) Base-mediated deprotonation of the formyl hydrogen, followed by elimination of the alkoxide to afford carbon monoxide.[74-75]

**Pathway 1:** Transition-metal-catalyzed decarbonylation




**Pathway 2:** Base-mediated decarbonylation

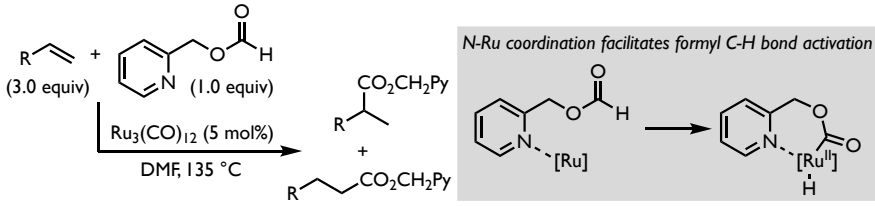



**Scheme 1.15** The decarbonylation of formate esters is either catalyzed by a transition-metal complex (pathway 1) or mediated by a base (pathway 2).

The following paragraphs will highlight some critical advances in the area of formate esters as CO precursors. Both alkyl formates as well as aryl formates will be discussed.

*Alkyl Formates*

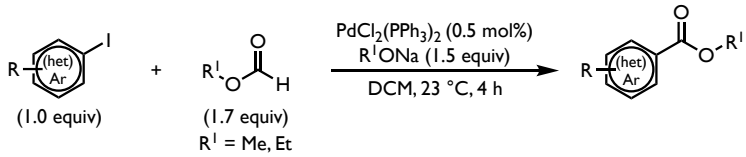
The work of Sneeden revealed that certain alkyl formates, and in particular methyl formate, are susceptible towards decarbonylation in the presence of a tricarbonyldichlororuthenium complex. Aside from carbon monoxide, methanol is being formed by the decomposition of methyl formate. By adding pressurized ethylene gas, this process was elegantly adapted for the synthesis of methyl propionate.[76] Almost two decades later, Chang and co-workers described a chelation-assisted hydroesterification procedure of alkenes. By making use of 2-pyridiyl methyl formate as the carbonyl source, high catalytic activity was achieved through coordination of the ruthenium complex and the pyridyl nitrogen which facilitated formyl C-H bond activation (Scheme 1.16).[77-78] Moreover, catalytic decarbonylation of alkyl formates can also be realized by other transition metals, such as molybdenum[79] and palladium.[80-82]




**Scheme 1.16** Chelation-assisted hydroesterification of alkenes by employing 2-pyridyl methyl formate as a carbonyl source.[77]

In 1991 Petit *et al.* reported a base-mediated decarbonylative decomposition of alkyl formates. Strong bases, such as sodium ethoxide, were typically required to release carbon monoxide in dichloromethane at

room temperature (Scheme 1.17). Interestingly, a proper solvent choice could steer the decomposition rate by altering the nucleophilicity of the base through the solvent's polarity.[74] Although strong bases readily convert alkyl formates into carbon monoxide, the presence of hard nucleophiles limits the reaction to the synthesis of esters. This issue was partly addressed by the introduction of aryl formates as a CO source.




**Scheme 1.17** Palladium-catalyzed alkoxycarbonylation of (hetero)aryl iodides by using alkyl formates as a CO source.[74]

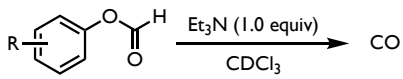
*Aryl Formates*

Similar to alkyl formates, the catalytic decarbonylation of aryl formates can be mediated by a transition metal.[83] However, the true potential of aryl formates lies within their ability to undergo decarbonylation in the presence of a weak base, typically triethylamine. This was independently discovered by the Manabe[84] and the Tsuji group.[85] Although details of the exact reaction mechanism are still under debate, both experimental and theoretical work suggest that carbon monoxide release proceeds *via* an E2 concerted $\alpha$-elimination pathway.[75] This study also revealed that the gas release rate is governed by the polarity of the solvent, the basicity of the base and the electronic effects of the substituents on the aromatic ring.[75]

Notwithstanding the importance of base-mediated conversion of phenyl formates into carbon monoxide, elevated temperatures (60 – 80 °C) were required to ensure full conversion (Table 1.1, entry 1).[84-85] In an attempt to synthesize a more reactive CO surrogate, electron-withdrawing groups were installed in the *ortho*- and *para*-position of phenyl formate. The Manabe group hypothesized that CO release could be accelerated by decreasing the electron density of the phenoxy group. Furthermore, the change in electronic properties might simultaneously affect the acidity of the formyl proton. Indeed, in the presence of triethylamine, 2,4,6-trichlorophenyl formate decarbonylated rapidly within a few minutes at room temperature (Table 1.1, entry 3).[86] Alonso *et al.* applied this

precursor molecule in a continuous flow protocol for carbonylation of a variety of (pseudo)haloarenes.[87]

**Table 1.1** Decarbonylation of aryl formates with triethylamine.[86]



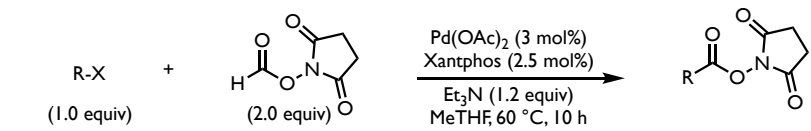

(1.0 equiv)

| Entry | Formate (R) | T (°C) | Time | Decarbonylation (%)[a] |
|---|---|---|---|---|
| 1 | H | 80 | 6 h | 100 |
| 2 | H | 23 | 24 h | 16 |
| 3 | 2,4,6-$Cl_3$ | 23 | 10 min | 92 |
| 4 | 2,4,6-$Cl_3$ | 23 | 24 h | 100 |

[a]Determined by $^1$H-NMR.

Another issue associated with phenyl formate stems from the *in situ* formation of phenol after decarbonylation. Due to the good nucleophilicity of the hydroxyl group, phenol might participate in the catalytic cycle and react with an intermediate acyl-transition-metal complex, limiting the reaction scope to the synthesis of esters. Fortunately, this can be circumvented, either by the formation of activated esters, which can be readily converted into various carbonyl derivatives[86, 88] or by designing aryl formates that decompose into CO and non-nucleophilic byproducts.[89]

In 2015, Levacher and co-workers investigated a rather unusual formate ester: *N*-hydroxysuccinimidyl formate.[88] Although efficient in the carbonylative synthesis of *N*-hydroxysuccinimidyl esters from aryl halides, the CO releasing ability was comparable to phenyl formate as it required elevated temperatures to smoothly release carbon monoxide (Scheme 1.18).[88]



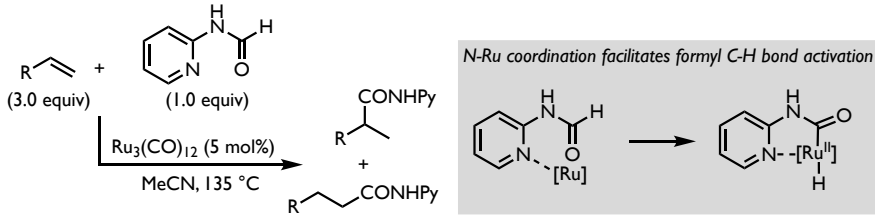

X = Br, I
R = (Hetero)aryl, benzyl, vinyl, allyl

**Scheme 1.18** Palladium-catalyzed carbonylation of (hetero)aryl, alkenyl and allyl halides by employing *N*-hydroxysuccinimidyl formate as a CO precursor.[88]

*1.2.3.3. Formamides*

Formamides can be exploited as a CO source either by transition-metal catalyzed activation of the formyl C-H bond or by base-induced abstraction of the formyl hydrogen. It should come as no surprise that the decarbonylation pathways are similar to those discussed in the previous section. Formate esters, formamides, and aldehydes (see section 1.2.3.4) all contain a formyl C-H bond, which is of key importance to releasing carbon monoxide.

In analogy with formate esters, both *N*-alkyl and *N*-aryl formamides have been used as carbonyl sources in ruthenium-catalyzed hydroamidation reactions of alkenes.[90-91] The Chang group improved this reaction by employing *N*-(2-pyridyl)formamide. Chelation of the pyridyl nitrogen with the ruthenium complex was pivotal as it fostered the oxidative addition into the formyl C-H bond (Scheme 1.19).[92]

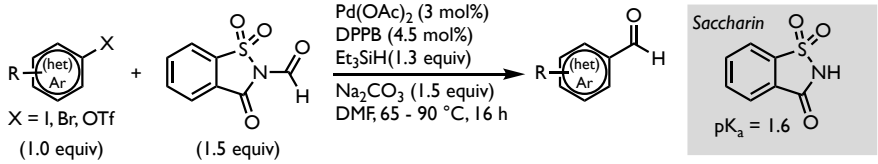



**Scheme 1.19** Chelation-assisted hydroamidation of alkenes by using *N*-(2-pyridyl) formamide as a carbonyl source.[92]

In 2002, Hallberg and co-workers demonstrated that base-mediated decarbonylation of dimethylformamide was a viable strategy to perform palladium-catalyzed aminocarbonylation, albeit at extreme temperatures (180 °C).[93]

A major breakthrough in this area unintendedly sprouted from the development of a new powerful formylating agent by the Cossy group: *N*-formylsaccharin.[94] This formamide readily releases CO in the presence of a weak base at room temperature.[95-96] In addition to gas formation, a low nucleophilic saccharin salt ($pK_{aH}$ = 1.6)[94] is produced, which turned out to be highly beneficial. Recall, one of the inherent issues associated with formate esters is the *in situ* formation of a nucleophilic byproduct that may interfere in the catalytic cycle, and thus limiting the reaction scope. The Manabe group recognized that by using *N*-formyl saccharin as the carbon

monoxide source, this side reaction could be avoided. As a result, *N*-formylsaccharin efficiently provided carbon monoxide for the palladium-catalyzed reductive carbonylation of aryl halides, without hampering the catalytic cycle (Scheme 1.20).[95]




**Scheme 1.20** Palladium-catalyzed reductive carbonylation of (hetero)aryl (pseudo)halides with *N*-formylsaccharin as a CO source.[95]

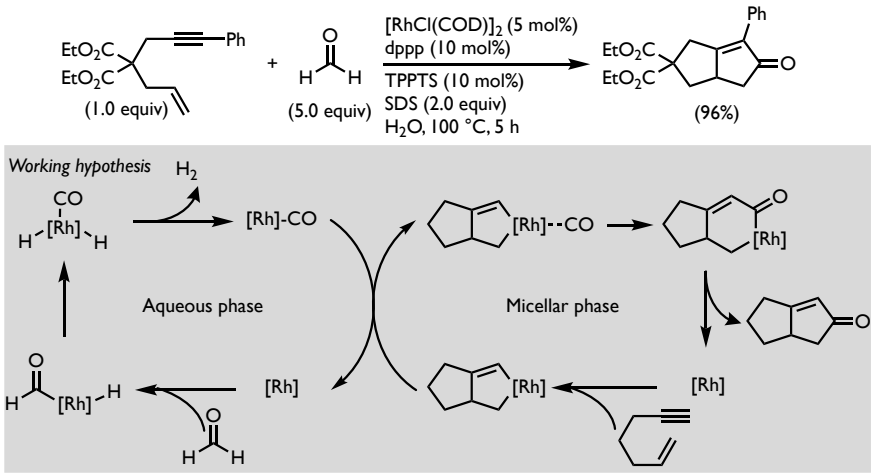
*1.2.3.4. Aldehydes*

One of the earliest observations concerning aldehydes as carbon monoxide source can be found in a small paragraph of a report on catalytic dehydrogenation by Newman and Zahm in 1943.[97] The decarbonylative mechanism of aldehydes by transition metals can be explained by an initial oxidative activation of the formyl C-H bond, followed by decarbonylation of the *in situ* generated acyl-transition-metal complex.[98-100]

*Formaldehyde*

Strictly speaking, formaldehyde should not be discussed in this section as it is a source of synthesis gas, rather than merely carbon monoxide gas.[101] Nevertheless, a few recent literature examples will be pointed out in which formaldehyde was intentionally used as a CO source. The structure of formaldehyde is more complicated than one might initially suspect. Pure formaldehyde spontaneously self-condensates, forming a mixture of oligomers, such as trioxane, and polymers (paraformaldehyde). An aqueous solution of formaldehyde, also known as formalin, consists of small oligomers of methanediol. Both paraformaldehyde and formalin have found applications in carbonylation chemistry.[102-103]

One of formaldehyde's interesting properties is its solubility in water. This has prompted researchers to develop an aqueous micellar two-phase system in which the decarbonylation of formaldehyde occurred in the aqueous phase and carbonylation of the substrate in the micelle. In this respect, formaldehyde can be considered as a water-soluble carbon monoxide source (Scheme 1.21).[102]

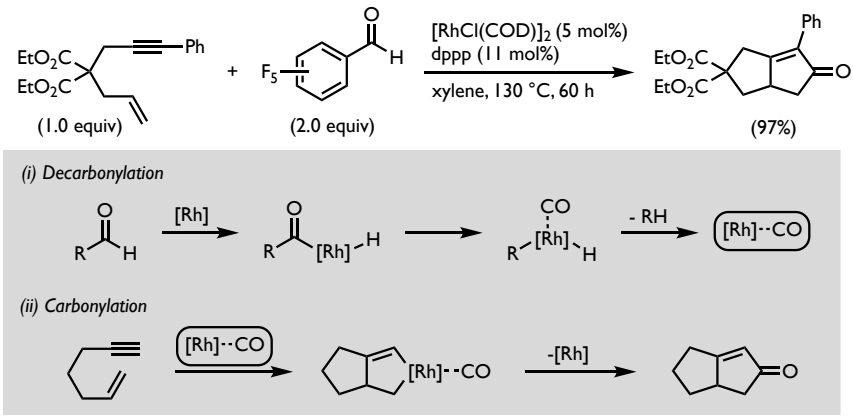



**Scheme 1.21** An aqueous catalytic Pauson-Khand-type reaction of enynes with formaldehyde. The mechanism relies on transfer carbonylation involving an aqueous decarbonylation and a micellar carbonylation.[102]

In 2014, Beller and co-workers described a palladium-catalyzed carbonylation of aryl bromides by using paraformaldehyde as the carbonyl source for the synthesis of aldehydes and esters.[103] Other carbonylative transformations using this precursor have been reported as well.[104-105]

*Higher aldehydes*

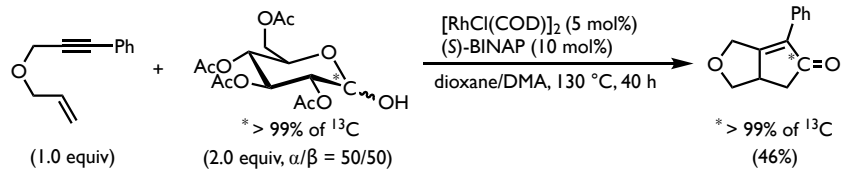
The carbonylative coupling of alkenes and alkynes mediated by a stoichiometric amount of $Co_2(CO)_8$ to produce α,β-cyclopentenones was originally reported by Pauson and Khand.[106-107] In 2002, the Kakiuchi[108] and the Takagi group[109] independently reported a rhodium-catalyzed modification of this reaction by employing aldehydes as a CO source. Although a broad variety of aldehydes were useful, the best results were achieved with electron-deficient aromatic aldehydes, such as pentafluorobenzaldehyde (scheme 1.22),[108] as well as α,β-unsaturated aldehydes (*e.g.* cinnamaldehyde).[109] Interestingly, no hydroacylation occurred between the rhodium-acyl complex and the alkene or alkyne.[108] Iridium complexes are also known to catalyze the sequence of aldehyde decarbonylation and Pauson-Khand carbonylation.[110]




**Scheme 1.22** Catalytic Pauson-Khand-type reaction of enynes with 2,3,4,5,6-pentafluorobenzaldehyde as a CO source.[108]

*Carbohydrates*

In 2010, aldoses were documented for the first time as a carbonyl source in a rhodium-catalyzed Pauson-Khand-type reaction.[111] These cyclic compounds are known to be in equilibrium with their open aldehyde form, albeit in low concentration. The Kakiuchi group envisioned that the latter could undergo catalytic decarbonylation in the presence of a rhodium complex. $^{13}$C-Labeling experiments confirmed this hypothesis and proved that the carbonyl carbon of the final product exclusively stemmed from the anomeric carbon of the aldose (Scheme 1.23). A variety of aldoses were suitable as CO source, however initial experiments indicated that the aldoses needed to be acylated to prevent solubility issues. Some examples are: 2,3,4,6-tetra-*O*-acetyl-D-glucose, 2,3,4,6-tetra-*O*-acetyl-D-galactose, and 2,3,4,6-tetra-*O*-acetyl-D-mannose.[111]

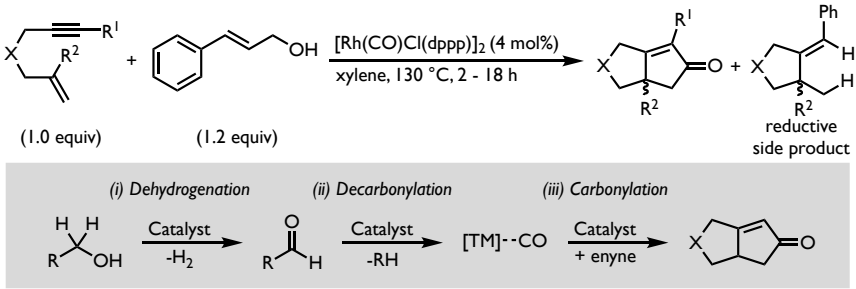



**Scheme 1.23** Cyclocarbonylation of enynes with acetyl-masked aldoses as a carbonyl source.[111]

*1.2.3.5. Alcohols and polyols*

Since aldehydes are commonly produced from alcohols, it seemed merely a matter of time before the first alcohol-based CO surrogates were

reported. In 2010, Chung and co-workers used cinnamyl alcohol as the carbon monoxide source in a Pauson-Khand-type reaction.[112] A rhodium complex was necessary to catalyze three consecutive transformations (Scheme 1.24). First, catalytic dehydrogenation of the alcohol, followed by catalytic decarbonylation of the *in situ* generated aldehyde and finally, catalytic carbonylation of the enyne. Although dehydrogenation of the alcohol was imperative to produce the active CO surrogate, the hydrogen gas interfered with the catalytic cycle, thereby inducing the formation of a reductive side product.[112]




**Scheme 1.24** Rhodium-catalyzed Pauson-Khand-type reaction employing cinnamyl alcohol as a source of carbon monoxide.

Nielsen *et al.* encountered a similar issue when glycerol was employed as a CO releasing molecule. Fortunately, the addition of a stoichiometric amount of oxidant, in their case 1,4-benzoquinone, elegantly suppressed hydrogen gas formation.[113]

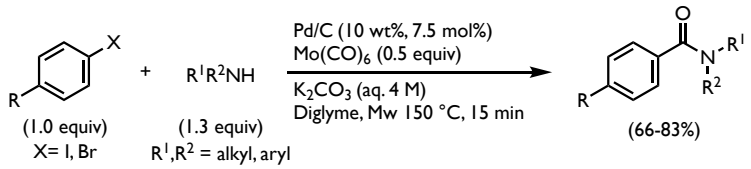
### *1.2.3.6. Metal carbonyls*

The seminal work of Corey and Hegedus on nickel tetracarbonyl in alkoxy- and aminocarbonylation chemistry, encouraged many researchers to explore the use of metal carbonyl complexes as a CO surrogate.[114] Unfortunately, these compounds are generally undesired in terms of atom economy as stoichiometric amounts are often required to ensure a steady rate of CO release. Even more alarming is the toxicity of metal carbonyl complexes. For example, nickel tetracarbonyl is an extremely hazardous compound. Its high level of toxicity is not only explained by its ability to release carbon monoxide, but also stems from the inherent toxicity of the metal as well as the volatility and instability of the metal complex.[115] Despite the disadvantages of metal carbonyls as a CO source, numerous

reports have appeared in literature. The most pivotal cases are covered in the following paragraphs.

*Molybdenum hexacarbonyl*

The Larhed group is considered one of the leading groups in the field of metal carbonyls.[54] In 2002, they documented their observations on molybdenum hexacarbonyl as a convenient CO source in the palladium-catalyzed hydroxy- and aminocarbonylation of various aryl halides (Scheme 1.25).[116] Other metal carbonyls were screened as well, such as nickel tetracarbonyl, chromium hexacarbonyl, and iron pentacarbonyl. Nevertheless, $Mo(CO)_6$ was the reagent of choice based on its high reactivity and relatively low toxicity compared to other metal carbonyls. This complex readily releases carbon monoxide at 150 °C.[116] In the presence of an activator, such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[117] or acetonitrile,[118] decarbonylation occurred under milder reaction conditions, thereby widening the substrate scope. In terms of functional group tolerance, molybdenum hexacarbonyl has one major flaw: its tendency to reduce nitro compounds.[119] This could be prevented by either using a different metal carbonyl complex (see next paragraph)[120] or utilizing a two-chamber reactor.[121] In the latter approach, molybdenum hexacarbonyl is spatially separated from the substrate, eliminating unwanted side reactions.[121] Interestingly, Larhed and co-workers recognized that molybdenum hexacarbonyl's ability to cleave N-O bonds could be used to their advantage to produce ammonia *in situ* (for details, see section 1.2.8).[122]




**Scheme 1.25** Microwave-assisted aminocarbonylation of aryl halides with molybdenum hexacarbonyl as a CO source.

*Tungsten hexacarbonyl*

As mentioned above, the Larhed group noticed undesired N-O bond-cleaved side products during the development of a $Mo(CO)_6$-mediated carbonylative synthesis of Weinreb amides.[120] Substituting this metal

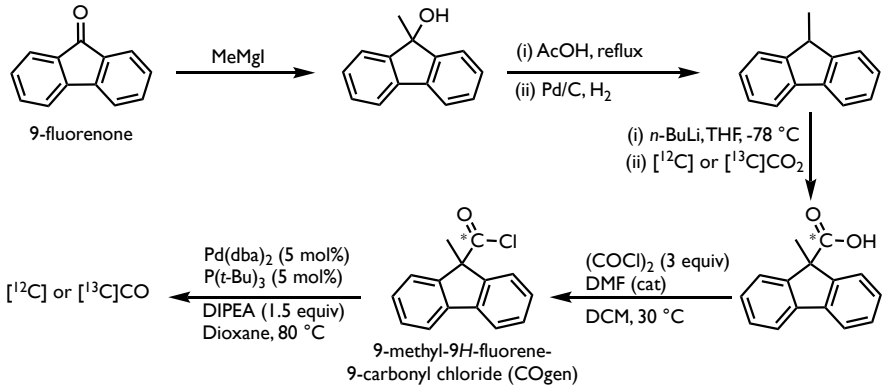
carbonyl complex with the less reactive $W(CO)_6$, brought solace to some extent. The competing N-O bond cleavage process could be suppressed for some substrates, while it persisted for others.[120]

### *1.2.3.7. Employing carbon dioxide*

The transformation of carbon dioxide into valuable platform chemicals, including carbon monoxide, formic acid, and methanol, is a topic of continuous interest.[123] Consequently, it would be propitious if carbon monoxide could be substituted by the cheaper, more abundant and less toxic carbon dioxide as a CO source in carbonylation chemistry. However, this comes with a major challenge: the chemical activation of carbon dioxide.[124] A significant breakthrough would be the discovery of reaction conditions that are highly efficient in promoting oxygen-abstraction from carbon dioxide and concomitantly being compatible with transition metal-mediated carbonylation chemistry. In the last few years, remarkable progress has been made which will be reviewed in this section. First, carbon monoxide releasing molecules relying on the indirect use of carbon dioxide will be treated, continued by the direct use of carbon dioxide.

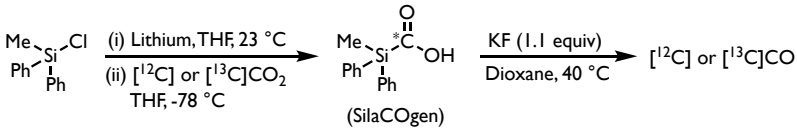
#### *Indirect use of carbon dioxide*

In 2011, Hermange *et al.* designed a new solid CO precursor: 9-methyl-9*H*-fluorene-9-carbonyl chloride, which was patented under the tradename COgen.[43] Particularly interesting is the synthetic pathway towards this compound. By using carbon dioxide as the carbonyl carbon source, both the $^{12}C$ as well as the $^{13}C$-isotope enriched variant could easily be synthesized (Scheme 1.26). This is especially compelling since $^{13}C$-carbon dioxide is one of the most abundant and cheapest sources of $^{13}C$ isotope-enriched carbon. The decarbonylative mechanism of COgen is catalyzed by a palladium complex in the presence of base. In brief, the cycle is initiated by a palladium-catalyzed decarbonylation of the acid chloride, followed by β-hydride elimination, and finally base-induced reductive elimination closes the cycle and regenerates the active catalyst.[43]




**Scheme 1.26** Synthetic route towards COgen, followed by palladium-catalyzed carbon monoxide release.[43]

Not long after, the same group documented a second CO releasing molecule: methyldiphenylsilacarboxylic acid, also called SilaCOgen (Scheme 1.27).[125] In analogy to its predecessor, carbon dioxide is used to provide the carbonyl carbon of silacarboxylic acid, thereby allowing straightforward access to the $^{13}$C-enriched variant. A catalytic amount of activator, typically potassium fluoride, ensured rapid release of carbon monoxide. Although the operating mechanism remained unclear, the authors speculated that the activator either promotes decarbonylation through a 1,2-Brook rearrangement[126] or substitutes the carboxylic acid group on the silicon atom, generating carbon monoxide and potassium hydroxide.[125]

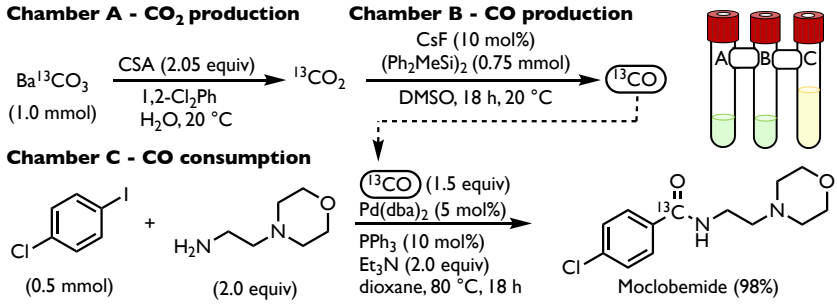



**Scheme 1.27** Synthesis and decarbonylation of silacarboxylic acid (SilaCOgen).[125]

*Direct use of carbon dioxide*

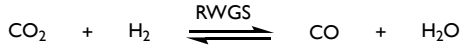
Aside from COgen and SilaCOgen, which indirectly use carbon dioxide as a CO source, the Skrydstrup group reported a mild and efficient strategy to directly convert carbon dioxide into carbon monoxide.[127] More specifically, efficient oxygen abstraction was achieved in the presence of a disilane and a catalytic amount of cesium fluoride in DMSO at room temperature. The mechanism is related to the one of SilaCOgen and relies on fluoride activation of the disilane, followed by carbon dioxide insertion

and a 1,2-Brook rearrangement, after which carbon monoxide is released.[128] Particularly interesting is the use of a three-chamber system to produce $^{13}CO$ from $Ba^{13}CO_3$. As shown in Scheme 1.28, $^{13}CO_2$ is liberated from the $^{13}C$-labeled barium carbonate under acidic conditions in chamber A. Next, the enriched carbon dioxide diffuses to the adjacent chamber, where it is converted into $^{13}CO$ under the optimized reaction conditions. In the last chamber, $^{13}CO$ is consumed in the palladium-catalyzed carbonylation reaction.[127] Although one might argue that a three-chamber system is specialized equipment, this setup made it feasible to transform an *in situ* generated gas into another, which was unprecedented at that time.



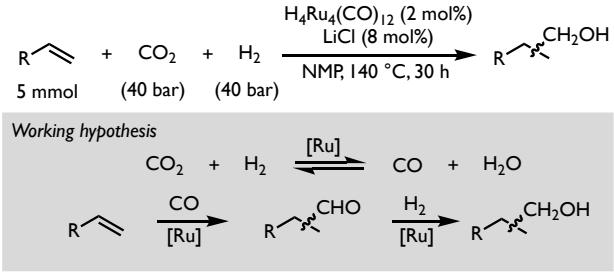

**Scheme 1.28** Production and consumption of $^{13}CO$ in a three-chamber system. Chamber A: conversion of $Ba^{13}CO_3$ into $^{13}CO_2$. Chamber B: production of $^{13}CO$ from $^{13}CO_2$. Chamber C: consumption of $^{13}CO$ for the synthesis of $^{13}C$-labeled moclobemide.[127]

A more general strategy to exploit carbon dioxide as a source of carbon monoxide makes use of the reverse water-gas shift (RWGS) reaction (Scheme 1.29).



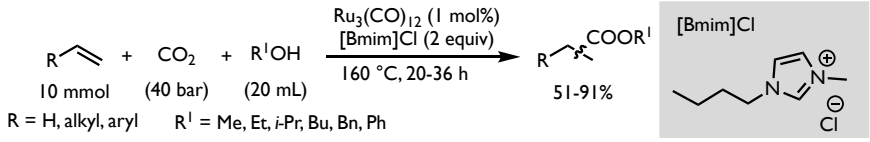

**Scheme 1.29** The reverse water-gas shift reaction (RWGS).

One of the earliest applications of this approach was reported by Tominaga (Scheme 1.30). Herein, the ruthenium complex served a dual purpose: first, promoting the RWGS reaction and second, catalyzing the hydroformylation of alkenes using the formed carbon monoxide.[129] Since then, a variety of ruthenium-based systems have been reported to improve this reaction and other related processes. Nevertheless, high temperatures and pressures of carbon dioxide and hydrogen were still required.[130-132]




**Scheme 1.30** Ruthenium-catalyzed hydroformylation of alkenes with carbon dioxide as a source of carbon monoxide.[129]

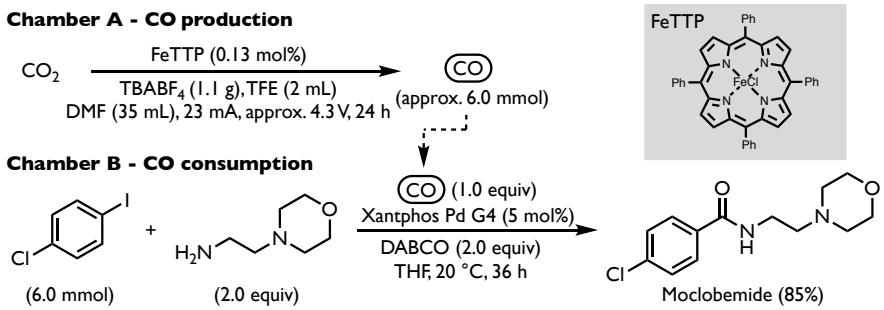
An intriguing modification of the reverse water-gas shift reaction was described by Beller and co-workers.[133] Alcohols, instead of water, were used for the reduction of carbon dioxide to carbon monoxide, thereby giving access to the synthesis of esters *via* a ruthenium-catalyzed alkoxycarbonylation of alkenes (scheme 1.31). Isotope-labeling experiments confirmed that the carbonyl carbon of the ester mainly stemmed from carbon dioxide.[133]




**Scheme 1.31** Ruthenium-catalyzed carboxylation of alkenes with carbon dioxide and alcohols.[133]

Another methodology to reduce carbon dioxide to carbon monoxide is *via* electrochemistry. Although this field is not short of publications on electrochemical reduction of carbon dioxide to carbon monoxide, there are only a few on the implementation of this transformation in carbonylation chemistry.[134] Jensen *et al.* successfully merged both electro- and carbonylation chemistry by employing a two-chamber system.[135] As portrayed in scheme 1.32, the electrochemical reduction of carbon dioxide to carbon monoxide occurred in chamber A and required the presence of iron tetraphenylporphyrin (electrocatalyst), trifluoroethanol (TFE, proton source),[136] $TBABF_4$ (electrolyte), DMF (solvent), and two stainless-steel electrodes. The rate of CO production was controlled by a galvanostat, also denoted ElectroWare. The gas subsequently diffused to chamber B, where it was consumed in the carbonylation reaction. Again, spatial separation between the two chambers was necessary to prevent

compatibility issues. Particularly interesting with this setup is the possibility the use of atmospheric $CO_2$ as CO source.[135]

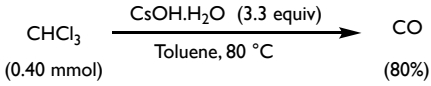



**Scheme 1.32** Electrochemical reduction of carbon dioxide to carbon monoxide for the carbonylative synthesis of moclobemide.[135]

*1.2.3.8. Miscellaneous*

*Chloroform*

The first report on base-mediated conversion of chloroform to carbon monoxide dates back to 1862.[137] In the 1990s, Grushin and Alper observed that in the presence of palladium, the *in situ* generated dichlorocarbene readily led to the formation of a palladium carbene complex.[138] The latter intermediate is prone to alkaline hydrolysis and smoothly generates carbon monoxide in the presence of water.[138] In a more recent example, Gockel and Hull documented the same transformation by only using an excess of cesium hydroxide hydrate at elevated temperatures, thereby omitting the need of a transition-metal catalyst (scheme 1.33).[139] Substituting the hydroxide salts with other counterions, such as lithium, sodium, and potassium, led to a drastic decrease in carbon monoxide production.[139]

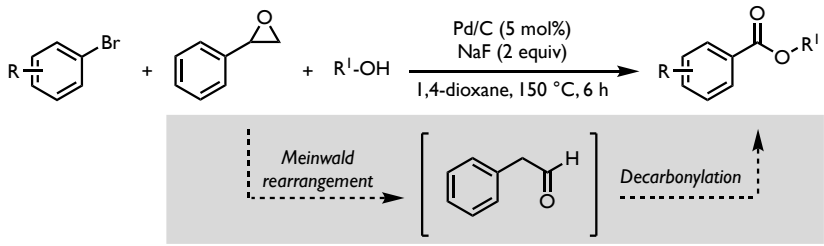



**Scheme 1.33** Heterogeneous chloroform hydrolysis for the production of CO. [139]

*Oxiranes*

2-Phenyl oxirane, a rather peculiar carbon monoxide surrogate was reported by Min and co-workers. Gas release occurred in the presence of palladium on carbon at 150 °C. Mechanistically, the authors assumed an

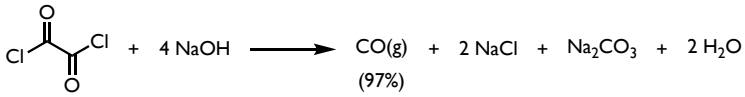
initial conversion of 2-phenyl oxirane into phenyl acetaldehyde through a Meinwald rearrangement,[140] followed by catalytic decarbonylation (scheme 1.34).[141]




**Scheme 1.34** Pd/C-catalyzed alkoxycarbonylation of aryl bromides by using phenyl oxirane as a CO source.[141]

*Oxalyl chloride*

Hydrolysis of oxalyl chloride into carbon monoxide, carbon dioxide, and hydrogen chloride has been known for a long time.[142] Hansen and Ulven hypothesized that if the reaction would occur under alkaline conditions, this could lead to exclusive carbon monoxide formation.[143] As expected, by reacting oxalyl chloride with aqueous sodium hydroxide (2 M), both HCl as well as $CO_2$ were respectively quenched as sodium chloride and sodium carbonate (Scheme 1.35). Consequently, only carbon monoxide is liberated due to its low solubility in water.[143] A few months later, the Gracza group reported a slightly modified procedure in which oxalyl chloride is reduced in the presence of metallic zinc.[144] In contrast to Hansen's method, where each molecule of oxalyl chloride only generates one molecule of CO, the Zn-mediated variant produces two molecules of carbon monoxide. Although this improved the overall efficiency, it has the disadvantage of consuming a stoichiometric amount of zinc.




**Scheme 1.35** Base-mediated hydrolysis of oxalyl chloride.[143]

*Glyoxylic acid*

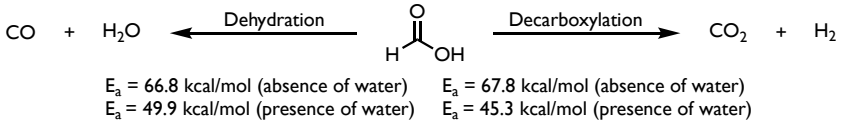
Inspired by the Morgan reaction, where formic acid is dehydrated by sulfuric acid for the production of carbon monoxide (see section 1.2.3.1),[63] Gracza and co-workers implemented similar conditions for the

decomposition of glyoxylic acid into two molecules of carbon monoxide. The best results were observed with fuming sulfuric acid at 130 °C. As such, this system suffers from harsh and corrosive reaction conditions.[145]

## 1.2.4. Synthesis gas

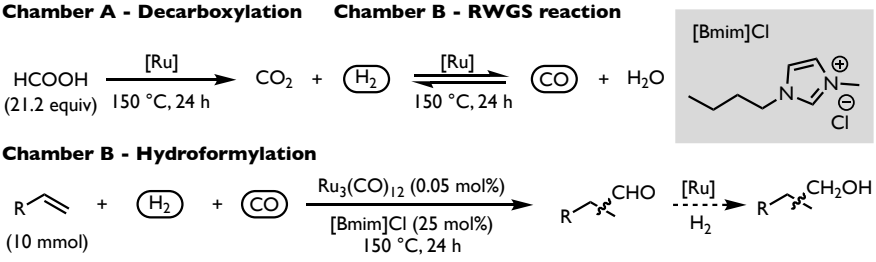
*Formic acid*

Depending on the energy provided, the presence of water and the applied catalyst, formic acid can decompose *via* two different pathways (scheme 1.36).[146] In the first one, carbon monoxide and water are generated, thereby rendering formic acid a potential CO surrogate (see section 1.2.3.1). In the second pathway, carbon dioxide and hydrogen gas are released.




**Scheme 1.36** Decomposition pathways of formic acid.[146]

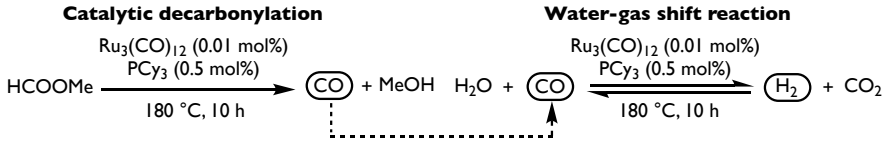
Porcheddu and co-workers exploited the latter for the on-demand production of synthesis gas (Scheme 1.37).[147] The chemistry was executed in a modified two-chamber system due to the requirement of pressures up to 90 bar. In the first chamber, catalytic decarboxylation of formic acid readily occurred in the presence of a ruthenium catalyst at 150 °C. In the adjacent chamber, a second ruthenium complex mediated both the reverse water-gas shift reaction (RWGS reaction), producing carbon monoxide, as well as the hydroformylation reaction, converting alkenes into aldehydes. Under the reaction conditions, the aldehydes were directly hydrogenated to their corresponding alcohols.[147]




**Scheme 1.37** Hydroformylation of olefins by employing formic acid as a source of synthesis gas.[147]

*Methyl formate*

In the early 90s, Jenner reported a closely related strategy to access synthesis gas from an aqueous solution of methyl formate. As depicted in scheme 1.38, catalytic decarbonylation of methyl formate, followed by the water-gas shift reaction proved to be a valid strategy. The liberated carbon monoxide and hydrogen gas were consumed in a ruthenium-catalyzed hydroformylation reaction of alkenes.[148-149]




**Scheme 1.38** Aqueous methyl formate as a source of CO and $H_2$ gas.[149]

*Formaldehyde and higher aldehydes*

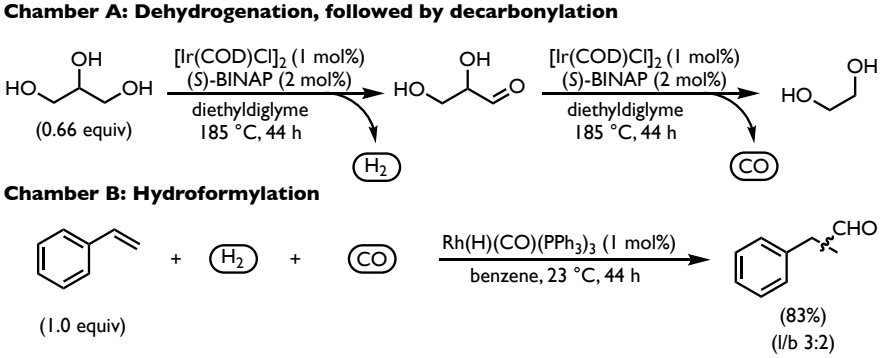
Since formaldehyde can be considered as a condensate of carbon monoxide and hydrogen gas, it forms an obvious source of synthesis gas. As already pointed out in section 1.2.3.4, transition-metal catalyzed decarbonylation of formaldehyde results in a 1:1 mixture of carbon monoxide and hydrogen gas. Often rhodium-phosphine complexes are selected due to their ability to catalyze both syngas formation as well as the subsequent hydroformylation reaction.[150-152]

*Alcohols and polyols*

Lastly, alcohols and polyols can be used to provide hydrogen and carbon monoxide gas. In 1986, Keim and co-workers illustrated this with a ruthenium-catalyzed hydroesterification of alkenes.[153] Due to the high energetic need of catalytic dehydrogenative decarbonylation of alcohols, extreme temperatures and pressures were required, respectively 230 °C and 400 bar.[153] Later, the Madsen group documented the same transformation by employing an iridium complex.[154-155]

Nowadays the conversion of biomass to high-value chemicals is a general topic of interest.[156] In this regard, the direct transfer of carbon monoxide and molecular hydrogen derived from polyols to value-added intermediates is highly desired. The Andersson group demonstrated this in a two-chamber system. In chamber A, an iridium-catalyzed

dehydrogenative decarbonylation of glycerol provided synthesis gas, which was subsequently used as building block for the hydroformylation reaction of styrene in the adjacent chamber (scheme 1.39).[157]




**Scheme 1.39** Hydroformylation of styrene by using glycerol as a synthesis gas source.[157]

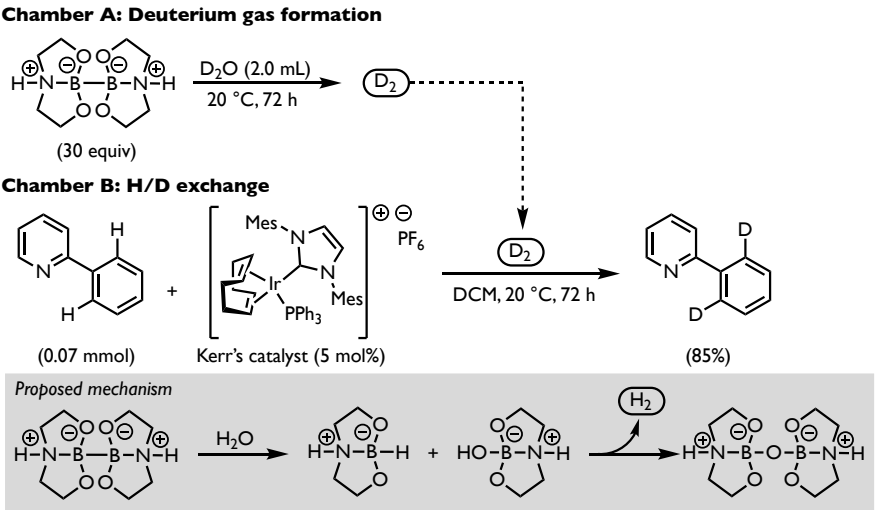
## 1.2.5. Hydrogen gas

Catalytic hydrogenation and hydrogen isotope exchange are two of the most commonly employed transformations that require dihydrogen.[158] This gas is usually provided from a pressurized cylinder or through transfer hydrogenation. The latter process refers to the addition of $H_2$ to a molecule from a non-hydrogen gas source.[158] Due to the plethora of hydrogen transfer reagents, including but not limited to hydrazine hydrate,[159] ammonium formate,[160] formic acid,[161-162] and cyclohexene,[163], this section will only cover recent literature examples where $H_2$ release occurred *ex situ*.

The Skrydstrup group reported the reduction of aqueous HCl (6 M) to hydrogen gas mediated by metallic zinc. Evidently, deuterium gas could be produced as well by using DCl in deuterated water.[164] Later, Watson and co-workers implemented this method for the reduction of azaheterocycles.[165]

A pressurized $H_2$ atmosphere can also be created from an $sp^3$-$sp^3$ diboron(4)-mediated reduction of water under ambient conditions.[166] Flinker *et al.* employed this reducing agent in a two-chamber system for the (semi)-hydrogenation of alkenes and alkynes. The setup was also amenable to hydrogen-deuterium exchange when deuterium oxide was used in chamber A and Kerr's catalyst[167] in chamber B (Scheme 1.40). Although

the exact mechanism of $H_2$ production remained unclear, the authors speculated that the reaction of the diboron complex with water first gives rise to a borohydride and a borinic acid derivative, followed by the formation of hydrogen gas (Scheme 1.40).[166]

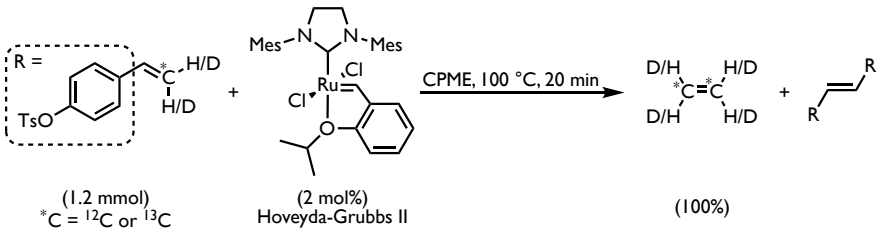



**Scheme 1.40** Hydrogen isotope exchange with $D_2$ and Kerr's catalyst. $D_2$ was produced from the reduction of deuterium oxide mediated by an $sp^3$-$sp^3$ diboron(4) compound.[166]

## 1.2.6. Ethylene and tetrafluoroethylene

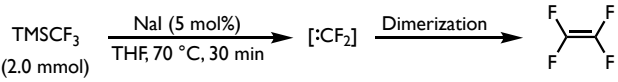
With a global annual production of roughly 150 million tons, ethylene has the highest production capacity of all organic compounds.[168] This simple olefin is of utmost importance in polymer industry since the main production routes for synthetic polymers (in)directly rely on this platform chemical. From a more academic perspective, D- and $^{13}C$-isotope labeled ethylene is of great interest, especially in unambiguous structure assignment of polymers and elucidation of reaction pathways involving ethylene.[169-170] Unfortunately, commercial vendors of isotope-labeled ethylene gas are scarce and 1,2-[$^{13}C_2$]-1,1,2,2-[$D_4$]ethylene, the fully labeled variant is not even available.

Min *et al.* partially alleviated this issue by developing a series of vinyl arenes.[171] Ethylene was readily liberated from these molecules through an olefin metathesis reaction mediated by the Hoveyda-Grubbs II catalyst.[172] By modifying the terminal $CH_2$-unit of the vinyl arene, the D- and/or $^{13}C$ isotope analogs of ethylene could be produced as well (Scheme 1.41).




**Scheme 1.41** Generation of (isotope-labeled) ethylene gas through an olefin metathesis reaction of (isotope-labeled) vinyl arenes.[171]

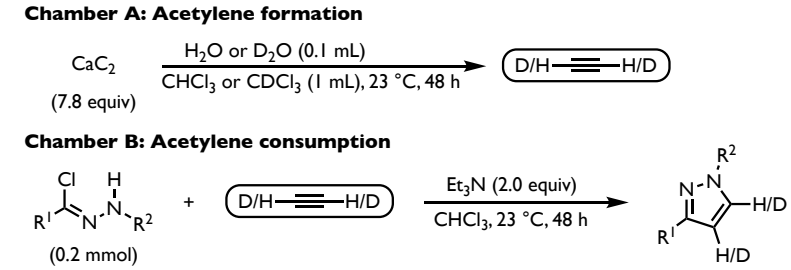
The on-demand synthesis of the fluorinated counterpart of ethylene, tetrafluoroethylene was recently documented by the Hu group.[46] In their approach, the Ruppert-Prakash reagent[173] was employed for the *in situ* formation of difluorocarbene by a catalytic amount of sodium iodide in tetrahydrofuran at 70 °C,[174] which subsequently dimerized to furnish tetrafluoroethylene gas (Scheme 1.42).




**Scheme 1.42** Production of tetrafluoroethylene from trifluoromethyltrimethylsilane.[46]

## 1.2.7. Acetylene

On lab-scale, the prevailing route to acetylene consists of mixing calcium carbide with water.[175-176] Conveniently, this approach can be modified for the production of deuterated acetylene by substituting water with deuterium oxide.[177] Despite its ease-of-operation, calcium carbide reacts violently with water, posing a severe safety risk. Matake *et al.* envisioned that the gas release rate could be reduced by adding a halogenated solvent to $CaC_2$, followed by water. Indeed, under slow stirring conditions, the organic layer prevented the acetylene formation from proceeding too fast.[178] Ananikov and co-workers employed this precursor in a two-chamber system, thereby circumventing compatibility issues that may arise between calcium carbide and the reagents or solvents in the reaction chamber (scheme 1.43).[48]

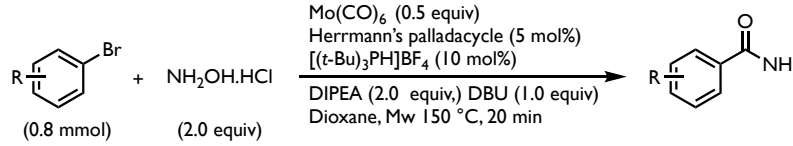



**Scheme 1.43** Generation of (deuterated) acetylene from calcium carbide for the synthesis of 1,3-disubstituted pyrazoles.[48]

## 1.2.8. Ammonia

A wide variety of surrogates are available to thwart the tricky use of ammonia gas, such as hexamethyldisilazane,[179] *tert*-butyl amine,[180] and allylamine,[181] to name a few. The following paragraphs will review precursor molecules that release ammonia *in* or *ex situ*.

In 2003, Hallberg and Larhed demonstrated that formamide could release ammonia as well as carbon monoxide under strong basic conditions and extreme temperatures (180 °C).[182] Three years later, Larhed and coworkers employed hydroxylamine as ammonia equivalent and molybdenum hexacarbonyl as CO source for the carbonylative synthesis of primary amides.[122] Although the combination of these two precursor molecules might seem trivial, it is not. Recall, N-O bonds are readily cleaved in the presence of $Mo(CO)_6$ (see section 1.2.3.6).[119] Larhed envisioned that this metal-carbonyl complex could serve a dual purpose by both providing CO and simultaneously acting as a reductant for the production of ammonia from hydroxylamine. This system has proven highly effective for the synthesis of primary amides from aryl bromides under microwave irradiation (scheme 1.44).[122]




**Scheme 1.44** Microwave-assisted synthesis of primary amides by employing molybdenum hexacarbonyl as a CO source and hydroxylamine as an ammonia equivalent.[122]

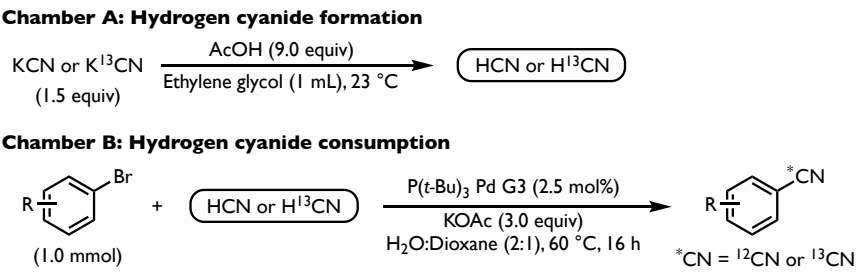
However, it should be noted that the use of ammonia in palladium-catalyzed carbonylation chemistry possesses an additional challenge besides the toxicity of $NH_3$ and CO gas. The poor nucleophilicity of ammonia in combination with its propensity to ligate strongly with Pd species, may hamper the catalytic cycle, especially in the presence of a large excess of ammonia.[183] Recently, Nielsen *et al.* encountered this issue during the development of a palladium-catalyzed carbonylative synthesis of primary amides.[184] Inspired by the work of Hartwig,[185] Josiphos was selected as a ligand to facilitate product formation. The chemistry was conducted in a two-chamber system, whereby ammonia was *in situ* released from ammonium carbonate[186] and CO *ex situ* from COgen.[184]

### 1.2.9. Hydrogen cyanide

Since hydrogen cyanide is a liquid at room temperature, one could argue that it falls outside the scope of this thesis. Nevertheless, this compound is included as its boiling point is just above standard condition temperatures (b.p. 26 – 27 °C).[187] A brief literature search revealed that only a handful of reports directly use hydrogen cyanide in organic synthesis, which can be explained by its acute toxicity.[187-189] Hydrogen cyanide releasing molecules might mitigate some of the safety concerns associated to handling hydrogen cyanide. Despite these advances, most procedures still rely on "masked" cyanide reagent, which deliver cyanide ions rather than HCN. One typical example is potassium hexacyanoferrate, a non-toxic reagent commonly applied in food industry.[190]

Similar to ammonia (see previous section), the main issue with palladium-catalyzed cyanation chemistry is catalyst deactivation due to the strong binding affinity of cyanide ions with palladium.[191] In order to avoid this issue, Beller and co-workers added acetone cyanohydrin, which is in equilibrium with acetone and hydrogen cyanide, *via* a syringe pump at low addition rates to ensure low cyanide concentrations in the reaction mixture.[192] Despite its simplicity, a broad variety of benzonitriles were successfully synthesized in excellent yields. In 2017, Kristensen *et al.* produced hydrogen cyanide *ex situ* in a two-chamber system.[193] This was accomplished upon mixing potassium cyanide and acetic acid in ethylene glycol (Scheme 1.45). In addition, extensive studies were performed to

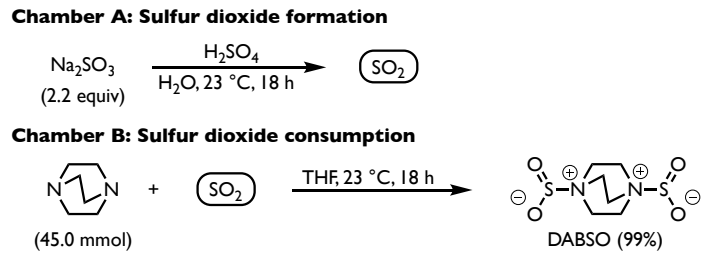
further elucidate the mechanism of palladium-catalyzed cyanation of aryl bromides.[193]




**Scheme 1.45** *Ex situ* generation of ($^{13}$C-labeled) hydrogen cyanide for the palladium-catalyzed cyanation of aryl bromides.[193]

## 1.2.10. Sulfur dioxide

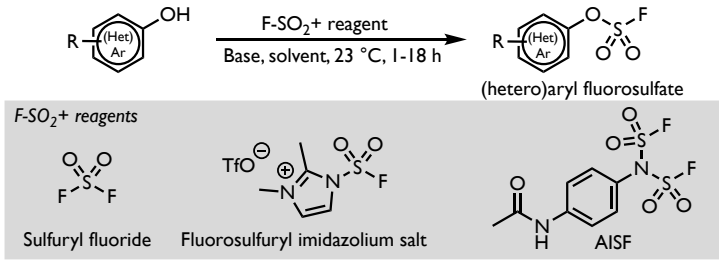
Recently, the Willis group published an excellent review on the topic of sulfur dioxide surrogates.[194] Although the use of $SO_2$ precursors is not yet a fully established method, interest in the field has been reinvigorated, especially since the recent development of DABSO.[195-196] This compound is a bis(sulfur dioxide) adduct of DABCO, and is applied as a solid and bench-stable equivalent of gaseous sulfur dioxide. A second approach to access $SO_2$ emanates from the reaction of a metal sulfite salt (e.g. $Na_2SO_3$) with concentrated sulfuric acid.[197] Recently, Van Mileghem *et al.* implemented this gas releasing system for the gram-scale production of DABSO in a two-chamber reactor (Scheme 1.46).[198] Thionyl chloride[199] and 3-sulfolene[200] are two other sulfur dioxide surrogates which have been used to a lesser extent. The first one spontaneously produces $SO_2$ in the presence of water, while the latter relies on a thermal [4+1] cheletropic extrusion, liberating 1,3-butadiene and sulfur dioxide.




**Scheme 1.46** *Ex situ* formation of sulfur dioxide from sodium sulfite for the synthesis of DABSO.[198]

## 1.2.11. Sulfuryl fluoride

In the USA, sulfuryl fluoride is a widely used insecticide for whole-structure fumigation and is manufactured and commercialized under the trade name Vikane by Dow Chemical Company.[201] Until 2014, it was one of the only gases produced on an industrial scale with little or no applications in organic synthesis. Since the seminal work of Sharpless on Sulfur(VI) Fluoride Exchange (SuFEx) chemistry, sulfuryl fluoride has gained a renewed interest as it is one of the key building blocks for the synthesis of fluorosulfates (scheme 1.47), the electrophilic coupling partner in the SuFEx reaction.[201-202]



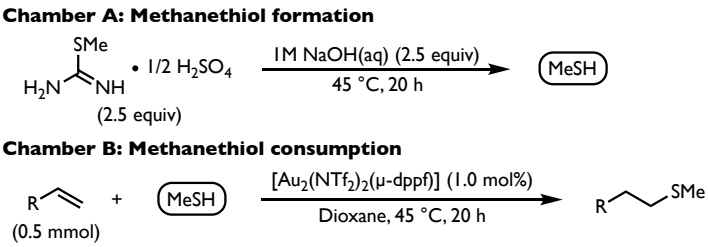

**Scheme 1.47** Fluorosulfation of (hetero)aryl phenols with F-$SO_2$+ reagents.

To expedite the development of SuFEx chemistry, our research group reported 1,1'-sulfonyldiimidazole as a sulfuryl fluoride surrogate in September 2017.[203] Gas release readily occurred in the presence of a fluoride salt under acidic conditions. In chapter 4, a more profound discussion will elaborate on the search of 1,1'-sulfonyldiimidazole as a $SO_2F_2$ source.

Only a few months later, Sharpless and co-workers designed a stable fluorosulfuryl imidazolium triflate salt as a fluorosulfuryl transfer agent (scheme 1.47).[204] Similar to our protocol, treating this compound with potassium fluoride resulted in the rapid formation of gaseous sulfuryl fluoride. One of the main drawbacks of this imidazolium salt is its synthetic route as it requires $SO_2F_2$ gas, thereby bringing the problem back to obtaining the $SO_2F_2$ gas. In the beginning of 2018, researchers at Pfizer introduced [4-(acetylamino)phenyl]imidodisulfuryl difluoride, or abbreviated AISF, as sulfuryl fluoride equivalent (scheme 1.47).[205]

## 1.2.12. Methanethiol

Methanethiol precursors are among the least studied gas releasing molecules, which might be explained by its toxicity and foul-smelling pungent odor. One example is *S*-methylisothiourea hemisulfate which readily generates methanethiol after basification. Kristensen *et al.* implemented this system in a two-chamber setup to exploit the released gas as a reagent in the gold-catalyzed hydrothiolation of olefins (scheme 1.48).[206] Other molecules, such as dimethyl disulfide[207] and dimethyl sulfoxide,[208] have also been used to install a methyl sulfide group.




**Scheme 1.48** *Ex situ* formation of methanethiol from *S*-methylisothiourea for the gold(I)-catalyzed hydrothiolation of olefins.[206]

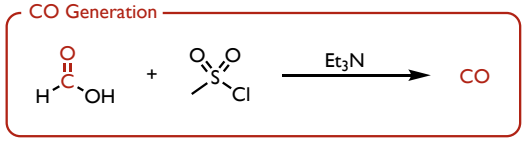
## 1.2.13. Summary

To conclude, the introduction of modern techniques, such as two-chamber systems and tube-in-tube reactors, have been an important stimulus in the search of novel gas releasing molecules and the development of fundamentally new chemistry. With carbon monoxide as the flagship molecule, a plethora of gas releasing molecules is currently available for the on-demand production of a variety of gases.

## 1.3. Objectives

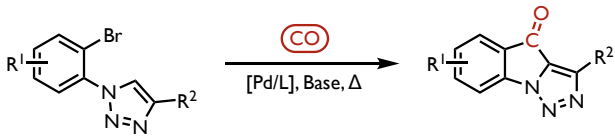
This thesis, entitled the generation and valorization of gases in organic synthesis, has two main objectives: (1) the search of novel gas releasing systems (chapter 2 and 4), and (2) the exploitation of these systems for the development of new synthetic transformations (chapter 3 and 5).

In chapter 2, we focus on the development of a novel carbon monoxide releasing system. Notwithstanding the plethora of CO precursor molecules available, it would be highly advantageous if inexpensive commodity chemicals could be used to release carbon monoxide at room temperature. Inspired by the Morgan reaction, we conceive that formic acid could be readily decomposed into carbon monoxide in the presence of mesyl chloride and triethylamine (Scheme 1.49).




**Scheme 1.49** A new carbon monoxide releasing system (chapter 2).

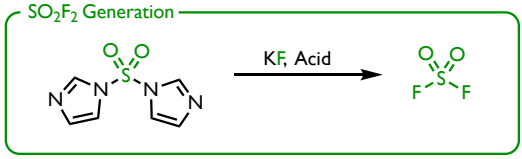
The synthesis of new heterocyclic compounds is a longstanding interest of our research group. With the CO releasing system in hand, we opt to explore the unprecedented carbonylative C-H functionalization of 1-(2-bromoaryl)-1,2,3-triazoles in chapter 3. Interestingly, this transformation gives access to a new heterocyclic scaffold, the triazolo[1,5-*a*]indolone ring system (scheme 1.50).




**Scheme 1.50** A new application of CO chemistry: the synthesis of triazolo[1,5-*a*]indolones (chapter 3).

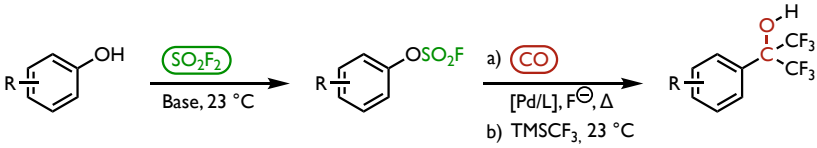
In chapter 4, we move away from carbon monoxide as our gas of interest. Since the seminal work of Sharpless on Sulfuryl(VI) Fluoride Exchange (SuFEx) chemistry, there is a renewed interest in sulfuryl fluoride gas ($SO_2F_2$) as it is one of the key reagents for the synthesis of aryl fluorosulfates, the electrophilic coupling partner in the SuFEx reaction.[201-

202] In sharp contrast to the fast-growing field of CO releasing molecules, no sulfuryl fluoride releasing molecules were reported at the time of performing this research, back in 2017. In this chapter, we aim to develop the first sulfuryl fluoride surrogate (scheme 1.51) to expedite the implementation of SuFEx chemistry within the scientific community.




**Scheme 1.51** The search of the first sulfuryl fluoride precursor (chapter 4).

Finally, in chapter 5, we are curious if it would be possible to merge the acquired expertise in the field of CO chemistry (chapter 2 and 3) and $SO_2F_2$ chemistry (chapter 4). In collaboration with the Skrydstrup group, one of the leading players in the field of *ex situ* carbon monoxide generation, the idea sprouted to synthesize α,α-bis(trifluoromethyl)carbinols from aryl bromides and fluorosulfates *via* a palladium-catalyzed carbonylative cross-coupling reaction (scheme 1.52).




**Scheme 1.52** Merging CO and $SO_2F_2$ chemistry: the synthesis of α,α-bis(trifluoromethyl)carbinols (chapter 5).

# CHAPTER 2

# A new carbon monoxide releasing system

This chapter is based on C. Veryser, S. Van Mileghem, B. Egle, P. Gilles, and W. M. De Borggraeve, 'Low-cost instant CO generation at room temperature using formic acid, mesyl chloride and triethylamine' in *React. Chem. Eng.* **2016**, *1*, 142-146.[71] and was reproduced with permission from the Royal Society of Chemistry.

*Author contributions*

C.V. and S.V.M. contributed equally to this study. B.E. conceived the CO releasing system. S.V.M. performed the initial experiments in a two-chamber reactor. C.V. conducted the optimization, the decomposition study, and the reaction scope. P.G. assisted with the reaction scope. W.M.D.B. coordinated the study. C.V. wrote the manuscript with input or editing from all co-authors.

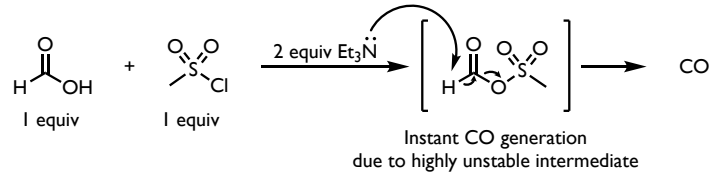
## 2.1. Introduction

Carbon monoxide is beyond doubt one of the most important C1 building blocks for organic synthesis, especially since it acts as an excellent ligand in transition-metal chemistry.[209-210] Safety issues, however, constrain the direct utility of this highly toxic gas. Particularly on lab scale in a typical research lab, storage and use of pure, pressurized carbon monoxide gas raise serious safety concerns. This has prompted researchers to explore and develop alternative sources of carbon monoxide.

As reviewed in the introductory chapter, a plethora of CO releasing molecules has been reported, such as formate esters,[84-85, 88] formamides,[93, 95] aldehydes,[108-109] metal carbonyl complexes,[116] acid chlorides,[43] silacarboxylic acids,[125] and chloroform,[139] to name a few. Unfortunately, some of these precursors are either very toxic themselves, require high temperatures for carbon monoxide liberation or are non-trivial specialty chemicals with an associated higher cost. It would be advantageous if inexpensive commodities could be used to release carbon monoxide at ambient temperature in a robust manner.

One textbook example that fulfills this requirement is the conversion of formic acid into carbon monoxide by sulfuric acid (the Morgan reaction).[63] Recently, zeolites have been proposed as safe substitutes for strong and corrosive acids to render the Morgan reaction more attractive for synthetic organic chemists.[211] Unfortunately, only a few specific zeolites can adequately decompose formic acid, hampering the robustness of the method.[64]

In 2016, our research group developed a new carbon monoxide releasing system that instantly generates CO from low-cost commodity chemicals at room temperature. As shown in Scheme 2.1, CO formation occurred by simply mixing three standard lab reagents: formic acid, mesyl chloride (MsCl), and triethylamine ($Et_3N$).[71]




**Scheme 2.1** Proposed decomposition mechanism of formic acid in the presence of mesyl chloride (1equiv) and triethylamine (2 equiv), leading to instant CO generation.

The decomposition of formic acid to carbon monoxide by mesyl chloride and triethylamine was investigated by $^{13}$C-NMR and will be the topic of the next section. In section 2.3 and 2.4, the new CO releasing system was employed in a two-chamber reactor for the synthesis of amides *via* a palladium-catalyzed aminocarbonylation of (hetero)aryl bromides. In addition, three pharmaceutical active compounds were isotopically labeled by using $^{13}$C-HCOOH as an obvious source of $^{13}$CO. Even more interesting is the fact that $^{13}$C-enriched formic acid is one of the most economical carbon monoxide precursors for $^{13}$C-carbonyl labeling (see section 2.5).

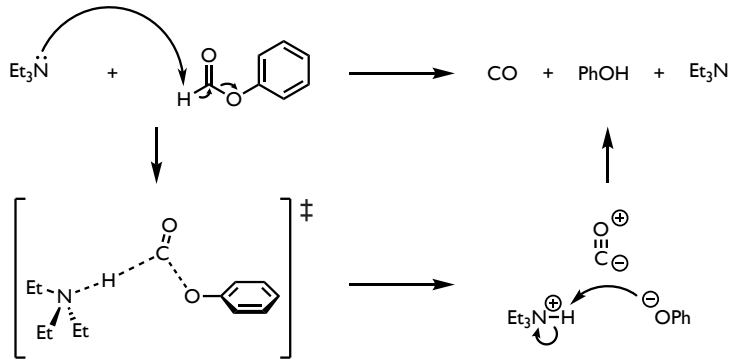
## 2.2. Decomposition mechanism

To gain more insight into the steps involved in the decomposition of formic acid to carbon monoxide in the presence of mesyl chloride and triethylamine, a $^{13}$C-NMR study was conducted at room temperature (Scheme 2.3). Spectra [A], [B], [E] show the reference ppm-values of formic acid (HCOOH = 162.7 ppm), mesyl chloride (MsCl = 53.3 ppm), and triethylammonium methanesulfonate ($MsO^-$ = 39.6 ppm) in 600 µL $CD_3CN$. First, 0.5 mmol mesyl chloride was added to a solution of 0.5 mmol HCOOH in $CD_3CN$ (Scheme 2.3[C]). At this point no changes seemed to occur in the NMR spectrum of the mixture, indicating that a base is needed to start the reaction. Subsequent dropwise addition of 1.0 mmol of $Et_3N$ resulted in vigorous gas development for several seconds. Afterwards the $^{13}$C-NMR spectrum was recorded (Scheme 2.3[D]) and complete decomposition of HCOOH was observed as the corresponding peak

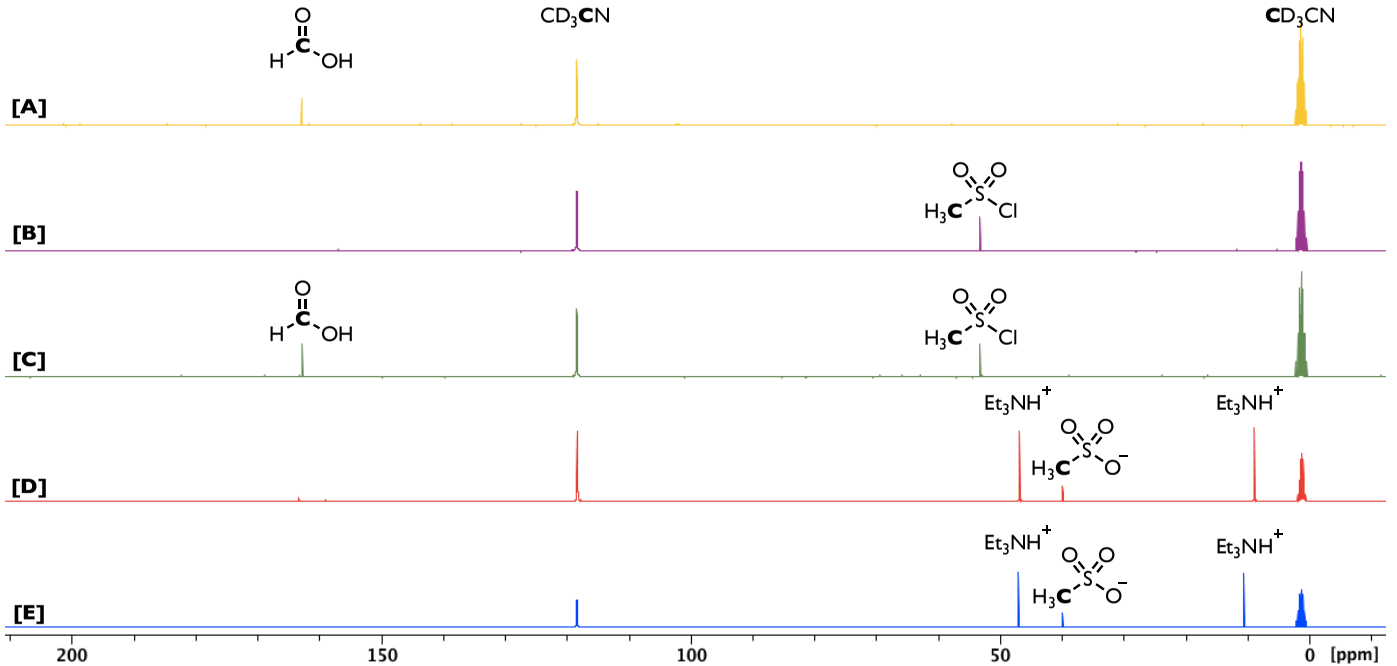
disappeared. MsCl also disappeared in the spectrum and a new peak appeared at a lower ppm-value (39.6 ppm), indicating the formation of the methanesulfonate anion and the triethylammonium cation (Scheme 2.3[E]).

These results suggest that once formic acid is deprotonated, it most probably reacts with mesyl chloride and forms a highly unstable mixed anhydride intermediate. A second deprotonation leads to instant CO formation, as the methanesulfonate is an excellent leaving group (Scheme 2.1). At this point it is not known whether the elimination of the sulfonate happens concerted with the deprotonation or not. We also found that other sulfonyl chlorides are equally able to decompose formic acid to carbon monoxide in the presence of triethylamine: tosyl chloride, triflyl chloride, nosyl chloride, etc. However, for reasons of atom economy, mesyl chloride was our reagent of choice.

A year after this manuscript was published, the Manabe group reported mechanistic details on a closely related CO releasing system: the weak-base-catalyzed decomposition of phenyl formate to carbon monoxide and phenol.[75] The theoretical and experimental data suggested that CO formation occurred *via* an E2 concerted $\alpha$-elimination pathway. As depicted in Scheme 2.2, this means that the bimolecular transition state involves both the base-catalyzed deprotonation of phenyl formate as well as the formation of carbon monoxide and phenoxide. This is followed by an acid-base reaction between the conjugated acid of the base and phenoxide, producing phenol and regenerating the base.[75]




**Scheme 2.2** Proposed mechanism of weak-base-catalyzed generation of carbon monoxide from phenyl formate. Scheme redrawn from reference[75] with permission from Wiley.



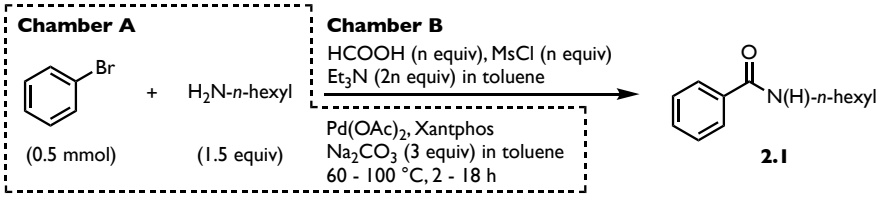

**Scheme 2.3** $^{13}$C-NMR study of the CO precursor at room temperature. [A] 0.5 mmol HCOOH in 600 µL $CD_3CN$. [B] 0.5 mmol MsCl in 600 µL $CD_3CN$. [C] 0.5 mmol HCOOH and 0.5 mmol MsCl in 600 µL $CD_3CN$. [D] 0.5 mmol HCOOH, 0.5 mmol MsCl and 1.0 mmol $Et_3N$ in 600 µL $CD_3CN$. [E] 0.5 mmol MsOH and 1.0 mmol $Et_3N$ in 600 µL $CD_3CN$.

## 2.3. Optimization study

Palladium-catalyzed aminocarbonylation of aryl bromides was chosen as the test case to demonstrate the utility of this CO precursor. It is important to note that decomposition of precursor molecules often lead to byproducts, which are not necessarily innocent spectator molecules. As exemplified by our CO releasing system, the amine moiety (needed to form an amide) could react with mesyl chloride and a mixture of compounds might be expected. Inspired by the two-chamber setup of the Skrydstrup group, *ex situ* CO generation was implemented to address these difficulties.[43-44]

We began our optimization by using the conditions reported by Buchwald and co-workers as a benchmark for the Pd-catalyzed aminocarbonylation chemistry.[212] Initially, chamber A was filled with 5 mol% $Pd(OAc)_2$/Xantphos, $Na_2CO_3$ (3 equiv), 3 mL of dry degassed toluene (0.167 M), bromobenzene (1 equiv) and *n*-hexylamine (1.5 equiv). Chamber B was loaded with 3 equivalents of formic acid and mesyl chloride. Finally, $Et_3N$ (6 equiv) was added by injection through the septum in chamber B at room temperature (Table 2.1). Performing the reaction at 60 °C resulted in 41% of the desired amide (**2.1**) after 18 hours (entry 1). To our delight an increased yield was observed at higher temperatures (entries 2 and 3). In contrast to our results at 100 °C, Buchwald reported an incomplete conversion of the starting material at this temperature. This unusual result was ascribed to decreased catalyst stability at higher temperature.[212] However, in our system, CO pressure builds up in the closed system. We assume that the generated pressure stabilizes the catalytic system and therefore higher temperatures and lower catalyst loadings can be applied. In order to increase the cost efficiency of this system, a reduction of CO and catalyst loading was investigated (entries 4-7). Performing the reaction with only 1 mol% $Pd(OAc)_2$/Xantphos in the presence of 1.3 equivalents of CO (assuming full conversion of the precursor) affords the amide in 94%. Further improvements were made by reducing the reaction time and increasing the concentration to 2 hours (entry 9) and 0.5 M (entry 11), respectively. The *ex situ* generated CO was successfully implemented in the Pd-catalyzed aminocarbonylation of bromobenzene with *n*-hexylamine, yielding the desired amide (**2.1**) in 98%.

**Table 2.1** Optimization of the reaction conditions[a]

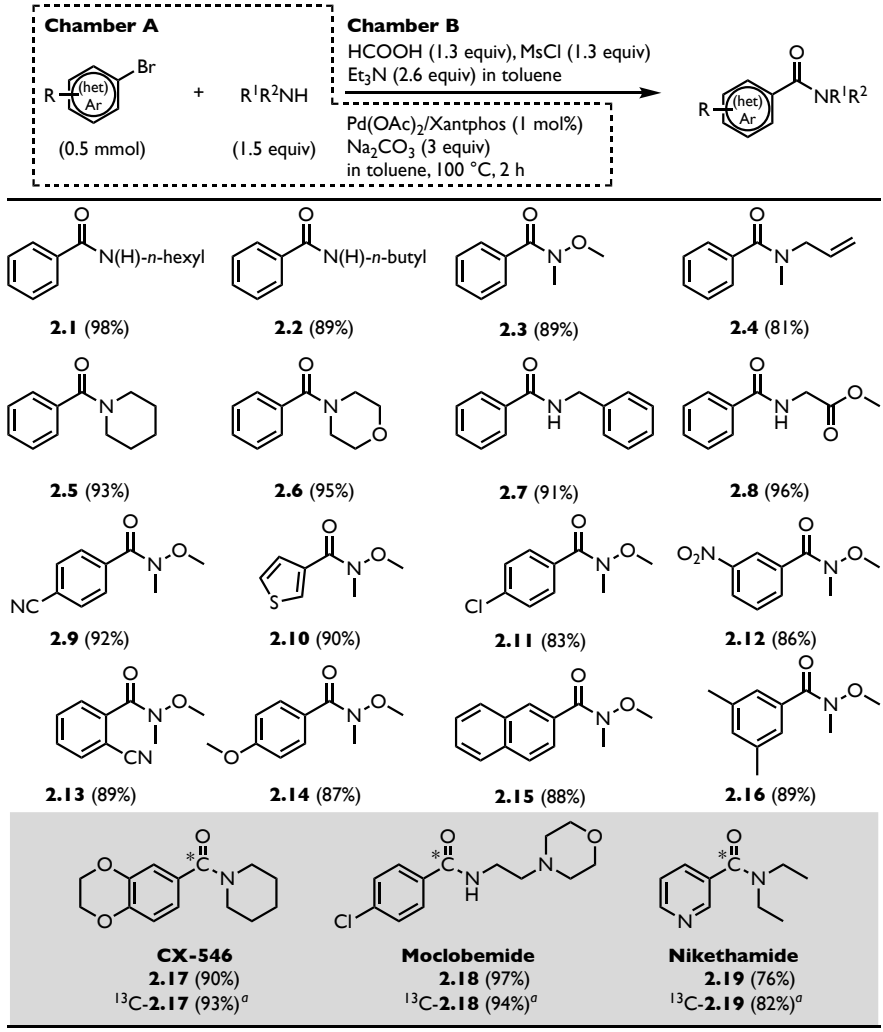



| Entry | T (°C) | t (h) | CO equiv | Catalyst/Ligand | Conc. (M) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | 60 | 18 | 3.0 | 5 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 41 |
| 2 | 80 | 18 | 3.0 | 5 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 80 |
| 3 | 100 | 18 | 3.0 | 5 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 96 |
| 4 | 100 | 18 | 2.0 | 5 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 95 |
| 5 | 100 | 18 | 1.3 | 5 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 93 |
| 6 | 100 | 18 | 1.3 | 2 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 96 |
| 7 | 100 | 18 | 1.3 | 1 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 94 |
| 8 | 100 | 18 | 1.3 | 1 mol% $Pd(PPh_3)_4$ | 0.167 | 19 |
| 9 | 100 | 2 | 1.3 | 1 mol% $Pd(OAc)_2$/Xantphos | 0.167 | 95 |
| 10 | 100 | 2 | 1.3 | 1 mol% $Pd(OAc)_2$/Xantphos | 0.250 | 96 |
| 11 | 100 | 2 | 1.3 | 1 mol% $Pd(OAc)_2$/Xantphos | 0.500 | 98 |

[a]Reaction conditions: Chamber A: bromobenzene (0.5 mmol), *n*-hexylamine (0.75 mmol, 1.5 equiv), $Na_2CO_3$ (1.5 mmol, 3.0 equiv), $Pd(OAc)_2$, Xantphos, and 1 mL of dry degassed toluene; Chamber B: formic acid, methanesulfonyl chloride in 2 mL of dry degassed toluene. Finally, $Et_3N$ was added by injection through the septum in chamber B at room temperature. After 2 minutes the reactor was placed in an oil-bath at 100 °C. [b]Isolated yield.

## 2.4. Reaction scope

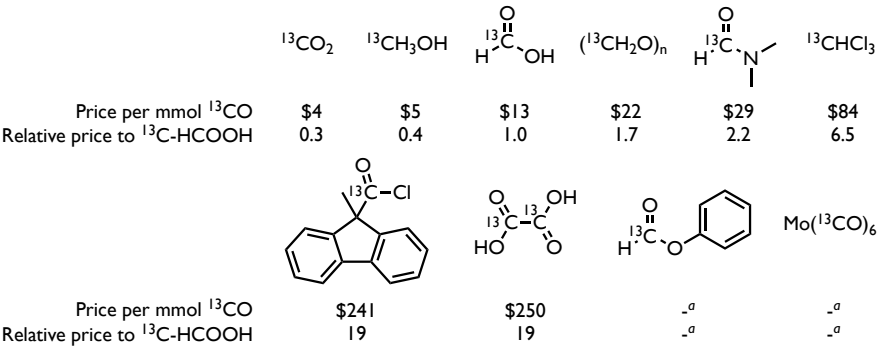
With the optimized conditions in hand, the scope of the Pd-catalyzed aminocarbonylation chemistry was further explored. As is shown in Scheme 2.4, a variety of benzamides and Weinreb amides were synthesized in good to excellent yields. The reaction conditions tolerate a wide variety of functional groups on both the aryl bromide and the amines, including allyl (**2.4**), nitrile (**2.9** and **2.13**), nitro (**2.12**), aryl chlorides (**2.11** and **2.18**) and esters (**2.8**). In addition, also heteroaryl bromides (thiophene **2.10** and pyridine **2.19**) gave good to excellent yields. This work was finalized with the synthesis of three relevant $^{13}C$-labeled pharmaceuticals: CX-546[213] (**2.17**), Moclobemide[214] (**2.18**), and Nikethamide[215] (**2.19**). These compounds were labeled using $^{13}C$-formic acid.




**Scheme 2.4** Palladium-catalyzed aminocarbonylation by employing formic acid, mesyl chloride and triethylamine as the CO generating system. Reaction conditions: Chamber A: (hetero)aryl bromide (0.5 mmol), amine (1.5 equiv), $Na_2CO_3$ (3.0 equiv), $Pd(OAc)_2$ (1 mol%), Xantphos (1 mol%) in 1 mL of dry degassed toluene; Chamber B: formic acid (1.3 equiv) and MsCl (1.3 equiv) in 2 mL of dry degassed toluene. Finally, $Et_3N$ (2.6 equiv) was added by injection through the septum in chamber B at room temperature. After 2 minutes the reactor was immersed in an oil-bath at 100 °C. Isolated yields. [a] $^{13}$C-HCOOH was used to generate $^{13}$CO.

## 2.5. $^{13}$C-enriched formic acid

Scheme 2.5 gives an overview of the ten most commonly used carbon monoxide precursors and its respective price per mmol $^{13}$CO based on the online catalogues of Cambridge Isotope Laboratories, Inc.[216] and Merck.[217] Notably, enriched $^{13}$C-HCOOH is amongst the most economical CO precursors for $^{13}$C-carbonyl labeling. Only $^{13}CO_2$ and carbon-enriched methanol are less expensive. However, two things should be noted here. First, the concept of precursor molecules is to step away from lecture bottles, making gaseous $^{13}CO_2$ as $^{13}$CO source less ideal. Second, precursor molecules alone don't generate carbon monoxide, they need to be activated by a catalyst or an additive. For example, the conversion carbon dioxide to carbon monoxide requires a sacrificial reductant, while the dehydrogenation-decarbonylation sequence of methanol to carbon monoxide is catalyzed by a transition-metal complex.[218] Since our CO releasing system relies on two inexpensive commodity chemicals for the production of carbon monoxide from formic acid, it is arguably even the most cost-efficient $^{13}$CO releasing system reported to date.




**Scheme 2.5** Price comparison of the most commonly applied $^{13}$C-enriched CO precursor molecules. The commercial price is based on the online catalogues of Cambridge Isotope Laboratories, Inc. and Merck. [a]Not commercially available.

## 2.6. Conclusion

In summary, we have developed a system to instantly generate CO at room temperature from formic acid, mesyl chloride and triethylamine. Since these reagents are inexpensive standard lab chemicals, this method belongs to one of the most economical and readily available CO releasing

systems. The *ex situ* generated CO was successfully applied in Pd-catalyzed aminocarbonylation chemistry resulting in high yielding amide formation. Remarkably, this is the first report on $^{13}$C-carbonylation labeling in a Pd-catalyzed reaction by decomposition of $^{13}$C-HCOOH into $^{13}$CO.

# CHAPTER 3

# A new application of CO chemistry: the synthesis of triazolo[1,5-*a*]indolones

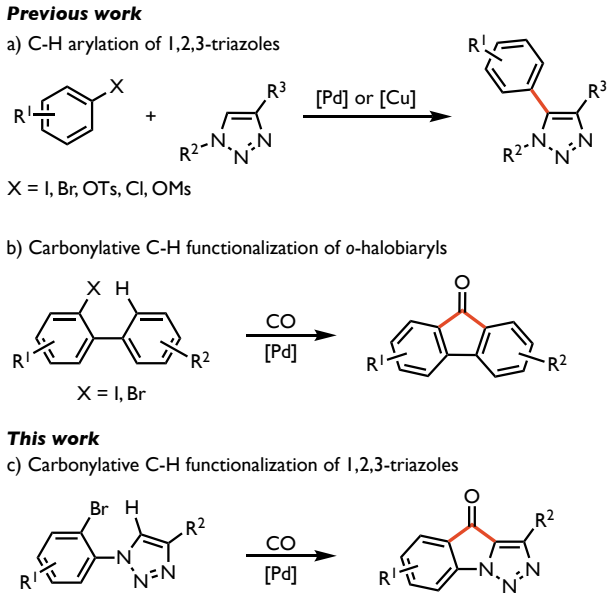
This chapter is based on C. Veryser, G. Steurs, L. Van Meervelt, and W. M. De Borggraeve, 'Intramolecular Carbonylative C-H Functionalization of 1,2,3-Triazoles for the Synthesis of Triazolo[1,5-*a*]indolones' *Adv. Synth. Catal.* **2017**, *359*, 1271-1276.[219] and was reproduced with permission from Wiley.

*Author contributions*

C.V. conceived the intramolecular carbonylative C-H functionalization of 1,2,3-triazoles. C.V. performed the optimization study and the reaction scope. G.S. assisted with the reaction scope and developed the alternative approach. L.V.M. measured the X-ray structure. W.M.D.B. coordinated the study. C.V. wrote the manuscript with input or editing from all co-authors.

## 3.1. Introduction

Over the past decade, transition metal-catalyzed C-H functionalization has emerged as a valuable strategy in organic synthesis.[220-224] This strategy is challenging, as it has to deal with the inertness of a C-H bond, but is also beneficial in terms of atom economy, since typical prefunctionalization steps (such as halogenation and borylation) can be circumvented by directly addressing a C-H bond. One relevant example for this study is the discovery of the direct arylation of 1,2,3-triazoles (Scheme 3.1a).[225-230]



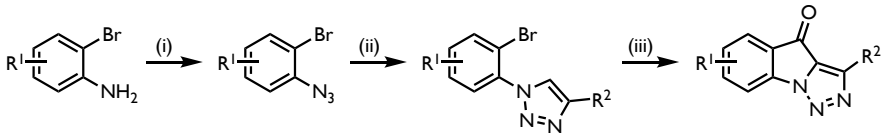

**Scheme 3.1** Transition metal-catalyzed (carbonylative) C-H functionalization.

While transition metal-catalyzed direct arylation is widely explored, the carbonylative equivalent still poses great scientific challenges to date.[231-233] This problem has partially been addressed by using activated substrates (*e.g.* polyfluoroarenes)[234] or intramolecular chelation (*e.g.* nitrogen

coordination and directing groups).[235-242] Other methods involve *in situ* formation of an organocuprate[243] or *in situ* halogenation.[244-245] One example is the pioneering work of the Larock group in 2000, discussing the intramolecular carbonylative C-H functionalization of *o*-halobiaryls for the synthesis of fluorenone derivates (Scheme 3.1b).[246] Recently, the scope of this transformation was expanded, as it turned out that (fused) 5-membered heterocycles were suitable substrates.[247-252] Progress has also been made on the more challenging intermolecular variant of this reaction as the Arndtsen group developed a general procedure to perform carbonylative C-H functionalization on 5-membered nitrogen-containing heterocycles.[253]

To our surprise, neither intra- nor intermolecular carbonylative C-H functionalization of 1,2,3-triazoles has been reported to date. This type of transformation could however be a valuable new strategy towards highly substituted triazoles, which are omnipresent since the discovery of the click reaction. In this chapter, we will present our results on the first intramolecular carbonylative C-H functionalization of triazoles. This pathway gave direct access to a new heterocyclic scaffold: the triazolo[1,5-*a*]indolone ring system (Scheme 3.1c).

The triazolo[1,5-*a*]indolones were prepared *via* a short synthetic sequence, using 2-bromoanilines as readily available starting materials (Scheme 3.2). First, 2-bromoanilines were converted into their corresponding azides by making use of *tert*-butyl nitrite and azidotrimethylsilane.[254] Then, cycloaddition of 2-bromophenyl azides with alkynes or enolizable aldehydes furnished 1-(2-bromoaryl)-1,2,3-triazoles (section 3.2). The last step consists of an unprecedented carbonylative C-H functionalization of the synthesized triazoles (section 3.3). Interestingly, isotopic labeling of the carbonyl carbon atom is possible by employing near stoichiometric amounts of $^{13}CO$. Furthermore, a complementary pathway to the same scaffold was investigated. This approach relied on a carbonylative Sonogashira coupling, followed by a two-step, one-pot azidation/cycloaddition and will be discussed in section 3.4.

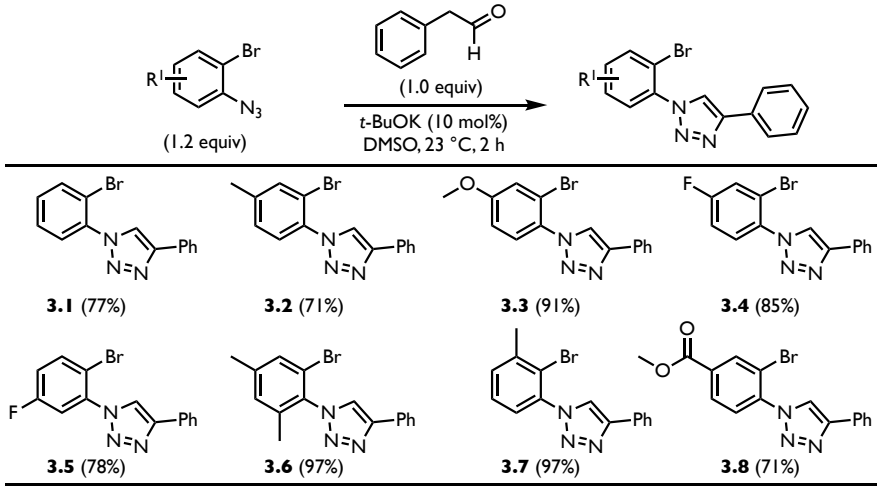


**Scheme 3.2** Synthetic route towards triazolo[1,5-*a*]indolones: (i) functional group interconversion, (ii) cycloaddition and (iii) carbonylative C-H functionalization.

## 3.2. Triazole synthesis

The second transformation in Scheme 3.2, the cycloaddition of 2-bromophenyl azides with alkynes or enolizable aldehydes to furnish 1-(2-bromophenyl)-1,2,3-triazoles, is challenging due to the steric hindrance of the *ortho*-bromo atom. In the literature, only a few of these triazole-containing precursors have been synthesized so far.[255-259] In order to generate a diverse library, two complementary methods were employed.

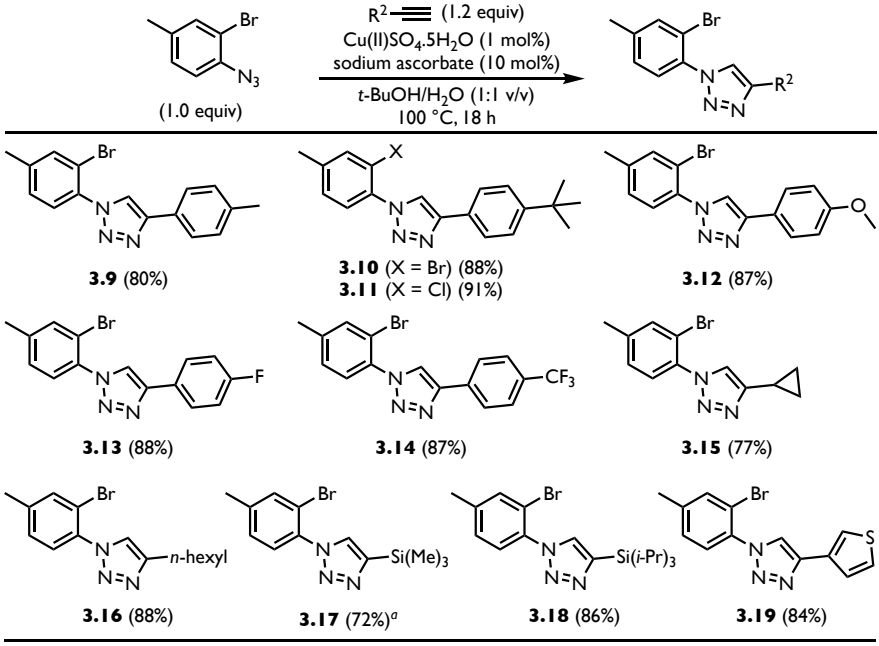
The first one is a metal-free enolate-mediated organocatalytic azide-aldehyde [3+2] cycloaddition.[257] As demonstrated in Scheme 3.3, different $R^1$ substituents were introduced through cycloaddition of phenylacetaldehyde with a variety of 2-bromophenyl azides in the presence of potassium *tert*-butoxide in DMSO at room temperature. Both unsubstituted (**3.1**) and substituted (**3.2**-**3.8**) 1-(2-bromophenyl)-1,2,3-triazoles were obtained in good to excellent yields, ranging from 71% to 97%.




**Scheme 3.3** Organocatalytic azide-aldehyde [3+2] cycloaddition: azide substrate scope. Reaction conditions: phenyl acetaldehyde (0.70 mmol), azide (0.84 mmol), *t*-BuOK (10 mol%) in 2 mL of DMSO at 23 °C for 2 hours. Isolated yields.

The second method, the copper-catalyzed azide-alkyne [3+2] cycloaddition (CuAAC), could allow variation of the $R^2$ substituent. However, upon reacting 2-bromo-4-methylphenyl azide with 4-ethynyltoluene using the original CuAAC conditions reported by Meldal[260] and Sharpless[261], only 14% of the desired product **3.9** was isolated, while vast amounts of starting material were still present. This observation could be explained by the steric hindrance of the bromo substituent. In order to get full conversion, a short optimization study was performed investigating the influence of the catalyst loading, the required amount of reducing agent and the reaction temperature. The details are summarized in the experimental section 7.3.

With the optimized conditions in hand, 1 mol% $CuSO_4.5H_2O$ and 10 mol% sodium ascorbate in a *t*-BuOH/water mixture (1:1 v/v) for 18 hours at 100 °C, full conversion of 2-bromo-4-methylphenyl azide was achieved, yielding 80% of **3.9**. Next, a variety of alkynes was employed to further investigate the scope of the cycloaddition (Scheme 3.4).




**Scheme 3.4** Copper-catalyzed azide-alkyne [3+2] cycloaddition: alkyne substrate scope. Reaction conditions: 2-bromo-4-methylphenyl azide (0.70 mmol), alkyne (0.84 mmol), $Cu(II)SO_4.5H_2O$ (1 mol%) and sodium ascorbate (10 mol%) in 3 mL of *t*-BuOH/$H_2O$ (1:1 v/v) at 100 °C for 18 hours. Isolated yields. [a]4 equivalents of trimethylsilylacetylene were used.

Arylalkynes bearing a *t*-Bu (**3.10** and **3.11**), an OMe (**3.12**), a F (**3.13**) and a $CF_3$ (**3.14**) group, were suitable for this transformation and gave excellent yields (87-91%). Both cyclopropylacetylene and 1-octyne afforded the desired products in satisfactory yields (77% for **3.15** and 88% for **3.16**, respectively). Subsequently, two silylated acetylenes were tested. Cycloaddition of 2-bromo-4-methylphenyl azide with 1.2 equivalents of trimethylsilylacetylene furnished **3.17** in only 35% yield.[262] Gratifyingly, performing the same reaction with 4 equivalents of trimethylsilylacetylene afforded 72% of the desired product. In the case of (triisopropylsilyl)acetylene, only 1.2 equivalents were required to obtain **3.18** in an excellent yield of 86%. The scope was finalized with the heterocyclic 3-ethynylthiophene, which provided product **3.19** in 84% yield.

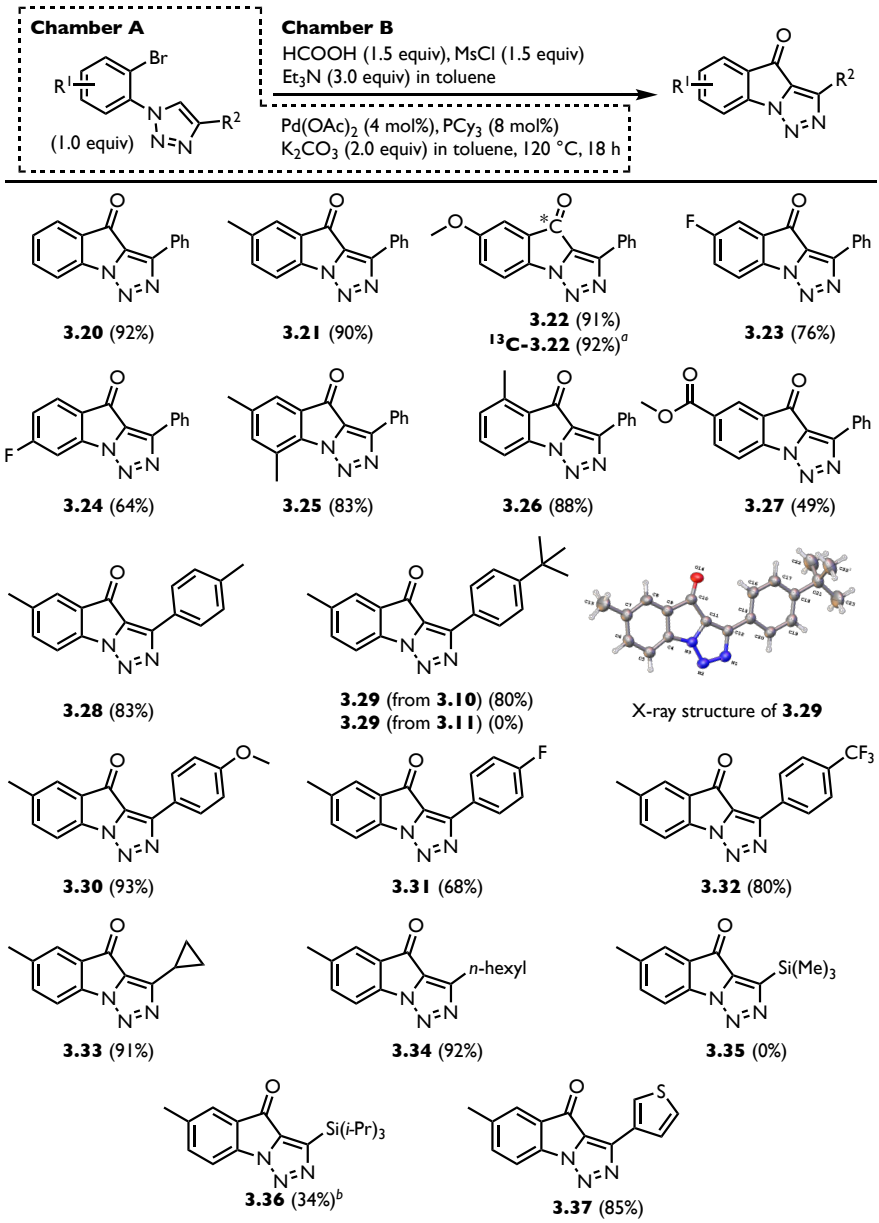
## 3.3. Triazolo[1,5-*a*]indolone synthesis

Next, we speculated that the 1-(2-bromophenyl)-1,2,3-triazoles could serve as suitable substrates for the palladium-catalyzed intramolecular carbonylative ring closure, generating a new heterocyclic scaffold: the triazolo[1,5-*a*]indolone. Although carbon monoxide represents one of the most important C1 building blocks, safety issues constrain the direct utility of this highly toxic gas. Recently, we have published a study revealing a low-cost and robust carbon monoxide precursor based on formic acid, mesyl chloride and triethylamine (see chapter 2).[71] This CO precursor can be used in a two-chamber reactor, in which the desired amount of CO is generated in one chamber and is consumed in the other.[43-44]

We started our investigation by screening different reaction conditions for the intramolecular carbonylative C-H functionalization of substrate **3.10**. The experimental details of the optimization study can be found in in section 7.3. Full conversion was achieved in the presence of 4 mol% $Pd(OAc)_2$, 8 mol% $PCy_3$, 1.5 equivalents of carbon monoxide and 2.0 equivalents of potassium carbonate in toluene at 120 °C for 18 hours, yielding **3.29** in 80% (Scheme 3.5). NMR and X-ray crystallography[263] confirmed the structure of this compound. Under these conditions, we tried to convert the other synthesized triazoles (**3.1**-**3.19**) into their corresponding triazolo[1,5-*a*]indolones. To our delight, unsubstituted and electron-rich 1-(2-bromophenyl)-1,2,3-triazoles were excellent substrates

as they provided the corresponding triazolo[1,5-*a*]indolones (**3.20**, **3.21**, **3.22** and **3.25**) in high yields, ranging from 83% to 92%. Even the substrate bearing an *ortho*-substituted methyl with respect to the bromine yielded the desired compound **3.26** in 88%. Electron-deficient 1-(2-bromophenyl)-1,2,3-triazoles were more challenging as not only the desired triazolo[1,5-*a*]indolones were formed, but also considerable amounts of the corresponding benzoic acid derivative.[264] Nevertheless, **3.23**, **3.24** and **3.27** were isolated in 76%, 64% and 49% yield, respectively. The nature of the aryl substituent at the 4-position of the triazole could also be varied to furnish the corresponding triazolo[1,5-*a*]indolones in moderate to excellent yields (83%, 93%, 68% and 80% for **3.28**, **3.30**, **3.31** and **3.32**, respectively). Triazoles with a cyclopropyl and an *n*-hexyl group turned out to be excellent substrates, yielding **3.33** in 91% and **3.34** in 92%. Subsequently, silylated triazoles were investigated. Unfortunately, the reaction of triazole **3.17** did not provide compound **3.35**, but a rather complex mixture. This could be ascribed to the instability of the trimethylsilyl group. Performing the same reaction with the more stable triisopropylsilyl group afforded an inseparable mixture of the starting material **3.18** and the desired compound **3.36**. Based on $^{1}$H-NMR, 34% of the **3.36** was formed. Reaction of the thiophene-substituted triazole **3.19**, yielded substrate **3.37** in 85%. The substrate scope was finalized with $^{13}$C-carbonyl labeling of **$^{13}$C-3.22**, using only near stoichiometric amounts of $^{13}$CO.

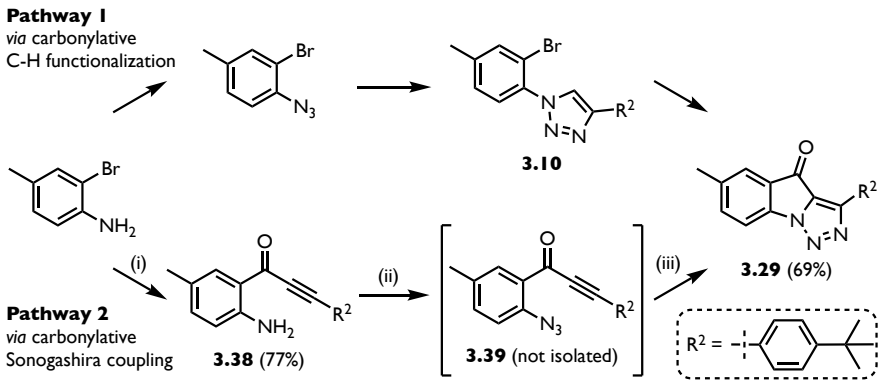
We also wondered whether 1-(2-chlorophenyl)-1,2,3-triazoles were suitable substrates in this transformation. Unfortunately, upon reacting substrate **3.11** under the same conditions, no conversion towards triazolo[1,5-*a*]indolone **3.29** was observed and the starting material was fully recovered.




**Scheme 3.5** Intramolecular carbonylative C-H functionalization of 1-(2-bromophenyl)-1,2,3-triazoles for the synthesis of triazolo[1,5-*a*]indolones. Reaction conditions: Chamber A: 1-(2-bromophenyl)-1,2,3-triazole (0.40 mmol), $Pd(OAc)_2$ (4 mol%), $PCy_3$ (8 mol%), $K_2CO_3$ (0.8 mmol) in 2 mL dry degassed toluene; Chamber B: formic acid (0.60 mmol, 1.5 equiv) and MsCl (0.60 mmol, 1.5 equiv) in 2 mL of dry degassed toluene. Finally, $Et_3N$ (1.2 mmol, 3.0 equiv) was added by injection through the septum in chamber B at room temperature. After 2 minutes the reactor was immersed in an oil-bath at 120 °C. [a]$^{13}$C-HCOOH was used to generate $^{13}CO$. [b]Yield based on $^1$H-NMR.

## 3.4. A complementary pathway for the synthesis of triazolo[1,5-*a*]indolones

In order to enhance the accessibility of the new heterocyclic scaffold, we investigated an alternative approach starting from the same reagents (Scheme 3.6). The viability of this approach was illustrated with one example. First, intermediate **3.38** was furnished in 77% *via* a palladium-catalyzed carbonylative Sonogashira coupling of 2-bromo-4-methylaniline with 4-*tert*-butylphenylacetylene.[265] Next, a two-step, one-pot procedure, in which the aniline was converted into the azide followed by ruthenium-catalyzed cycloaddition, yielded the triazolo[1,5-*a*]indolone **3.29** in 69%.[254, 266]




**Scheme 3.6** An alternative pathway towards triazolo[1,5-*a*]indolones: (i) carbonylative Sonogashira coupling, (ii) functional group interconversion (iii) and Ru-catalyzed azide-alkyne [3+2] cycloaddition. Reaction conditions: (i) 2-bromo-4-methylaniline (1.0 mmol), 4-*tert*-butylphenylacetylene (2.0 mmol), $PdCl_2$ (5 mol%), Xantphos (5 mol%), $Et_3N$ (3.0 mmol) and CO (1.5 mmol) in 2 mL of dry degassed dioxane for 18 h at 100 °C; (ii) compound **3.38** (0.40 mmol), *t*-BuONO (0.60 mmol), $TMSN_3$ (0.48 mmol) in 5 mL of acetonitrile for 30 min at 23 °C; (iii) intermediate **3.39** (0.40 mmol) and $Cp^*RuCl(PPh_3)_2$ (2 mol%) in 8 mL of dry degassed dioxane for 18 h at 60 °C.

## 3.5. Conclusion

In summary, we have presented a new and useful methodology to perform intramolecular ring closure of 1,2,3-triazoles *via* carbonylative C-H functionalization. This transformation gave direct access to the unprecedented triazolo[1,5-*a*]indolone ring system. Next, $^{13}C$-carbonyl labeling was performed to demonstrate the usefulness of late-stage installation of carbon isotopes. Moreover, only near-stoichiometric

amounts of CO were required in the synthesis, contributing to the safety aspects of this method. The study was finalized by enhancing the accessibility towards this new scaffold *via* an alternative pathway, using the same starting materials. Further applications of this new carbonylation strategy on triazoles are currently in progress in our laboratory.

# CHAPTER 4

# The search of the first sulfuryl fluoride precursor

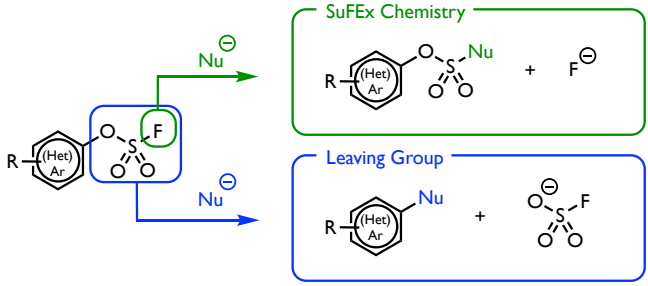
This chapter is based on C. Veryser, J. Demaerel, V. Bieliūnas, P. Gilles, and W. M. De Borggraeve, '*Ex situ* Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates' *Org. Lett.* **2017**, *19*, 5244-5247.[203] and was reproduced with permission from the American Chemical Society.

*Author contributions*

C.V. and J.D. contributed equally to this study. J.D. conceived the $SO_2F_2$ precursor. C.V. and J.D. performed the optimization and the reaction scope. P.G. and V.B. assisted with the reaction scope. C.V. conducted the decomposition study. J.D. determined the pressure profile of the reaction. W.M.D.B. coordinated the study. The manuscript was largely written by C.V. and redacted by J.D. and W.M.D.B. All authors were involved in proofreading.

## 4.1. Introduction

Since 2014, aryl fluorosulfates have sparked enormous interest as they give access to a broad and powerful set of applications.[201] This is primarily due to the dual modes of reactivity of the fluorosulfate group (Scheme 4.1).




**Scheme 4.1** Dual modes of reactivity of the fluorosulfate group.[201]

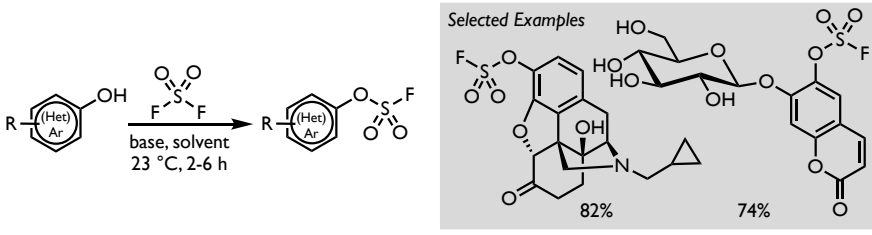
First, the S(VI)-F bond conveys onto the sulfur center an electrophilic behavior very different from other sulfonyl halides. Owing to these unique properties, the fluorosulfate moiety is inert toward most nucleophiles but reacts cleanly with either amines (by merit of protons solvating $F^-$) or aryl silyl ethers (metathesizing into a diaryl sulfate and an extremely strong Si-F bond). This set of Lewis base mediated "click" reactions was recently disclosed by Sharpless and co-workers and baptized as sulfur(VI) fluoride exchange (SuFEx) chemistry.[201] The SuFEx click reaction between aromatic bis(fluorosulfates) and bis(silyl ethers) can, for example, be applied for the synthesis of poly(aryl sulfates), sulfate-backboned analogs to polycarbonates which show promising mechanical properties.[267-268] SuFEx chemistry has also found intriguing applications in selective and orthogonal

post-polymerization modifications[269-270] as well as in biomolecular and peptide chemistry.[271-274]

Second, besides being a robust connector handle, fluorosulfates are also excellent pseudohalides in transition-metal-catalyzed cross-coupling reactions. Many applications have followed, including Suzuki-Miyaura,[275-279] Negishi,[280] or Stille-Migita coupling,[280-281] alkoxycarbonylation,[282-284] and Buchwald-Hartwig amination.[285-286] Consequently, they are often considered as efficient triflate surrogates, albeit at a much lower production cost. Furthermore, aryl fluorosulfates are also versatile intermediates as they can be converted into aryl fluorides,[287] aryl (*N*-acyl) sulfamate esters,[288-289] and others[290-292] or can even be used for the synthesis of anhydrous tetraalkylammonium fluoride salts.[293]

Historically, aryl fluorosulfates are mainly synthesized *via* four different approaches.[294] The first method relies on the pyrolysis of arenediazonium fluorosulfate salts.[295] In the other three strategies, the appropriate phenol (or phenolate) is combined with fluorosulfonic anhydride,[275, 280-283, 296] sulfuryl chloride fluoride,[297] or sulfuryl fluoride[298-301] in the presence of a base at low temperature. Unfortunately, these approaches either require highly toxic and/or expensive reagents or make use of complicated and nonreliable reaction procedures (*e.g.* gas condensation) which often results in low yields.

Recently, Sharpless and Ishii described a robust, reliable, and easy-to-execute synthesis of aryl fluorosulfates.[201, 267, 302-303] These compounds were prepared from phenols and sulfuryl fluoride in the presence of a base, typically triethylamine (Scheme 4.2). This finding has been foundational for the renewed interest in the fluorosulfate chemistry, considering that all newly discovered applications make use of this methodology.




**Scheme 4.2** Synthesis of aryl fluorosulfates from phenols and sulfuryl fluoride in the presence of a base.[201]

The $SO_2F_2$ gas is generally introduced by employing a balloon, filled from a pressurized lecture bottle. Other methods rely on the use of a stock solution of sulfuryl fluoride.[287] Although sulfuryl fluoride gas is produced on an industrial scale and widely used as a fumigant, its impact on human health and the environment should not be neglected.[304] The time-weighted average exposure limit for sulfuryl fluoride has been set to 5 ppm by the US National Institute for Occupational Safety and Health, indicating that long-term exposure is harmful for human well-being.[304-305] The gas was also recently identified as a greenhouse gas with a global warming potential of 4800 relative to carbon dioxide and an atmospheric lifetime of 36 years.[306-308] Moreover, the limited number of suppliers makes it challenging and expensive to obtain a gas cylinder, especially when taking into account the costs of transportation and disposal. Despite the inherent drawbacks of this reagent, all reported procedures (at the time of performing this study, back in 2017) make (in)direct use of pressurized sulfuryl fluoride gas bottles and thus are always associated with high cost and risks of explosion and leakage.

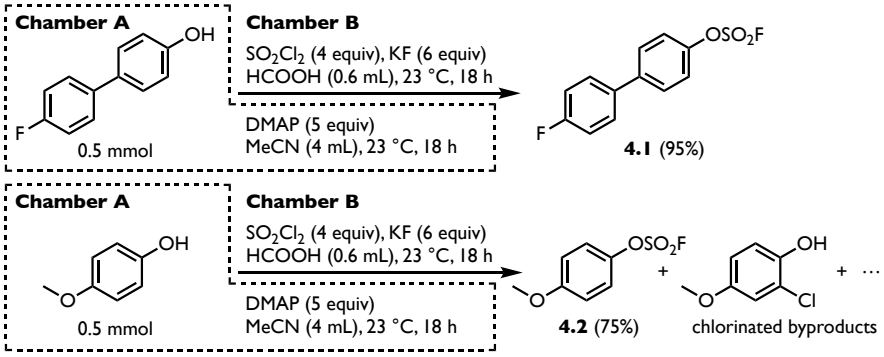
In summary, there is an urgent need to further develop new, convenient, and inherently safe methodologies to produce fluorosulfates, preferably starting from inexpensive and readily available commodity chemicals. In this chapter, we document the search and the development of the first procedure for the on-demand production of sulfuryl fluoride ($SO_2F_2$) for the synthesis of aryl fluorosulfates.

Initially we envisioned to employ gaseous sulfuryl chloride fluoride ($SO_2ClF$) instead of sulfuryl fluoride to convert phenols into aryl fluorosulfates. Although the preliminary results were promising, fluorosulfation of electron-rich phenols resulted in multiple chlorinated byproducts (see section 4.2). Therefore, the research was redirected to develop a sulfuryl fluoride precursor. This led to the discovery of 1,1'-sulfonyldiimidazole (SDI) as a solid $SO_2F_2$ source (section 4.3). Under the optimized reaction conditions, a variety of phenols and hydroxylated heteroarenes were fluorosulfated in good to excellent yields with only near-stoichiometric amounts of sulfuryl fluoride (section 4.4). With NMR studies, it was shown that $SO_2F_2$ generation from 1,1'-sulfonyldiimidazole and potassium fluoride under acidic conditions was extremely rapid (section 4.5).

## 4.2. Generation of sulfuryl chloride fluoride

Our investigation began by scanning literature to identify potential sulfuryl fluoride precursors or surrogates. Inspired by the report of Prakash, sulfuryl chloride fluoride was selected as our first candidate.[309] Therein, the $SO_2ClF$ gas could selectively be formed from sulfuryl chloride and a fluoride source in acidic medium and subsequently be isolated after gas condensation, albeit in low yield. We assumed that translating this work to a two-chamber reactor would significantly improve this method, as the generated gas can migrate to an adjacent chamber, where it is directly consumed and thus avoiding intermediate isolation.[43-44]

After an extensive optimization study (for details, see experimental section 7.4.2.1) the model substrate 4-fluoro-4′-hydroxybiphenyl was successfully converted into its corresponding aryl fluorosulfate **4.1** and isolated in 95% yield (Scheme 4.3). Unfortunately, under the optimized reaction conditions (4 equivalents of $SO_2Cl_2$ and 6 equivalents of KF in 0.6 mL of HCOOH) the transformation of the electron-rich 4-hydroxyanisole resulted in multiple chlorinated byproducts (Scheme 4.3).




**Scheme 4.3** Fluorosulfation of 4-fluoro-4'-hydroxybiphenyl and 4-hydroxyanisole with sulfuryl chloride fluoride.

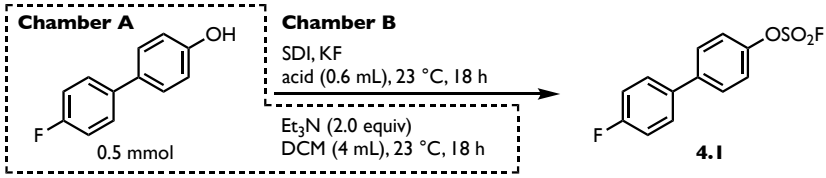
Considering sulfuryl chloride's known behavior as a chlorinating agent in electrophilic aromatic substitutions, we speculate that the volatile $SO_2Cl_2$ and/or the $SO_2ClF$ also participate in this type of reaction. A similar observation was reported when sulfuryl chloride was used for the synthesis of aryl chlorosulfates.[298]

## 4.3. Generation of sulfuryl fluoride

In order to eliminate the formation of chlorinated byproducts, we started looking for alternative nonvolatile precursors not containing chloride. In this respect, 1,1′-sulfonyldiimidazole (SDI) seemed an attractive sulfuryl fluoride precursor, as it is a commercially available solid. It can also easily be synthesized and isolated by precipitation on gram scale from sulfuryl chloride and imidazole (see section 7.4.1). As shown before, acidic conditions turn the imidazolium substituent into an excellent leaving group,[310-311] and it was postulated that a 2-fold displacement by fluoride would generate pure $SO_2F_2$ gas.

First, SDI was evaluated under the previously optimized reaction conditions. Gratifyingly, full conversion toward the desired fluorosulfate **4.1** was observed after 18 h (Table 4.1, entry 1). Next, the reaction conditions were further modified to minimize the required amount of precursor. In formic acid, the number of equivalents of SDI could be reduced to 3.0, without affecting the conversion (entry 2). Further decreasing the amount of SDI resulted in incomplete conversion (entry 3). Minor improvements were achieved when the amount of potassium fluoride was increased or when the reaction was performed at 40 °C (entries 4-5). However, when formic acid was replaced by trifluoroacetic acid, the number of equivalents of SDI and KF could be significantly reduced to 1.5 and 4.0, respectively. These conditions furnished fluorosulfate **4.1** in an isolated yield of 96% (entries 6-9). Again, product formation was hampered when the amount of SDI and/or KF were further decreased (entries 10-11). The optimization study was finalized by investigating the influence of the reaction duration. After 2 and 6 h, the yield was 84% and 94%, respectively (entries 12-13). We hypothesize that fluorosulfation is the rate-limiting step instead of the $SO_2F_2$ generation from SDI. $^{13}$C-NMR confirmed that SDI completely decomposed in less than 30 s under the optimized reaction conditions (see section 4.5). It was also shown that under these circumstances, the actual pressure inside the vessel remained well under the maximally allowed internal pressure, which is 5 bar (see section 7.4.2.4).

**Table 4.1** Optimization of the reaction conditions[a]

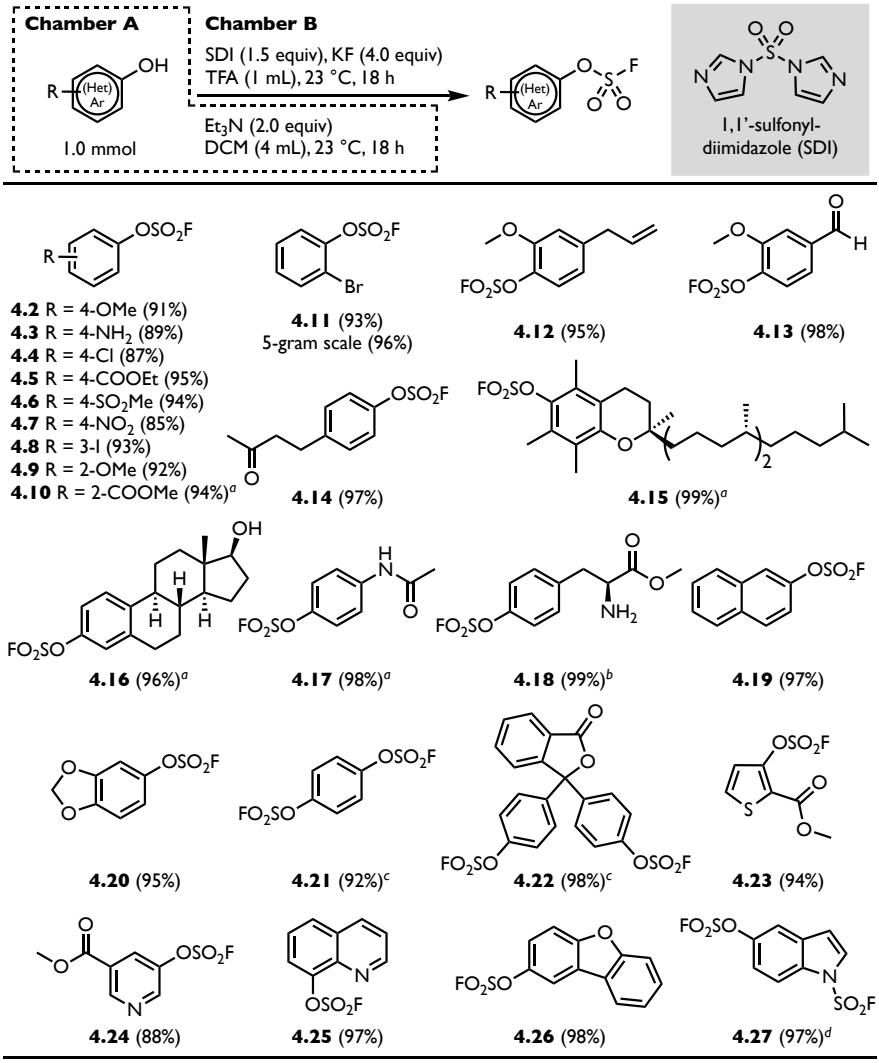



| Entry | SDI (equiv) | KF (equiv) | Acid | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 4.0 | 6.0 | Formic acid | >99 |
| 2 | 3.0 | 6.0 | Formic acid | >99 |
| 3 | 2.0 | 6.0 | Formic acid | 81 |
| 4[c] | 2.0 | 6.0 | Formic acid | 82 |
| 5 | 2.0 | 8.0 | Formic acid | 89 |
| 6 | 2.0 | 6.0 | Trifluoroacetic acid | >99 |
| 7 | 2.0 | 4.0 | Trifluoroacetic acid | >99 |
| 8 | 1.5 | 4.5 | Trifluoroacetic acid | >99 |
| 9 | 1.5 | 4.0 | Trifluoroacetic acid | >99 (96)[d] |
| 10 | 1.5 | 3.0 | Trifluoroacetic acid | 93 |
| 11 | 1.3 | 6.0 | Trifluoroacetic acid | 89 |
| 12[e] | 1.5 | 4.0 | Trifluoroacetic acid | 84 |
| 13[f] | 1.5 | 4.0 | Trifluoroacetic acid | 94 |

[a]Reaction conditions: Chamber A: 4-fluoro-4'-hydroxybiphenyl (0.5 mmol), $Et_3N$ (2.0 equiv) in dichloromethane (4 mL) at 23 °C for 18 h. Chamber B: 1,1'-sulfonyldiimidazole (SDI, 1.5 equiv), KF (4.0 equiv), and trifluoroacetic acid (TFA, 0.6 mL) at 23 °C for 18 h. [b]Determined by $^{19}F$-NMR using trifluorotoluene as internal standard. [c]Chamber A was heated to 40 °C. [d]Isolated yield. [e]Reaction run for 2 h. [f]Reaction run for 8 h.

## 4.4. Reaction scope

With the optimized conditions in hand, we first tried to convert 4-hydroxyanisole into its corresponding aryl fluorosulfate **4.2** as this transformation was unsuccessful with sulfuryl chloride as a precursor. To our delight, the starting material was fully consumed under these reaction conditions and yielded the desired aryl fluorosulfate **4.2** in 91% isolated yield (Scheme 4.4). This clearly showed the usefulness of 1,1'-sulfonyldiimidazole as a sulfuryl fluoride precursor, as no byproducts were formed. In order to further explore the scope of this methodology, a broad and diverse set of phenolic substrates was investigated (Scheme 4.4). First, monosubstituted electron-rich and -deficient phenols were successfully converted into their corresponding aryl fluorosulfates (**4.3**-**4.11**).




**Scheme 4.4** Synthesis of aryl fluorosulfates through *ex situ* generation of sulfuryl fluoride in a two-chamber reactor. Reaction conditions: Chamber A: (hetero)aryl alcohol (1.0 mmol), $Et_3N$ (2.0 equiv) in DCM. Chamber B: 1,1'-sulfonyldiimidazole (1.5 equiv), KF (4.0 equiv) in TFA. For experimental details and a typical pressure profile see experimental section 7.4. [a]Chamber A: DIPEA (3.0 equiv) in MeCN. [b]Chamber A: DIPEA (4.0 equiv) in MeCN. [c]Chamber A: (hetero)aryl alcohol (0.5 mmol), $Et_3N$ (4.0 equiv) in DCM. [d]Chamber A: (hetero)aryl alcohol (0.5 mmol), DIPEA (6.0 equiv) in MeCN.

These results illustrate that the electronic properties of the phenol derivates not significantly influence the fluorosulfation reaction. Even sterically hindered aryl fluorosulfates were furnished in excellent yields (**4.9**, **4.10**, **4.11**, and **4.15**). Also, naturally occurring phenols, such as

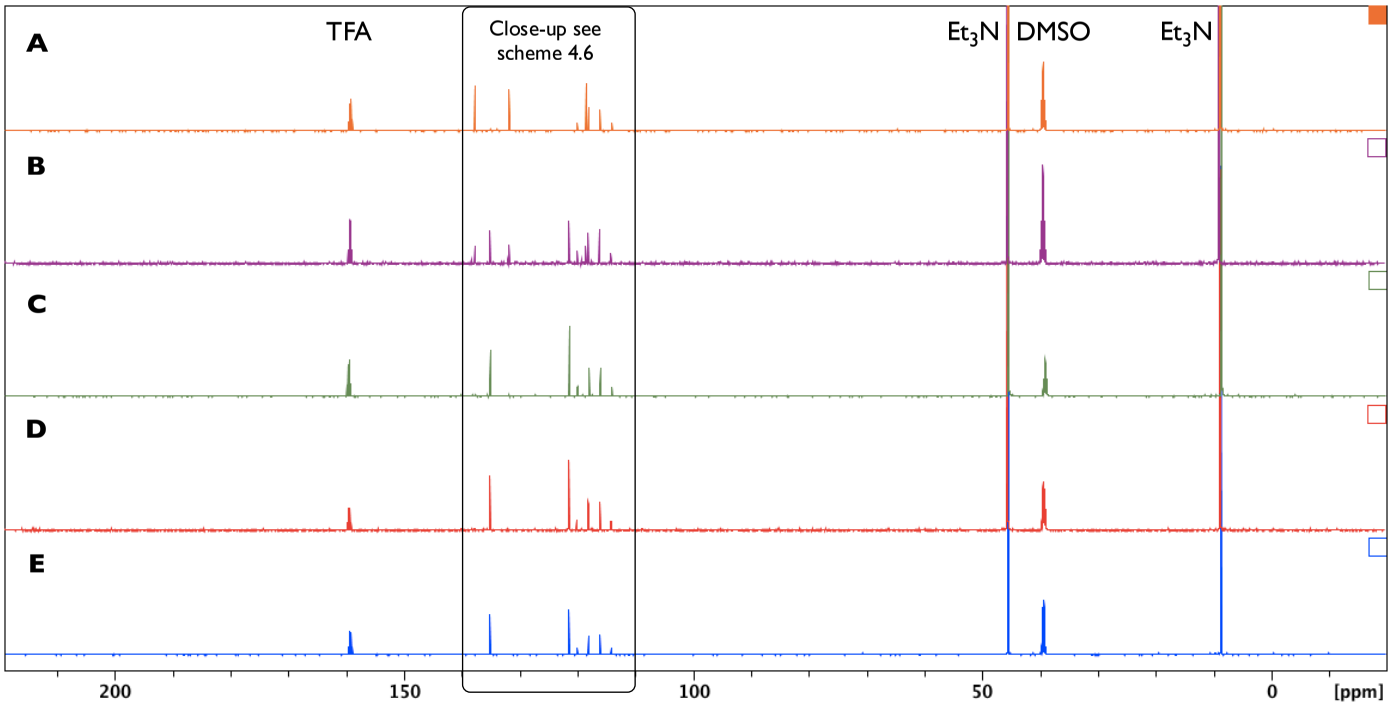
eugenol, vanillin, and raspberry ketone turned out to be suitable substrates for this transformation (**4.12**, **4.13**, and **4.14**), while D-α-tocopherol and β-estradiol produced only moderate conversion under the optimized reaction conditions. Gratifyingly, when the triethylamine dichloromethane system was substituted by *N*,*N*-diisopropylethylamine (DIPEA) in acetonitrile,[312] the corresponding aryl fluorosulfates were acquired in near-quantitative yields (**4.15** and **4.16**). These slightly modified conditions were also required for the fluorosulfation of paracetamol and L-tyrosine methyl ester (**4.17** and **4.18**). Next, two bicyclic phenol derivates were successfully tested (**4.19** and **4.20**). For the reaction of hydroquinone and phenolphthalein, 3.0 equivalents of SDI and 4.0 equivalents of triethylamine were added, resulting in the exclusive formation of the corresponding bis(fluorosulfates) (**4.21** and **4.22**). The scope was finalized by the synthesis of five heteroaryl fluorosulfates (**4.23**-**4.27**). It is worth noting that, under the applied reaction conditions, anilines, aliphatic alcohols, and aliphatic amines were tolerated, as only aromatic hydroxyl groups reacted with sulfuryl fluoride (**4.3**, **4.16**, and **4.18**). This observation is in agreement with the results reported by the Sharpless group.[201]

The developed method is easily scaled up by simply using a larger two-chamber reactor. This was illustrated by synthesizing compound **4.11** on 5-gram scale. After an aqueous acid/base wash, the desired aryl fluorosulfate was achieved in 96% yield.

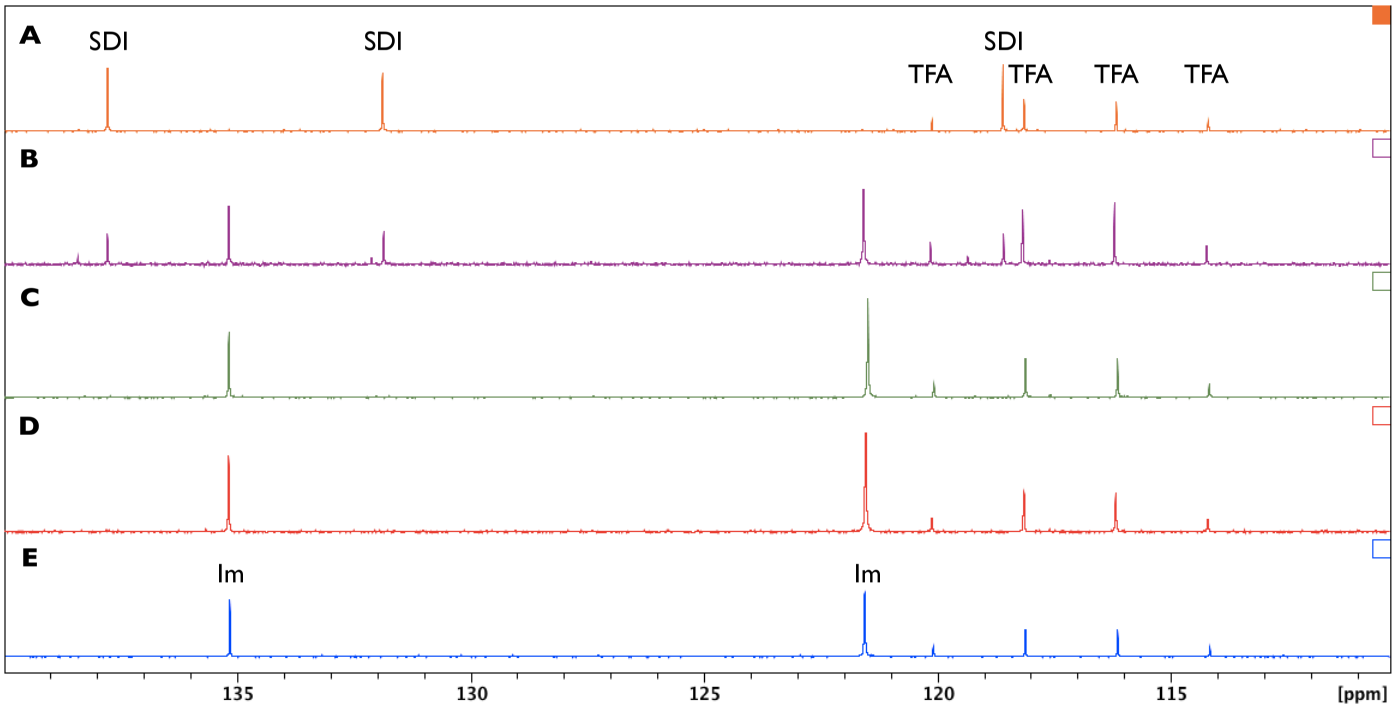
## 4.5. Decomposition study

We hypothesized that 1,1'-sulfonyldiimidazole could generate pure $SO_2F_2$ gas when mixed with a fluoride salt in the presence of an acid. The acidic conditions should turn the imidazolium substituents into an excellent leaving group. After a twofold displacement by fluoride, the desired gas should be released together with an imidazolium salt as byproduct.

In order to confirm this hypothesis, a $^{13}$C-NMR study was conducted at room temperature (Scheme 4.5 and Scheme 4.6). First, two control samples were measured. Spectrum A shows the reference ppm-values of 1,1'-sulfonyldiimidazole (118.6, 131.8 and 137.7 ppm) in trifluoroacetic acid and spectrum E shows the reference ppm-values of imidazole (121.6 and 135.2 ppm) in TFA.




**Scheme 4.5** $^{13}$C-NMR decomposition study of 1,1'-sulfonyldiimidazole (SDI). All spectra were recorded in DMSO-$d_6$. Spectrum A: SDI in TFA quenched with $Et_3N$ after 2 minutes. Spectrum B: SDI and KF in TFA quenched with $Et_3N$ after 5 seconds. Spectrum C: SDI and KF in TFA quenched with $Et_3N$ after 30 seconds. Spectrum D: SDI and KF in TFA quenched with $Et_3N$ after 1 minute. Spectrum E: Imidazole and KF in TFA quenched with $Et_3N$ after 2 minutes.




**Scheme 4.6** Close-up of the $^{13}$C-NMR decomposition study of 1,1'-sulfonyldiimidazole (SDI). All spectra were recorded in DMSO-$d_6$. Spectrum A: SDI in TFA quenched with $Et_3N$ after 2 minutes. Spectrum B: SDI and KF in TFA quenched with $Et_3N$ after 5 seconds. Spectrum C: SDI and KF in TFA quenched with $Et_3N$ after 30 seconds. Spectrum D: SDI and KF in TFA quenched with $Et_3N$ after 1 minute. Spectrum E: Imidazole and KF in TFA quenched with $Et_3N$ after 2 minutes.

Then, TFA was added to a mixture of 1,1'-sulfonyldiimidazole and KF which resulted in gas formation for several seconds. This experiment was performed three times and quenched with an excess of triethylamine after 5, 30, and 60 seconds (spectrum B, C and D, respectively). In spectrum B, two new intense peaks appeared at 121.6 and 135.2 ppm and were identified as imidazole as they corresponded to the signals in spectrum E. In addition, three small peaks were observed at 119.4, 132.2 and 138.5 ppm. We speculate that these peaks originate from the *in situ* formed intermediate Im-$SO_2$-F. After 30 seconds, the SDI peaks completely disappeared and only imidazole peaks were observed (spectrum C). This indicates that SDI completely decomposes in less than half a minute under the applied reaction conditions. The same observations were true when the reaction was quenched after one minute (spectrum D).

## 4.6. Conclusion

In conclusion, we have demonstrated a new, practical, and efficient way of transforming phenols into their corresponding aryl fluorosulfates in good to excellent yields. The proposed method relies on *ex situ* generation of sulfuryl fluoride gas from cheap and readily available commodity chemicals in a two-chamber reactor. This provides a convenient means of transforming common phenolic substances, including some drug-like and naturally occurring compounds, into reactive aromatic intermediates. Furthermore, it is easily scaled up as evidenced by the preparation of analytically pure 2-bromophenyl fluorosulfate on multigram scale using only extractive workup as the purification step. Further implementation of this promising chemistry within the larger research community can herewith be accelerated, where otherwise it might remain less explored due to the cumbersome handling of gaseous reagents. We speculate that the demand for these electrophilic functional handles will increase as they find their way into many more applications, by merit of their leaving group ability or as SuFEx partners.

# CHAPTER 5

# Merging CO and $SO_2F_2$ chemistry: the synthesis of bis(trifluoromethyl)carbinols

This chapter is based on K. Domino, C. Veryser, B. A. Wahlqvist, C. Gaardbo, K. T. Neumann, K. Daasbjerg, W. M. De Borggraeve, T. Skrydstrup, 'Direct Access to Aryl Bis(trifluoromethyl)carbinols from Aryl Bromides or Fluorosulfates: Palladium-Catalyzed Carbonylation' *Angew. Chem. Int. Ed.* **2018**, *57*, 6858-6862.[313] and was reproduced with permission from Wiley.

*Author contributions*

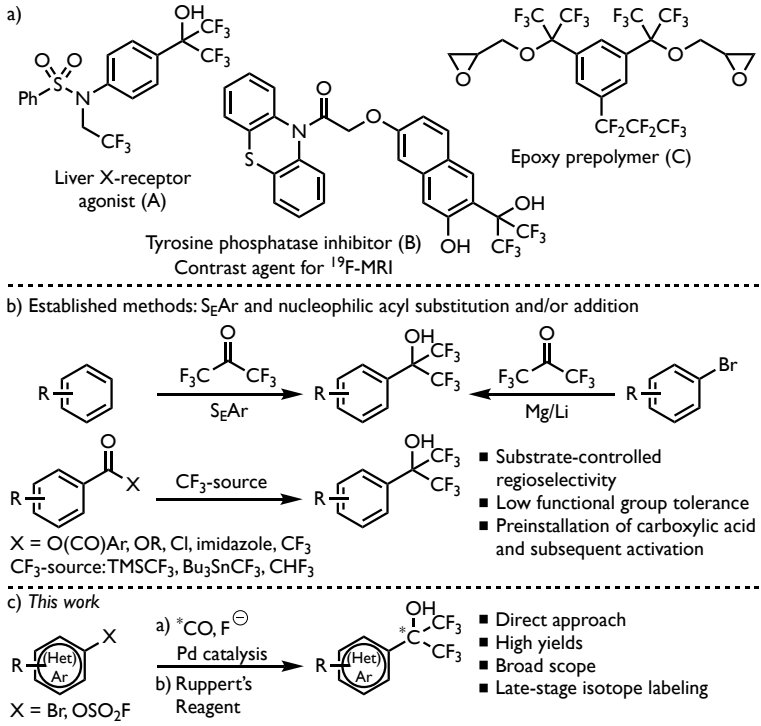
K.D. and C.V. contributed equally to this study. T.S. conceived and coordinated the study. K.D. and C.V. performed the optimization study. The synthesis of α,α-bis(trifluoromethyl)carbinols from aryl bromides was conducted by K.D., B.A.W. and C.G. The synthesis of α,α-bis(trifluoromethyl)carbinols from aryl fluorosulfates was conducted by C.V. The manuscript was largely written by K.D. and redacted by C.V. and T.S. All authors were involved in proofreading.

## 5.1. Introduction

The introduction of a fluorine atom into bioactive molecules can strategically alter their chemical and biological properties.[314-317] In recent years, an increasing number of fluorine-containing drugs have been launched, thus justifying the need for new synthetic methodologies centered on the incorporation of fluorine-containing motifs.[317] One of these privileged motifs is the α,α-bis(trifluoromethyl)carbinol group. Compounds containing this substructure have shown biological activity against cancer, diabetes, hepatitis C, dyslipidemia, and inflammation (Scheme 5.1a).[318-323] An interesting feature of this motif is the presence of a large number of fluorine atoms, which renders them as promising contrast agents for $^{19}$F-MRI.[324-326] This technique allowed in vivo target identification of carbinol B, a tyrosine phosphatase inhibitor (Scheme 5.1a).[325] Furthermore, aryl α,α-bis(trifluoromethyl)carbinol-containing polymers display excellent material properties, as well as high thermal stability and flame resistance.[327-329] The hexafluoroisopropanol group can also be found in ligand design, either by merit of its inductive electron-withdrawing properties or as a bulky substituent.[330-332] Other applications include their use for the detection of nerve agents[333-334] and as precursors for the synthesis of Martin's spirosilanes.[335-336]

Despite the multidisciplinary impact of this fluorine motif, only few synthetic strategies have been reported for its installation (Scheme 5.1b). Most procedures rely on electrophilic aromatic substitution or the use of organolithium or organomagnesium reagents in the presence of hexafluoroacetone.[337-339] Alternatively, α,α-bis(trifluoromethyl)carbinols can be prepared from the corresponding carboxylic acid derivatives or

from trifluoroacetophenones using a nucleophilic $CF_3$-source (Scheme 5.1).[340-344] Nevertheless, these methods are limited by substrate-biased regioselectivity, low functional group tolerance, the use of toxic reagents,[345] and/or the need of extra steps for preliminary introduction or activation of the carbonyl functionality.



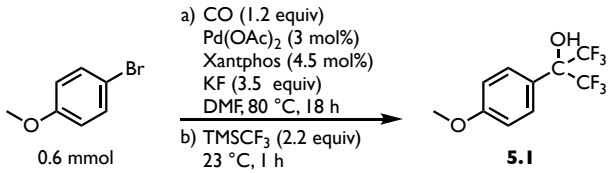

**Scheme 5.1** Examples of bis(trifluoromethyl)carbinol-containing bio-active molecules and polymer materials, and previous strategies for the introduction of this functional group.

In this chapter, we report a palladium-catalyzed carbonylative approach for the synthesis of α,α-bis(trifluoromethyl)carbinols. This method only employs stoichiometric amounts of carbon monoxide and trifluoromethyltrimethylsilane (section 5.2). Under the optimized reaction conditions, a broad and diverse set of (hetero)aryl bromides (section 5.3) and fluorosulfates (section 5.4) were converted into their corresponding α,α-bis(trifluoromethyl)carbinols in high yields. Interestingly, the latter class of substrates indirectly allows phenols as substrates for this transformation. In the last section, a few additional experiments were performed, amongst which a competition experiment to examine the comparative reactivity of aryl bromides and fluorosulfates in this reaction.

## 5.2. Optimization study

We started our investigation by optimizing the carbonylation of 4-bromoanisole with a nucleophilic $CF_3$-source, using a two-chamber system and the *ex situ* generation of carbon monoxide from COgen.[43-44] After thorough evaluation of the reaction parameters, the desired α,α-bis(trifluoromethyl)carbinol **5.1** was successfully isolated in an 81% yield (Table 5.1, entry 1). The optimized reaction conditions comprise the aryl bromide with $Pd(OAc)_2$ (3 mol%), Xantphos (4.5 mol%), CO (1.2 equiv), and KF (3.5 equiv), heated in DMF for 18 hours, and subsequent addition of Ruppert's reagent at room temperature in a one-pot fashion. We suspect the reaction initially generates an acyl halide intermediate,[96, 253, 346-347] which subsequently reacts with $TMSCF_3$.

**Table 5.1** Optimization of the reaction conditions[a]



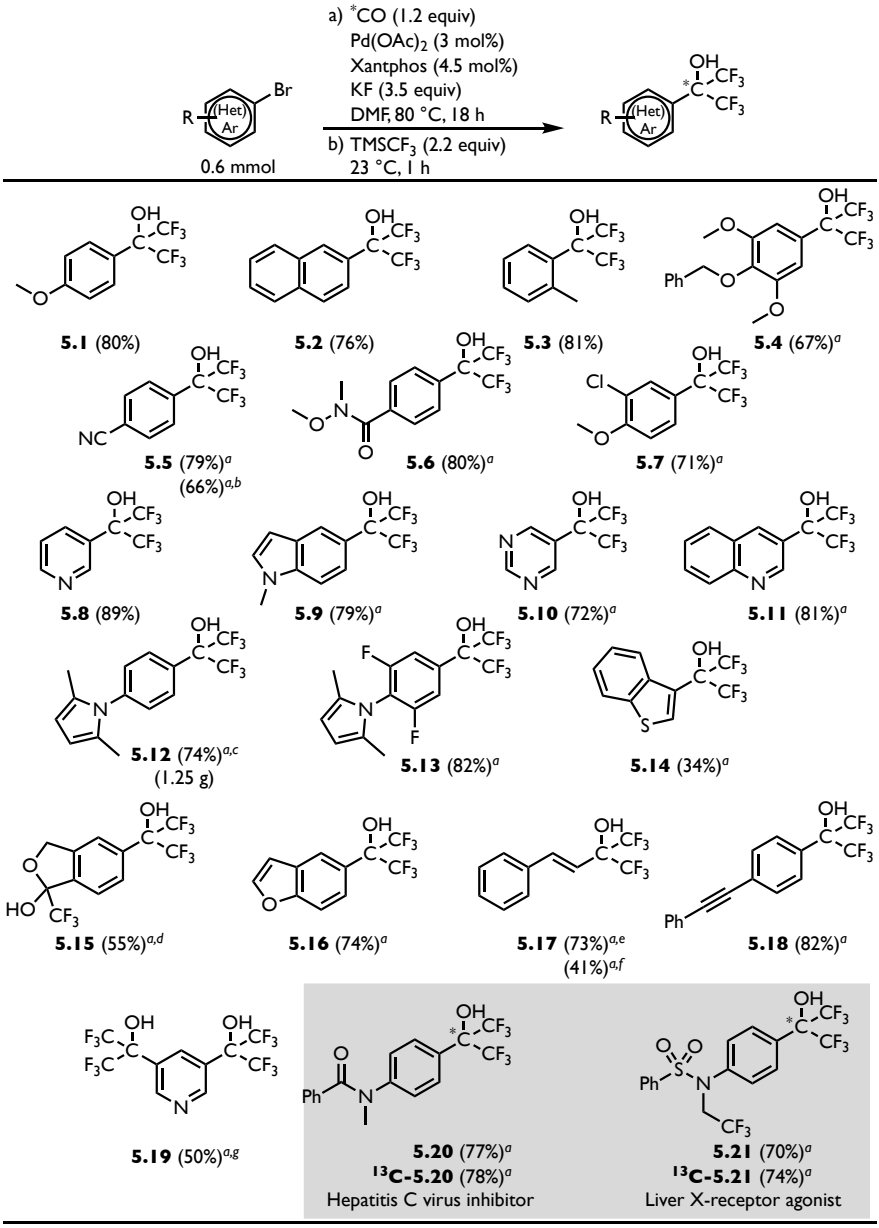

| Entry | Deviation from standard conditions | Yield (%)[b] |
|---|---|---|
| 1 | None | 89 (81)[c] |
| 2 | Xantphos Pd G4 instead of $Pd(OAc)_2$ and Xantphos | 89 |
| 3 | $Pd(dba)_2$ instead of $Pd(OAc)_2$ | 0 |
| 4 | Dppf instead of Xanpthos | 76 |
| 5 | DPEPhos instead of Xantphos | 83 |
| 6 | MeCN instead of DMF | 38 |
| 7 | 1,4-Dioxane instead of DMF | 0 |
| 8 | CsF instead of KF | 47 |
| 9 | $[Me_4N]F$ instead of KF | 0 |
| 10 | KF (2.1equiv) | 83 |
| 11 | No KF | 0 |
| 12 | $TESCF_3$ instead of $TMSCF_3$ | 74 |
| 13 | $TMSCF_3$ (2.05 equiv) | 77 |
| 14 | $TMSCF_3$ (1.0 equiv) | 22 |

[a]All reactions were performed in a two-chamber reactor. CO was released from a solid precursor in one chamber (see section 7.5 for full details). [b]Yield determined by $^1$H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [c]Yield of isolated product. The carboxylic acid was observed as the major side product. dba = dibenzylideneacetone, dppf = 1,1'-ferrocenediyl-bis(diphenylphosphine), DMF = *N,N*-dimethylformamide, TMS = trimethylsilyl, TES = triethylsilyl.

Performing the carbonylative coupling with the Xantphos Pd G4 precatalyst[348-349] instead of $Pd(OAc)_2$ provided a similar reaction outcome (entry 2). In contrast, no conversion was observed with $Pd(dba)_2$, and the starting material was fully recovered (entry 3). Substituting Xantphos with other bidentate phosphine ligands resulted in slightly lower yields (entries 4 and 5). Next, several other solvents were screened, however, they provided moderate to no conversion of 4-bromoanisole (entries 6 and 7). Optimization of the fluoride source revealed that CsF and $Me_4NF$ were inferior to KF. When the amount of KF was lowered to 2.1 equivalents, a slight decrease in yield was observed. In the absence of a fluoride source, no product was formed, and the starting material was fully recovered (entries 8-11), whereas replacement of Ruppert's reagent with $TESCF_3$ led to a drop in yield (entry 12). Conducting the palladium-catalyzed carbonylative coupling in the presence of $TMSCF_3$ had a detrimental effect on the reaction outcome, as only starting materials could be recovered (results not shown). The group of Marshall has previously reported that the $CF_3$ anion can exchange with Xantphos on the metal center, possibly hampering the catalytic cycle.[350-351] Efforts to lower the amount of Ruppert's reagent, provided only lower conversions into **5.1** (entries 13 and 14). Notably, in the presence of one equivalent of $TMSCF_3$, a mixture of *para*-methoxy trifluoroacetophenone and **5.1** was observed, indicating that selective formation of the trifluoroacetophenone derivative could not be achieved under the applied reaction conditions. Finally, we observed that performing the reaction with a balloon of CO only led to a 6% yield of **5.1**.[352]

## 5.3. The synthesis of aryl bis(trifluoromethyl) carbinols from aryl bromides

With the optimized reaction conditions in hand, we commenced an investigation on the generality of this transformation (Scheme 5.2). Initially, it was established that aryl bromides containing either only electron-rich (**5.1**-**5.3**) or electron-poor (**5.5** and **5.6**) substituents could be efficiently transformed into the corresponding $\alpha,\alpha$-bis(trifluoromethyl)carbinols in high yields. The effect of *ortho* substituents was not detrimental for the outcome of the reaction as shown for **5.3**. At this point, the beneficial effect of adding KF in two portions was observed. This approach ensures




**Scheme 5.2** The synthesis of aryl bis(trifluoromethyl)carbinols from aryl bromides. All reactions were performed in a two-chamber reactor. CO was released from a solid precursor in one chamber (see section 7.5 for full details). Yields are those of the isolated product and are the average of duplicates. [a]1.5 equiv of KF were initially added, followed by 2.5 equiv of KF after the carbonylation step. [b]Reaction performed on the corresponding ArCl at 120 °C. [c]Reaction performed on a 5.0 mmol scale. [d]Starting from 5-bromophthalide using 3.2 equiv of $TMSCF_3$. [e]From an approx. 4:1 mixture of (*E*)- and (*Z*)-bromostyrene. [f]From (*Z*)-bromostyrene. [g]The reaction was performed with 0.3 mmol of the aryl dibromide and 4.4 equiv of $TMSCF_3$.

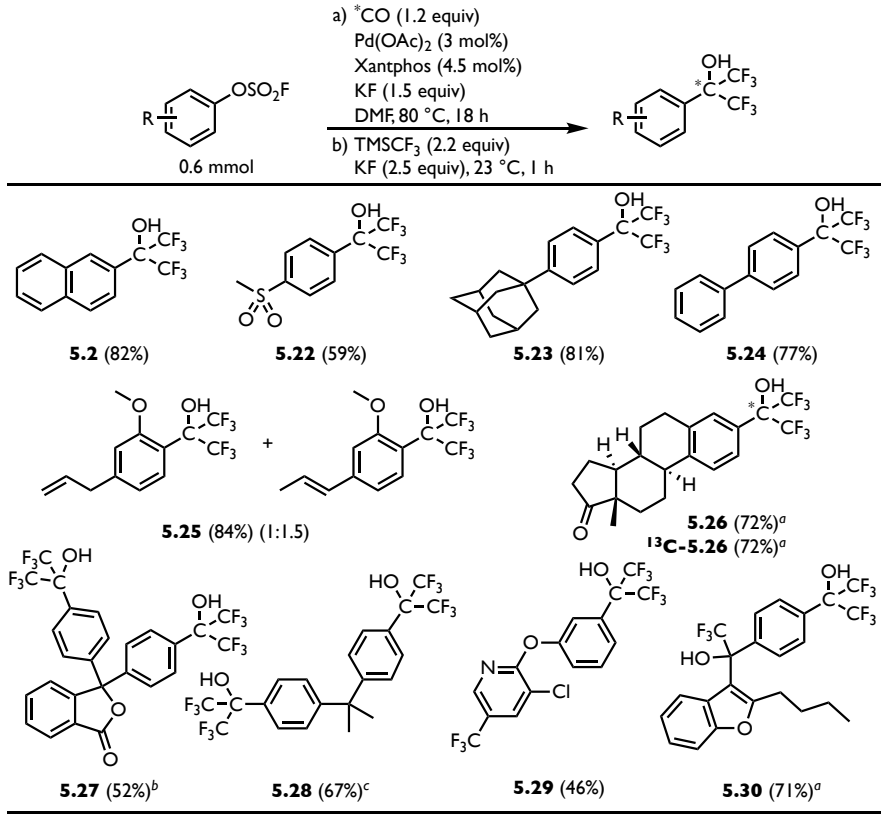
that fluoride is present to activate Ruppert's reagent upon its addition. As shown with **5.7** and **5.13**, halide substituents, including chloride or fluoride, were well tolerated, with the former representing a useful handle for possible post-functionalization of the carbinol product. Heteroaromatic bromides, including pyridine, indole, pyrimidine, quinoline, and benzothiophene, were also applicable for the synthesis of α,α-bis(trifluoromethyl)carbinols (**5.8**-**5.11**, **5.14**, and **5.19**). Even heterocycles as substituents or fused to the benzene ring were tolerated as exemplified by **5.12**, **5.13**, **5.15**, and **5.16**. Further adaptation to a gram-scale synthesis was shown for the pyrrole-substituted compound **5.12**. Addition of a third trifluoromethyl group was observed with 5-bromophthalide involving the lactone carbonyl group to give **5.15**. Both *cis*- and *trans*-bromostyrene were found to be viable substrates for this carbonylative coupling. Interestingly, the two stereoisomers led to the same *trans*-product **5.17** in 73 and 41% yield.[353] An internal alkyne was tolerated under the applied reaction conditions as illustrated with **5.18**. Finally, an activated aryl chloride was attempted, thus providing the corresponding bis(trifluoromethyl)carbinol **5.5** in a 66% yield, though with a reaction temperature of 120 °C.

Our methodology could be adapted to the efficient preparation of two bioactive molecules, including late-stage $^{13}$C-isotopic labeling.[43, 354-355] As such, the hepatitis C virus inhibitor **5.20** was synthesized in two steps from 4-bromo-*N*-methylaniline with a 77% yield for the carbinol formation (Scheme 5.2). Similarly, the liver X-receptor agonist **5.21** could be prepared in only three steps from 4-bromoaniline under mild reaction conditions. Importantly, a $^{13}$C-isotope label was introduced in the last step by using $^{13}$C-COgen, and yields were similar to those obtained for the unlabeled counterparts.

## 5.4. The synthesis of aryl bis(trifluoromethyl) carbinols from aryl fluorosulfates

Aryl fluorosulfates are easily prepared from phenols and have gained increased interest either as a robust connector in SuFEx click chemistry or as a leaving group.[201-202] We therefore investigated the possible application of these electrophilic substrates for the synthesis of aryl α,α-

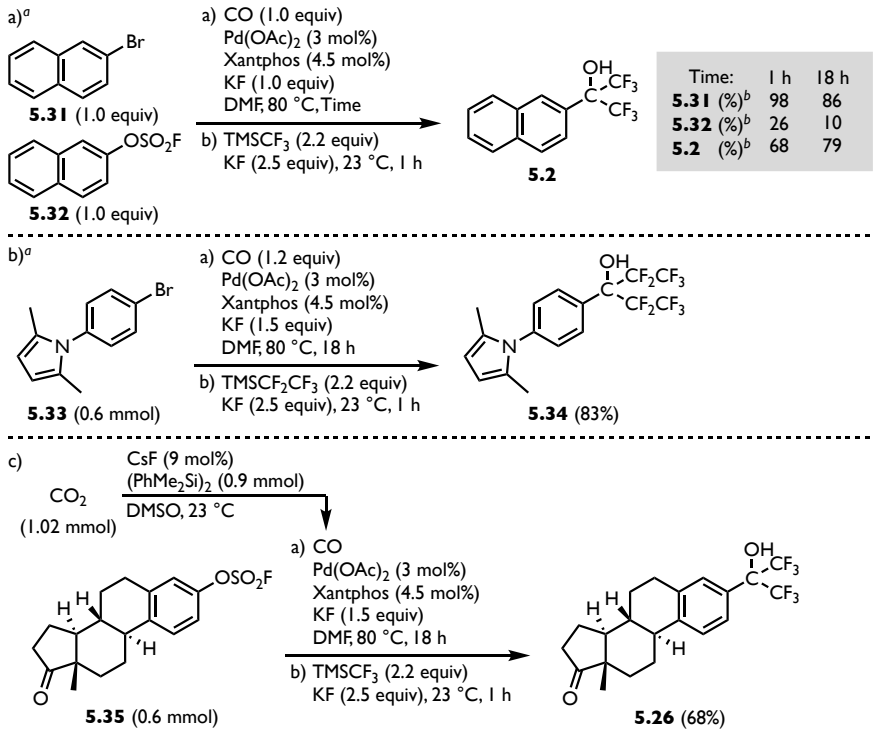
bis(trifluoromethyl)carbinols. Initially, the aryl fluorosulfates were prepared from the corresponding phenols according to a recent procedure relying on the *ex situ* generation of gaseous sulfuryl fluoride in the two-chamber reactor (see chapter 4).[203] As depicted in Scheme 5.3, these electrophiles proved to be well suited for the catalytic protocol providing the bis(trifluoromethyl)carbinols in good yields as shown for the introduction of one carbinol unit with products **5.2**, **5.22**-**5.26**, **5.29**, and **5.30**, and two units with **5.27** and **5.28**. Interestingly, some double-bond migration was observed for the allylic benzene **5.25**. Finally, the bis(trifluoromethyl)carbinol obtained from estrone could easily be prepared with specific incorporation of a $^{13}C$ label (**$^{13}$C-5.26**).




**Scheme 5.3** The synthesis of aryl bis(trifluoromethyl)carbinols from aryl fluorosulfates. All reactions were performed in a two-chamber reactor. CO was released from a solid precursor in one chamber (see section 7.5 for full details). Yields are those of the isolated product and are the average of duplicates. [a]3.2 equiv of $TMSCF_3$ was used. [b]The reaction was performed with 0.3 mmol of the aryl fluorosulfate and 6.4 equiv of $TMSCF_3$. [c]The reaction was performed with 0.3 mmol of the aryl fluorosulfate and 4.4 equiv of $TMSCF_3$.

## 5.5. Additional experiments

To conclude, additional experiments were performed to examine the comparative reactivity of aryl bromides and fluorosulfates in the palladium-mediated carbonylation step. As can be seen in Scheme 5.4a with **5.31** and **5.32** in equal amounts, the naphthyl fluorosulfate proved to be substantially more reactive in the transformation into **5.2**. In a second experiment, we demonstrated that pentafluoroethyltrimethylsilane can be exploited for the generation of the bis(pentafluoroethyl)carbinols, as illustrated in the transformation of **5.33** into **5.34**, in a satisfactory yield of 83% (Scheme 5.4b). Lastly, this protocol could be coupled up to the efficient disilane-mediated reduction of $CO_2$ to carbon monoxide for the conversion of the estronyl fluorosulfate **5.35** into the corresponding **5.26** in a 68% yield (Scheme 5.4c).[127]




**Scheme 5.4** Additional experiments with aryl bromides and fluorosulfates. a) Competition experiment between aryl bromide **5.31** and aryl fluorosulfate **5.32**. b) An example with pentafluoroethyltrimethylsilane. c) An application with $CO_2$ as the CO source. [a]Reaction was performed in a two-chamber system. CO was released from a solid precursor in one chamber (see section 7.5 for full details). [b]Yields determined by GC using dodecane as an internal standard.

## 5.6. Conclusion

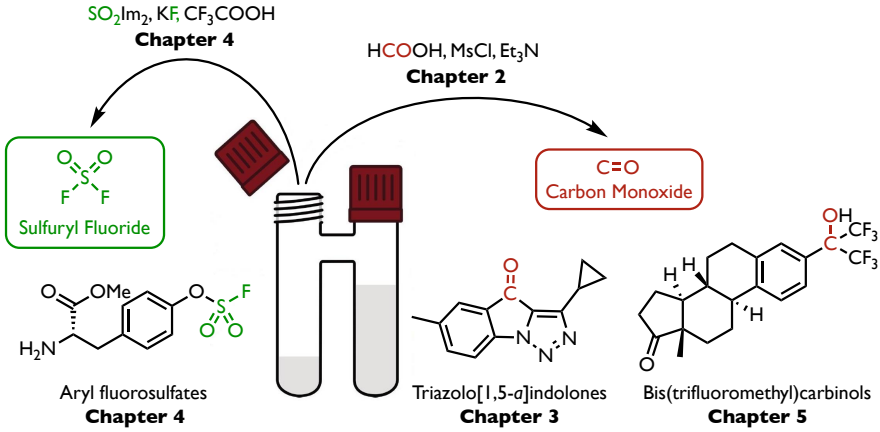
In summary, an efficient procedure for the direct formation of (hetero)aryl α,α-bis(trifluoromethyl)carbinols from the corresponding (hetero)aryl bromides and fluorosulfates has been demonstrated and relies on palladium-mediated carbonylation with stoichiometric amounts of carbon monoxide and trifluoromethyltrimethylsilane. Particularly noteworthy with this protocol is its ease in operation, but also its suitability even in the presence of a wide range of other functional groups. This chemistry will undoubtedly allow the rapid introduction of the bis(trifluoromethyl)carbinol unit into a wide variety of pharmaceutically relevant molecules.

# CHAPTER 6

# Conclusions and future directions

## 6.1. General conclusions

In summary, this thesis aimed (1) to design new gas releasing systems and (2) to exploit these systems for the development of novel synthetic transformations. As portrayed in scheme 6.1, both objectives have been reached. More specifically, a novel approach was documented for the *ex situ* release of carbon monoxide and sulfuryl fluoride in a two-chamber reactor. Both gases have been valorized in organic synthesis, respectively for the construction of triazolo[1,5-*a*]indolones and for the synthesis of aryl fluorosulfates. In collaboration with the Skrydstrup group, the acquired expertise in the field of CO and $SO_2F_2$ chemistry was merged for the palladium-catalyzed carbonylative synthesis of α,α-bis(trifluoromethyl) carbinols from (hetero)aryl bromides and fluorosulfates.

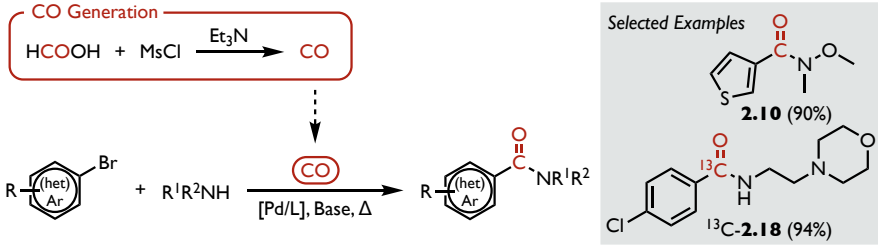



**Scheme 6.1** A summary of the research performed in this thesis.

In the following paragraphs, a more detailed description of the accomplished goals per chapter will be given.

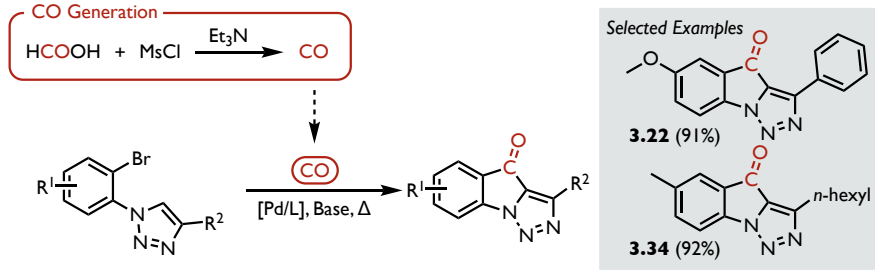
In chapter 2, we have discovered that upon mixing formic acid, mesyl chloride and triethylamine in toluene, CO is instantly liberated at room temperature. Since these reagents are inexpensive standard lab chemicals, this system belongs to one of the most cost-efficient ways to produce CO on-demand. By employing the CO generating system in a two-chamber reactor, 19 different amides were obtained in high yields *via* palladium-catalyzed aminocarbonylation chemistry (scheme 6.2). The scope was

finalized with the synthesis of three $^{13}$C-carbonyl labeled pharmaceuticals by using $^{13}$C-HCOOH as the $^{13}$CO source.




**Scheme 6.2** Palladium-catalyzed aminocarbonylation by employing formic acid, mesyl chloride and triethylamine as the CO generating system.

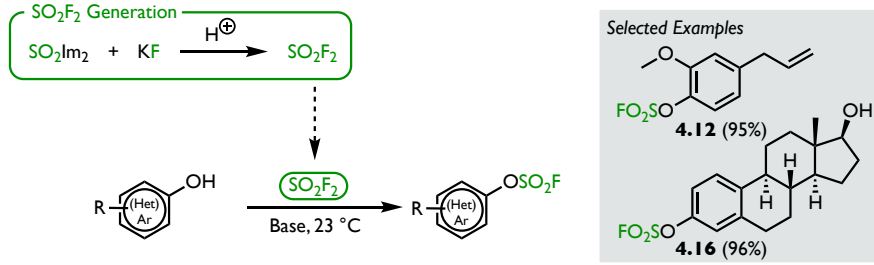
Taking advantage of our newly developed CO releasing system, the *ex situ* generated carbon monoxide was applied in a myriad of palladium-catalyzed transformations. In chapter 3, this led to the discovery of an unprecedented intramolecular carbonylative C-H activation of 1-(2-bromo)-1,2,3-triazoles, enabling the synthesis of a novel heterocyclic scaffold: the triazolo[1,5-*a*]indolone ring system. The 1-(2-bromo)-1,2,3-triazole precursor molecules were synthesized *via* two different methods to introduce a variety of substituents at the $R^1$ and $R^2$ position. Subjecting this library to the optimized reaction conditions resulted in the formation of 17 triazolo[1,5-*a*]indolone derivates (scheme 6.3).




**Scheme 6.3** Intramolecular carbonylative C-H functionalization of 1-(2-bromophenyl)-1,2,3-triazoles for the synthesis of triazolo[1,5-*a*]indolones.

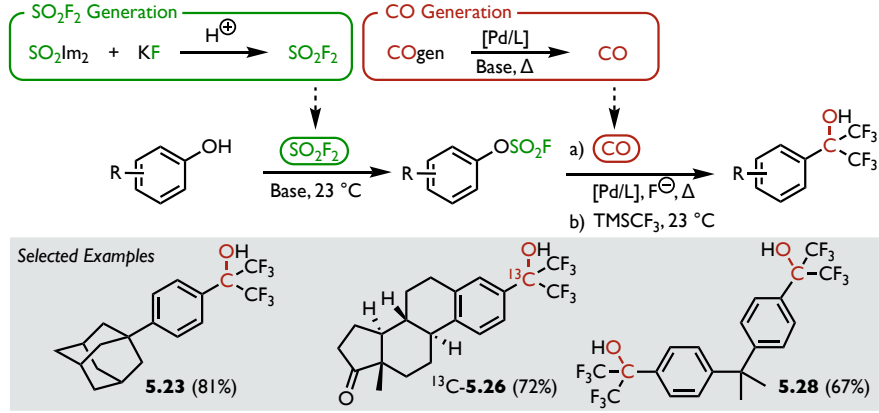
Since a plethora of CO releasing molecules have been documented, we opted to explore new horizons and search for surrogates of other useful gases. A thorough literature study revealed the renewed interest in sulfuryl fluoride gas ($SO_2F_2$), one of the key reagents for the synthesis of aryl fluorosulfates from phenols. In chapter 4, we identified 1,1'-

sulfonyldiimidazole as a solid $SO_2F_2$ source. NMR studies confirmed that gas release readily occurred in the presence of a fluoride salt under acidic conditions. By employing a two-chamber reactor, a variety of phenols and hydroxylated heteroarenes were fluorosulfated in good to excellent yields with only near-stoichiometric amounts of *ex situ* generated sulfuryl fluoride (scheme 6.4).




**Scheme 6.4** *Ex situ* generation of sulfuryl fluoride for the synthesis of (hetero)aryl fluorosulfates.

In chapter 5, we have described a palladium-catalyzed carbonylative synthesis of (hetero)aryl α,α-bis(trifluoromethyl)carbinols from (hetero)aryl bromides and fluorosulfates. Interestingly, the latter class of substrates indirectly allows phenols as substrates for this transformation (scheme 6.5). Furthermore, a competition experiment revealed that aryl fluorosulfates are significantly more reactive than aryl bromides in this transformation. Lastly, the developed method is amenable to the synthesis of bis(pentafluoroethyl)carbinols when pentafluoroethyltrimethylsilane is used instead of Ruppert's reagent.



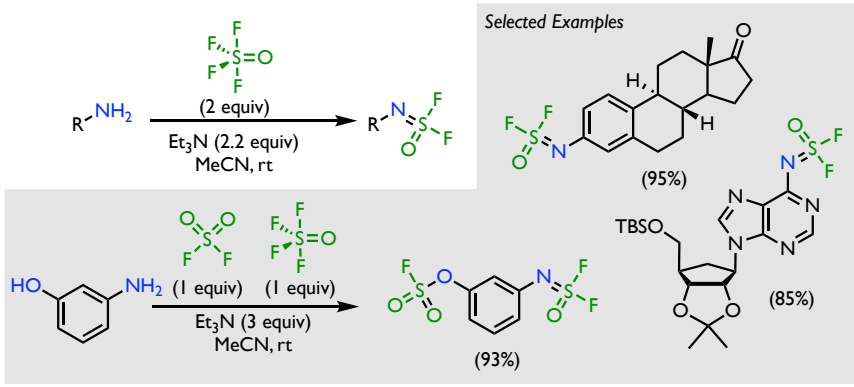

**Scheme 6.5** The synthesis of aryl bis(trifluoromethyl)carbinols from aryl fluorosulfates.

## 6.2. Future directions

As thoroughly discussed in the introductory chapter, the current state of the art in the field of gas releasing molecules is mainly limited to the on-demand production of industrial gases, such as CO, $H_2$, $SO_2$, $C_2H_4$, and syngas, to name a few. In the last two years, however, four new gas releasing molecules were published for the production of specialty gases: tetrafluoroethylene,[46] hydrogen cyanide,[193] sulfuryl fluoride,[203] and methanethiol.[206]

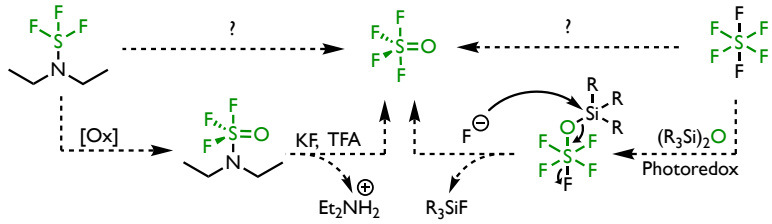
We, as well as other research groups, recognized that the true potential of on-demand gas release lies in the relatively unexplored reactivity of gaseous reagents that are not or only sparingly available. For example, the production of fluorinated gases, such as vinyl fluorides, fluoroform, hexafluoroacetone, and triflyl fluoride could be highly beneficial for the installation of fluorine-containing motifs in pharmaceutically relevant molecules, as well as for the construction of intermediate reactive handles.

As a first future direction, we are interested in the development of a thionyl tetrafluoride ($SOF_4$) precursor molecule. $SOF_4$ gas cleanly reacts with primary amines to form iminosulfur oxydifluorides which exhibits the same SuFEx behavior as found in aryl fluorosulfates.[356] Particularly noteworthy with this gas is its selectivity towards primary amines as it leaves aliphatic alcohols and phenols untouched, thereby allowing orthogonal functionalization of aminophenols with sulfuryl fluoride (see scheme 6.6).




**Scheme 6.6** Synthesis of iminosulfur oxydifluorides from primary amines and thionyl tetrafluoride in the presence of a base.[356]

Sulfuryl tetrafluoride is currently prepared from oxidation of sulfur tetrafluoride with molecular oxygen in the presence of a catalytic amount of nitrogen dioxide at 238 °C in a stainless-steel autoclave under extreme pressure (120 bar). Besides the obvious risks of this procedure, severe corrosion of the stainless-steel apparatus has been observed, thereby demonstrating the urge to develop new and safer methodologies to produce $SOF_4$. Here, we propose two strategies (see scheme 6.7). First, sulfur oxidation of an N-$SF_3$-containing reagent, such as (diethylamino)sulfur trifluoride, followed by fluoride displacement in acidic medium to release $SOF_4$. Second, the reaction of sulfur hexafluoride with disiloxane for the synthesis of a Si-O-$SF_5$ intermediate, which subsequently collapses in the presence of a fluoride and liberates $SOF_4$. Although the second approach might be less feasible due to the relative inertness of sulfur hexafluoride, a recent publication documented the photoredox activation of $SF_6$ for the deoxyfluorination of allylic alcohols.[357]



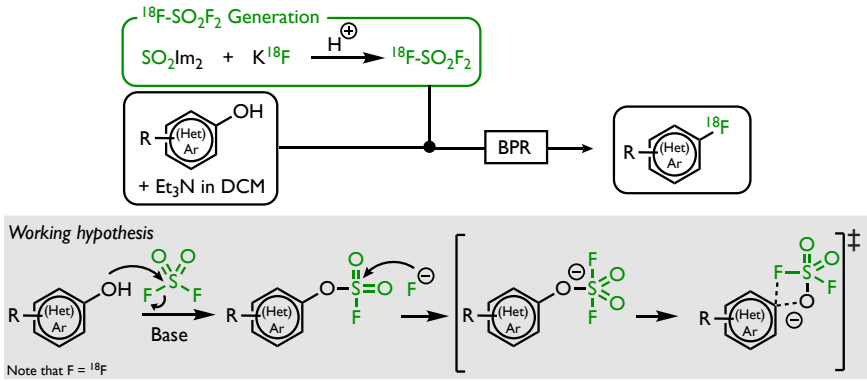

**Scheme 6.7** Proposed synthetic strategies towards the on-demand production of $SOF_4$.

A second future direction would be to step away from a two-chamber reactor to engage gases in organic synthesis. Even though this device is easy-to-use and mitigates the risk associated with handling gaseous reagents, its spatial dimensions limits the scale of the chemical reaction. This shortcoming in combination with the (enormous) waste generated from the gas precursor renders the two-chamber reactor unsuitable for industrial purposes. In this perspective, flow chemistry could bridge the gap between academia and industry. Here, gases can directly be used in a safe and convenient way, while the system remains scalable.

To date, there are no examples known in the literature where sulfuryl fluoride gas is used in flow chemistry. Recently, the Sanford group reported the nucleophilic deoxyfluorination of phenols with sulfuryl fluoride and tetramethylammonium fluoride.[287] We hypothesize that by translating this system to a continuous flow process, the fluoride, which is expelled upon

*in situ* aryl fluorosulfate formation, can activate the sulfur(VI) atom of the fluorosulfate group, and subsequently produce the desired aryl fluoride. Preliminary mechanistic investigations suggest that the activation of the sulfur(VI) atom takes place *via* the formation of a pentacoordinated intermediate. The subsequent transition state consists of the concomitant cleavage of the C($sp^2$)-O bond and the formation of the C($sp^2$)-F bond, without the generation of a discrete Meisenheimer complex (scheme 6.8).[287] Since the proposed method would be conducted in a flow reactor, the deoxyfluorination reaction would not require an additional nucleophilic fluoride source (e.g. TMAF) due to the temperatures and pressures that can be reached in comparison to traditional batch chemistry.

Particularly interesting is that the proposed method can be extended to the synthesis of $^{18}$F-aryl fluorides. By employing our in-house developed $SO_2F_2$ generating system, radiolabeled K$^{18}$F can be used to produce $^{18}$F-$SO_2F_2$ (Scheme 6.8). It should however be noted that this approach is only feasible when no additional fluoride source is present. Otherwise isotope scrambling will occur, which will decrease the incorporation of the $^{18}$F radiolabel in the final product.




**Scheme 6.8** Deoxyfluorination of phenols for the synthesis of $^{18}$F-labeled aryl fluorides by using *in situ* generated $^{18}$F-$SO_2F_2$ in a continuous flow setup.

# CHAPTER 7

# Experimental

# 7.1. General considerations

## 7.1.1. General experimental conditions

All reagents were obtained from commercially available sources and were used as purchased without further purification. Chromatography solvents were distilled prior to use. Reactions were magnetically stirred. Compounds were visualized by UV irradiation (254 nm) on pre-coated silica gel F254 (250 μm) glass-supported TLC plates. Flash column chromatography was performed by using an MPLC apparatus. Solvents were evaporated with a rotavapor at a temperature of 50 °C. Yields refer to isolated compounds after chromatography. All moisture-sensitive reactions were carried out under nitrogen atmosphere and in flame-dried glassware.

Column chromatography was performed with a MPLC apparatus: Buchi Sepacore™ flash apparatus, consisting of a C-660 Buchi fraction collector, C-615 Pump manager, C-635 UV-photometer, two C-605 pump modules and a Linseis D120S plotter.

$^{1}$H-NMR spectra were recorded on Bruker Avance 300 (300 MHz), Bruker Avance 400 III HD (400 MHz) and Bruker Avance II$^{+}$ 600 (600 MHz) spectrometers. Samples were dissolved in $CDCl_3$ (7.26 ppm), DMSO-$d_6$ (2.50 ppm), $CD_3CN$ (1.94 ppm), $CD_3OD$ (4.87 ppm and 3.31 ppm) or $(CD_3)_2CO$ (2.05 ppm) and tetramethylsilane was used as an internal standard. The δ-values are expressed in parts per million (ppm).

$^{13}$C-NMR spectra were recorded on Bruker Avance 300 (operating at 75 MHz), Bruker Avance III HD 400 (operating at 101 MHz) and Bruker Avance II$^{+}$ 600 (operating at 151 MHz) spectrometers. The deuterated solvents were used as internal standard ($CDCl_3$: 77.2 ppm, DMSO-$d_6$: 39.5 ppm, $CD_3CN$: 118.7 ppm and 1.4 ppm, $CD_3OD$: 49.1 ppm, $(CD_3)_2CO$: 206.7 ppm and 29.9 ppm). The δ-values are expressed in parts per million (ppm).

$^{19}$F-NMR spectra were recorded on Bruker Avance 400 (working at 376 MHz) and Bruker Avance II$^{+}$ 600 (working at 565 MHz) spectrometers. Samples were dissolved in $CDCl_3$, DMSO-$d_6$, $CD_3CN$, $CD_3OD$ or

$(CD_3)_2CO$ and trichlorofluoromethane was used as an internal standard. The δ-values are expressed in parts per million (ppm).

All NMR spectra are reported as follows: (multiplicity; coupling constant(s) in Hz; integration). The following abbreviations are used to indicate the multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet, brd = broad signal, dd = doublet of doublets, dt = doublet of triplets, ap = apparent.

IR spectra, Bruker Alpha-T FT-IR spectrometer with universal sampling module. Opus software was used to process the data.

Melting points were determined on a Mettler-Toledo DSC1 instrument, using a heating rate of 10 °C $min^{-1}$ under helium atmosphere.

CHN (carbon, hydrogen, nitrogen) elemental analyses were obtained with the aid of a Thermo Scientific Interscience Flash 2000 Elemental analyzer.

High-resolution mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 μL/min and spectra were obtained in positive (or negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass.

Crystal structures were determined on an Agilent SuperNova diffractometer (single source at offset, Eos detector). Using Olex2, the structure was solved with the Superflip structure solution program using Charge Flipping and refined with the ShelXL refinement package using least-squares minimization.

## 7.1.2. Two-chamber reactor: a device under pressure

A two-chamber reactor is a safe and user-friendly tool to employ gases in organic synthesis. In this device, a gas is released from a precursor molecule in one chamber, which subsequently diffuses to the adjacent chamber, where it is consumed in a chemical reaction. Consequently, the risk of direct contact between the operator and the gaseous reagent is completely eliminated.

**Caution!** Since gases are generated in a closed system, there is always a risk of explosion and the reaction should therefore be carried out behind a blast screen (see Figure 7.1). The commercialized two-chamber reactor (COware) is constructed of pyrex glass and even though it can endure up to 15 bar without failure, the recommended maximum pressure of 5 bar should never be exceeded. The safety concerns can be further alleviated by installing a pressure relief valve or by actively monitoring the pressure inside the vessel with a manometer.

In a small two-chamber reactor (inner volume of 20 mL), the amount of generated gas is limited to 2.5 mmol at room temperature. This calculation is based on an inner volume of 15 mL (20 mL total minus 5 mL solvent). For a large two-chamber vessel (inner volume om 400 mL), the maximum permitted amount of generated gas is 50 mmol at room temperature. This calculation is based on an inner volume of 300 mL (400 mL total minus 100 mL solvent).

A detailed risk-assessment is available on the KU Leuven groupware.[358]

**Figure 7.1.** Performing a gas-mediated reaction in a two-chamber reactor behind a blast screen.

## 7.1.3. Chemical safety

All the experimental work performed in this thesis is compliant with the stringent safety requirements set by the HSE office of Leuven Chem&Tech. The Corelab safety module on chemical safety in combination with the internal HSE audits and the reports on recently occurred incidents create a stimulating environment where safety is of paramount importance. This challenges the PhD student to constantly evaluate whether improvements are needed to minimize the potential hazards of a certain chemical reaction, especially when employing dangerous and toxic reagents.

This thesis focuses on how we can improve the chemical safety when working with dangerous gases. The HSE policy at Leuven Chem&Tech discourages the use of pressurized cylinders filled with highly toxic gases. Therefore, the author was tasked to develop novel gas releasing molecules for the on-demand production of the gaseous reagent of interest. Throughout the PhD program, carbon monoxide and sulfuryl fluoride were generated on a nearly daily basis in a two-chamber reactor to explore its reactivity in new chemical reactions. Although these gases were only produced in small amounts, this does not eliminate their inherent hazardous properties. For this reason, the toxicity profile of carbon monoxide and sulfuryl fluoride will be discussed in the next two sections.

### *7.1.3.1. Carbon monoxide*

*General information*

There exists a certain reluctance to work with carbon monoxide amongst researchers. This hesitation is understandable as CO is a flammable and highly toxic gas that cannot be detected by human senses. It has a boiling point of -192 °C, approximately the same density as air and is only poorly soluble in water (0.03 g/liter at 25 °C).

*Toxicity profile*

The toxicity of carbon monoxide is primarily due to its strong binding affinity to hemoglobin, which hampers the uptake of $O_2$ in the human body. In addition, the formed carboxyhemoglobin complex binds oxygen tighter

in one of its three other subunits, causing a decreased oxygen release. This dual effect leads to oxygen deprivation and asphyxiation.

The time-weighted average exposure limit of carbon monoxide has been set to 35 ppm by the US National Institute for Occupational Safety and Health (NIOSH).[359] Symptoms of prolonged and repeated exposure to high concentrations are headache, dizziness and nauseas, which may eventually result in death.

#### *7.1.3.2. Sulfuryl fluoride*

*General information*

Sulfuryl fluoride is a widely used pest control agent for whole-structure fumigation in the USA. In the 1950s, it was manufactured and commercialized by Dow Chemical under the trade name Vikane. Sulfuryl fluoride is a non-flammable, colorless and odorless gas with a boiling point of -55 °C. This gas is approximately 3.5 times heavier than air and has a solubility of 0.75 g/liter water at 25 °C.[201]

*Toxicity profile*

Sulfuryl fluoride is relatively inert in gaseous form. Under alkaline aqueous conditions, however, it tends to hydrolyze rapidly to produce fluorosulfate and fluoride ions.[201] Even though both metabolites are suspected to be harmful, it is believed that fluorosulfation of proteins is the primary toxin. This was suggested by a study on fumigation of household items with radioisotopic $^{35}SO_2F_2$. The researchers observed very little radiolabel incorporation, except for proteinaceous food.[360]

The time-weighted average exposure limit of sulfuryl fluoride has been set to 5 ppm by the US National Institute for Occupational Safety and Health (NIOSH).[361] Symptoms of prolonged and repeated exposure to high concentrations are eye and respiratory irritation, coughing and vomiting, which may eventually result in lung and kidney damage.

## 7.2. Experimental details of chapter 2

### 7.2.1. Palladium-catalyzed aminocarbonylation

#### *7.2.1.1. General procedure*

Chamber A of a flame-dried two-chamber reactor (Figure 7.2.) was filled with 1 mg palladium(II) acetate (5.00 μmol, 1 mol%), 3 mg Xantphos (5.00 μmol, 1 mol%) and 159 mg sodium carbonate (1.50 mmol, 3 equiv). The reactor was brought under argon atmosphere by two consecutive vacuum-argon cycles. Next, chamber B was filled with 2 mL dry degassed toluene, 51 μL mesyl chloride (0.65 mmol, 1.3 equiv) and 25 μL formic acid (0.65 mmol, 1.3 equiv). In chamber A, 1 mL dry degassed toluene was added, followed by 0.5 mmol aryl bromide (1 equiv) and 0.75 mmol amine (1.5 equiv). Finally, 181 μL triethylamine (1.3 mmol, 2.6 equiv) was added by injection through the septum in chamber B at room temperature and instant gas formation was observed. After 2 minutes, the reactor was immersed in an oil-bath at 100 °C.

An instructional video of the last step is available on https://doi.org/10.1039/C6RE00006A

Remark: when the aryl bromide and/or the amine were solids at room temperature, they were added to chamber A after the addition of palladium(II) acetate and Xantphos.

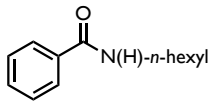
Remark: 25 μL of $^{13}$C-HCOOH (95 wt. % in $H_2O$) was used for the synthesis of the $^{13}$C-isotope labeled pharmaceuticals.

**Figure 7.2.** Two-chamber reactor[43-44]
with an inner volume of approximately 20 mL

After 2 hours, the reactor was brought to room temperature and excess CO was released by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was left stirring at room temperature for another 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. This chamber was washed 5 times with 2 mL of ethyl acetate, these fractions were added to the same flask. After the addition of 1 gram Celite®535, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel.

*7.2.1.2. Reaction scope*

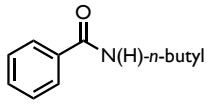
### *N*-hexylbenzamide (2.1)




The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 99 µL *n*-hexylamine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colorless oil (101 mg, 98%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.85 – 7.30 (5 H, m), 6.65 (1 H, brd), 3.39 (2 H, td, *J* = 7.2, 5.9 Hz), 1.65 – 1.50 (2H, m), 1.42 – 1.16 (6 H, m), 0.86 (3H, t, *J* = 6.7 Hz). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 167.7, 134.9, 131.3, 128.5, 127.0, 40.2, 31.6, 29.7, 26.7, 22.6,14.1. These data are in agreement with literature data.[362]

### *N*-butylbenzamide (2.2)

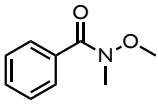



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 74 µL *N*-butylamine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica

gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colorless oil (79 mg, 89%).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 8.42 (1 H, brd), 7.48 (5 H, m), 3.26 (2 H, dd, $J$ = 12.8, 6.9 Hz), 1.57 – 1.45 (2 H, m), 1.39 – 1.27 (2 H, m), 0.90 (3 H, t, $J$ = 7.3 Hz). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 166.1, 134.78, 130.9, 128.2, 127.1, 38.9, 31.3, 19.7, 13.7. These data are in agreement with literature data.[139]

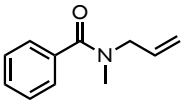
### *N*-methoxy-*N*-methylbenzamide (2.3)



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colorless oil (73 mg, 89%).

$^1$H-NMR (300 MHz, $CDCl_3$): δ 7.69 – 7.34 (5 H, m), 3.54 (3 H, s), 3.35 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 170.1, 134.2, 130.67, 128.2, 128.1, 61.1, 33.8. These data are in agreement with literature data.[363]

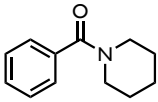
### *N*-allyl-*N*-methylbenzamide (2.4)



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 71 µL *N*-methylprop-2-en-1-amine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colorless oil (71 mg, 81%).

$^1$H-NMR (600 MHz, DMSO-$d_6$): δ 7.47 – 7.35 (5 H, m), 5.89 – 5.75 (1 H, m), 5.24 – 5.15 (2 H, m), 3.94 (2 H, s), 2.90 (3 H, s). $^{13}$C-NMR (151 MHz, DMSO-$d_6$): δ 167.0, 136.3, 133.1, 128.8, 127.8, 126.1, 116.5, 50.8, 34.0. These data are in agreement with literature data.[364]

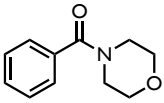
**Phenyl(piperidin-1-yl)methanone (2.5)**



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 74 µL piperidine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colorless oil (88 mg, 93%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.36 (5 H, s), 3.68 (2 H, brd), 3.31 (2 H, brd), 1.64 (4 H, brd), 1.49 (2 H, brd). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 170.3, 136.5, 129.3, 128.4, 126.8, 48.7, 43.1, 26.5, 25.7, 24.6. These data are in agreement with literature data.[365]

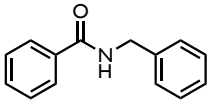
**Morpholino(phenyl)methanone (2.6)**



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 66 µL morpholine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (50:50 heptane/ethyl acetate). The title compound was obtained as a colorless oil (91 mg, 95%).

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.38 (5 H, s), 3.63 (8 H, brd). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 170.5, 135.7, 129.9, 128.6, 127.2, 67.0, 46.9 (brd). These data are in agreement with literature data.[139]

***N*-benzylbenzamide (2.7)**

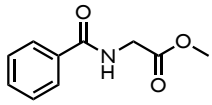


The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 82 µL phenylmethanamine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on

silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a white solid (96 mg, 91%).

$^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 9.04 (1 H, brd), 7.95 – 7.86 (2 H, m), 7.58 – 7.43 (3 H, m), 7.33 (4 H, d, $J$ = 4.3 Hz), 7.24 (1 H, dd, $J$ = 8.6, 4.4 Hz), 4.49 (2 H, d, $J$ = 6.0 Hz). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 166.2, 139.7, 134.3, 131.2, 128.3, 128.3, 127.2, 127.2, 126.7, 42.6. These data are in agreement with literature data.[139]

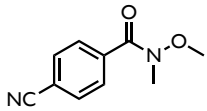
**Methyl 2-benzamidoacetate (2.8)**



The general procedure was followed using 53 µL bromobenzene (0.5 mmol, 1 equiv) and 94 mg methyl glycinate hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a white solid (93 mg, 96%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.82 – 7.75 (2 H, m), 7.52 – 7.34 (3 H, m), 7.06 (1 H, brd), 4.18 (2 H, d, $J$ = 5.3 Hz), 3.73 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 170.2, 167.3, 133.2, 131.4, 128.2, 126.7, 52.0, 41.3. These data are in agreement with literature data.[366]

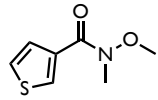
**4-isocyano-*N*-methoxy-*N*-methylbenzamide (2.9)**



The general procedure was followed using 91 mg 4-bromobenzonitrile (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (60:40 heptane/ethyl acetate). The title compound was obtained as a light-yellow oil (87 mg, 92%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.72 (4 H, dd, $J$ = 20.6, 8.5 Hz), 3.50 (3 H, s), 3.35 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 168.0, 138.3, 131.9, 128.9, 118.2, 114.2, 61.4, 33.3. These data are in agreement with literature data.[212]

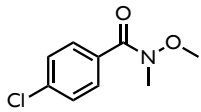
### *N*-methoxy-*N*-methylthiophene-3-carboxamide (2.10)



The general procedure was followed using 47 µL 3-bromothiophene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a light-yellow oil (77 mg, 90%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 8.06 (1 H, dd, *J* = 3.0, 1.2 Hz), 7.56 (1 H, dd, *J* = 5.1, 1.2 Hz), 7.27 (1 H, dd, *J* = 5.1, 3.0 Hz), 3.64 (3 H, s), 3.35 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 163.4, 134.1, 130.5, 128.7, 124.5, 60.9, 32.9. These data are in agreement with literature data.[212]

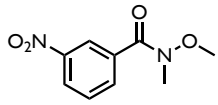
### 4-chloro-*N*-methoxy-*N*-methylbenzamide (2.11)



The general procedure was followed using 144 mg 1-bromo-4-chlorobenzene (0.75 mmol, 1.5 equiv) and 49 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.50 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colorless oil (83 mg, 83%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.64 (2 H, d, *J* = 8.7 Hz), 7.36 (2 H, d, *J* = 8.7 Hz), 3.52 (3 H, s), 3.34 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 168.7, 136.8, 132.3, 129.9, 128.4, 61.2, 33.6. These data are in agreement with literature data.[212]

### *N*-methoxy-*N*-methyl-3-nitrobenzamide (2.12)

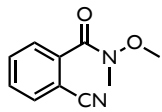


The general procedure was followed using 101 mg 1-bromo-3-nitrobenzene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine

hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (75:25 heptane/ethyl acetate). The title compound was obtained as a light-yellow oil (90 mg, 86%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 8.57 – 8.53 (1 H, m), 8.34 – 8.27 (1 H, m), 8.05 – 7.99 (1 H, m), 7.60 (1 H, t, *J* = 8.0 Hz), 3.54 (3 H, s), 3.38 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 167.3, 147.8, 135.6, 134.4, 129.3, 125.4, 123.6, 61.5, 33.3. These data are in agreement with literature data.[212]

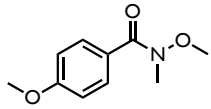
### 2-cyano-*N*-methoxy-*N*-methylbenzamide (2.13)



The general procedure was followed using 92 mg 2-bromobenzonitrile (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (70:30 heptane/ethyl acetate). The title compound was obtained as a colorless oil (85 mg, 89%).

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.74 – 7.45 (4 H, m), 3.52 (3 H, s), 3.36 (3 H, s). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 166.9, 139.1, 132.9, 132.5, 129.9, 128.0, 116.9, 110.9, 61.5, 33.3. These data are in agreement with literature data.[212]

### *N*,4-dimethoxy-*N*-methylbenzamide (2.14)

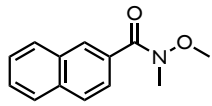


The general procedure was followed using 63 µL 1-bromo-4-methoxybenzene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a colorless oil (85 mg, 87%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.70 (2 H, d, *J* = 8.9 Hz), 6.87 (2 H, d, *J* = 8.9 Hz), 3.81 (3 H, s), 3.53 (3 H, s), 3.32 (3 H, s). $^{13}$C-NMR (75 MHz,

$CDCl_3$): δ 169.0, 161.1, 130.1, 125.6, 112.8, 60.5, 54.92, 33.5. These data are in agreement with literature data.[212]

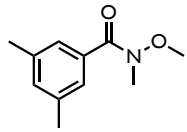
### *N*-methoxy-*N*-methyl-2-naphthamide (2.15)



The general procedure was followed using 104 mg 2-bromonaphtalene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85:15 heptane/ethyl acetate). The title compound was obtained as a colorless oil (94 mg, 88%).

$^1$H-NMR (300 MHz, $CDCl_3$): δ 8.22 (1 H, s), 7.92 – 7.73 (4 H, m), 7.58 – 7.47 (2 H, m), 3.55 (3 H, s), 3.40 (3 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 169.9, 134.2, 132.5, 131.4, 128.9, 128.7, 127.7, 127.7, 127.4, 126.5, 125.1, 61.2, 33.9. These data are in agreement with literature data.[363]

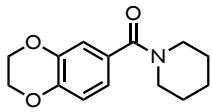
### *N*-methoxy-*N*,3,5-trimethylbenzamide (2.16)



The general procedure was followed using 68 µL 1-bromo-3,5-dimethylbenzene (0.5 mmol, 1 equiv) and 73 mg *N*,*O*-dimethylhydroxylamine hydrochloride (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (70:30 heptane/ethyl acetate). The title compound was obtained as a colorless oil (86 mg, 89%).

$^1$H-NMR (300 MHz, $CDCl_3$): δ 7.22 (2 H, s), 7.06 (1 H, s), 3.56 (3 H, s), 3.31 (3 H, s), 2.32 (6 H, s). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 170.5, 137.7, 134.2, 132.2, 125.6, 61.0, 34.1, 21.3. These data are in agreement with literature data.[367]

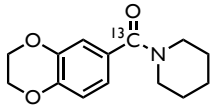
### (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl) methanone (2.17)



The general procedure was followed using 67 µL 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (0.5 mmol, 1 equiv) and 74 µL piperidine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a white solid (111 mg, 90%).

$^{1}$H-NMR (600 MHz, $CDCl_3$): δ 6.95 – 6.82 (3 H, m), 4.25 (4 H, m), 3.52 (4 H, m), 1.68 – 1.64 (2 H, m), 1.57 (4 H, m). $^{13}$C-NMR (151 MHz, $CDCl_3$): δ 167.0, 144.9, 143.6, 130.0, 120.7, 117.3, 116.7, 64.7, 64.5, 46.0 (brd), 26.3, 24.9. These data are in agreement with literature data.[139]

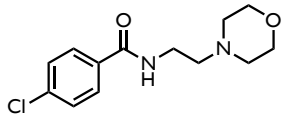
### $^{13}$C-labeled (2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)(piperidin-1-yl)methanone ($^{13}$C-2.17)



The general procedure was followed using 67 µL 6-bromo-2,3-dihydrobenzo[*b*][1,4]dioxine (0.5 mmol, 1 equiv) and 74 µL piperidine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (80:20 heptane/ethyl acetate). The title compound was obtained as a white solid (124 mg, 94%). Remark: 25 µL of $^{13}$C-HCOOH (95 wt. % in $H_2O$) was used instead of HCOOH.

$^{1}$H-NMR (600 MHz, $CDCl_3$): δ 6.94 – 6.81 (3 H, m), 4.26 – 4.20 (4 H, m), 3.66 – 3.38 (4 H, m), 1.68 – 1.62 (2 H, m), 1.61 – 1.52 (4 H, m). $^{13}$C-NMR (151 MHz, $CDCl_3$): δ 169.9 (s), 144.9 (s), 143.5 (s), 130.0 (d, *J* = 67.7 Hz), 120.6 (s), 117.2 (d, *J* = 4.9 Hz), 116.6 (d, *J* = 2.3 Hz), 64.6 (s), 64.5 (s), 46.2 (brd), 26.2 (s), 24.8 (s).

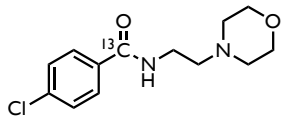
### 4-chloro-*N*-(2-morpholinoethyl)benzamide (2.18)



The general procedure was followed using 98 mg 1-bromo-4-chlorobenzene (0.5 mmol, 1 equiv) and 99 µL 2-morpholinoethan-1-amine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (96:4 dichloromethane/methanol). The title compound was obtained as a white solid (130 mg, 97%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.75 – 7.68 (2 H, m), 7.45 – 7.37 (2 H, m), 6.76 (1 H, brd), 3.77 – 3.68 (4 H, m), 3.57 – 3.48 (2 H, m), 2.63 – 2.56 (2 H, m), 2.54 – 2.43 (4 H, m). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 166.4, 137.8, 133.1, 129.0, 128.5, 67.1, 56.9, 53.4, 36.2 These data are in agreement with literature data.[127]

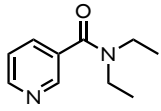
### $^{13}$C-labeled 4-chloro-*N*-(2-morpholinoethyl) benzamide ($^{13}$C-2.18)



The general procedure was followed using 98 mg 1-bromo-4-chlorobenzene (0.5 mmol, 1 equiv) and 99 µL 2-morpholinoethan-1-amine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (96:4 dichloromethane/methanol). The title compound was obtained as a white solid (126 mg, 94%). Remark: 25 µL of $^{13}$C-HCOOH (95 wt. % in $H_2O$) was used instead of HCOOH.

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 7.73 – 7.68 (2 H, m), 7.43 – 7.37 (2 H, m), 6.80 (1 H, brd), 3.78 – 3.64 (4 H, m), 3.59 – 3.48 (2 H, m), 2.60 – 2.55 (2 H, m), 2.54 – 2.41 (4 H, m). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 166.4 (s), 137.7 (s), 133.0 (d, $J$ = 65.2 Hz), 128.9 (d, $J$ = 4.4 Hz), 128.5 (d, $J$ = 2.5 Hz), 67.1 (s), 56.9 (s), 53.4 (s), 36.2 (s). These data are in agreement with literature data.[127]

### *N*,*N*-diethylnicotinamide (2.19)

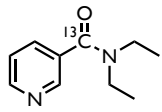


The general procedure was followed using 49 µL 3-bromopyridine (0.5 mmol, 1 equiv) and 78 µL diethylamine (0.75 mmol, 1.5 equiv). The crude

mixture was purified by solid-phase flash column chromatography on silica gel (97:3 dichloromethane/methanol). The title compound was obtained as a yellow oil (68 mg, 76%).

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 8.58 (2 H, m), 7.71 – 7.62 (1 H, m), 7.34 – 7.26 (1 H, m), 3.36 (4 H, m), 1.14 (6 H, m). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 168.6, 150.3, 147.2, 134.3, 133.0, 123.4, 43.5, 39.6, 14.3, 12.9. These data are in agreement with literature data.[139]

### $^{13}$C-labeled *N*,*N*-diethylnicotinamide ($^{13}$C-2.19)



The general procedure was followed using 49 µL 3-bromopyridine (0.5 mmol, 1 equiv) and 78 µL diethylamine (0.75 mmol, 1.5 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (97:3 dichloromethane/methanol). The title compound was obtained as a yellow oil (73 mg, 82%). Remark: 25 µL of $^{13}$C-HCOOH (95 wt. % in $H_2O$) was used instead of HCOOH.

$^{1}$H-NMR (300 MHz, $CDCl_3$): δ 8.60 (2 H, m), 7.78 – 7.57 (1 H, m), 7.38 – 7.26 (1 H, m), 3.37 (4 H, m), 1.15 (6 H, m). $^{13}$C-NMR (75 MHz, $CDCl_3$): δ 168.6 (s), 150.3 (s), 147.2 (d, *J* = 3.0 Hz), 134.3 (d, *J* = 1.6 Hz), 133.0 (d, *J* = 66.7 Hz), 123.5 (s), 43.5 (s), 39.6 (s), 14.3 (s), 12.9 (s).

## 7.3. Experimental details of chapter 3

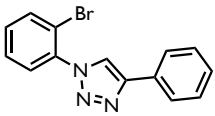
### 7.3.1. Triazole synthesis *via* azide-aldehyde [3+2] cycloaddition

#### *7.3.1.1. General procedure*

Phenylacetaldehyde (0.70 mmol, 1.0 equiv) and aryl azide (0.84 mmol, 1.2 equiv) were dissolved in DMSO (2 mL) in a 10 mL round-bottomed flask. Then, *tert*-BuOK (8.0 mg, 98 wt%, 0.07 mmol, 0.1 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. The crude mixture was worked up with a saturated aqueous $NH_4Cl$ solution (20 mL), which was extracted three times with dichloromethane (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The crude product was purified by flash column chromatography on silica gel. This procedure is based on reference [257].

#### *7.3.1.2. Reaction scope*

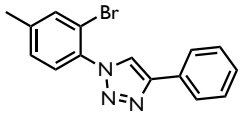
**1-(2-bromophenyl)-4-phenyl-1*H*-1,2,3-triazole (3.1)**




The general procedure was followed using 84 μL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 166 mg of 1-azido-2-bromobenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (162 mg, 77%).

Melting point (°C): 104 – 105. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 9.03 (s, 1H), 8.05 – 7.84 (m, 3H), 7.76 – 7.72 (m, 1H), 7.69 – 7.62 (m, 1H), 7.62 – 7.56 (m, 1H), 7.53 – 7.47 (m, 2H), 7.42 – 7.35 (m, $J$ = 7.4 Hz, 1H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 146.4, 136.2, 133.7, 132.1, 130.2, 129.0, 129.0, 128.7, 128.2, 125.3, 123.6, 119.0. IR (neat) cm$^{-1}$: 3131 (C-H stretch triazole). HR-MS (ESI) *m/z*: calculated mass 300.0131 $[M + H]^+$, found 300.0132.

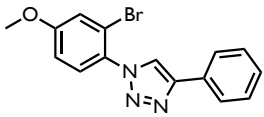
**1-(2-bromo-4-methylphenyl)-4-phenyl-1*H*-1,2,3-triazole (3.2)**



The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 178 mg of 1-azido-2-bromo-4-methylbenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (156 mg, 71%).

Melting point (°C): 85 – 86. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.97 (s, 1H), 7.97 – 7.92 (m, 2H), 7.78 (d, $J$ = 1.0 Hz, 1H), 7.60 (d, $J$ = 8.0 Hz, 1H), 7.51 – 7.42 (m, 3H), 7.41 – 7.35 (m, 1H), 2.43 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 146.6, 142.5, 133.8, 133.7, 130.3, 129.4, 129.0, 128.3, 128.2, 125.3, 123.7, 118.6, 20.4. IR (neat) cm$^{-1}$: 3148 (C-H stretch triazole), 2921 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 314.0288 $[M + H]^+$, found 314.0288.

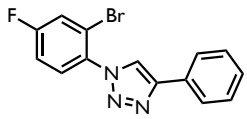
### 1-(2-bromo-4-methoxyphenyl)-4-phenyl-1*H*-1,2,3-triazole (3.3)



The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 192 mg of 1-azido-2-bromo-4-methoxybenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (75/25 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (210 mg, 91%).

Melting point (°C): 126 – 127. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.94 (s, 1H), 8.01 – 7.92 (m, 2H), 7.64 (d, $J$ = 8.8 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.42 – 7.33 (m, 1H), 7.18 (dd, $J$ = 8.8, 2.6 Hz, 1H), 3.88 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 160.9, 146.3, 130.3, 129.4, 129.2, 129.0, 128.2, 125.3, 123.9, 120.0, 118.3, 114.4, 56.2. IR (neat) cm$^{-1}$: 3142 (C-H stretch triazole), 2954 (C-H stretch methyl), 1238 (aryl-O stretch). HR-MS (ESI) *m/z*: calculated mass 330.0237 $[M + H]^+$, found 330.0241.

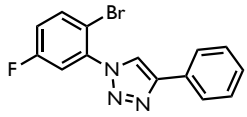
### 1-(2-bromo-4-fluorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3.4)



The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 181 mg of 1-azido-2-bromo-4-fluorobenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (189 mg, 85%).

Melting point (°C): 109 – 110. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 9.01 (s, 1H), 7.97 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.96 – 7.92 (m, 2H), 7.84 (dd, *J* = 8.6, 5.5 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.52 – 7.47 (m, 2H), 7.42 – 7.36 (m, 1H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 162.3 (d, *J* = 252.4 Hz), 146.5, 133.1 (d, *J* = 3.4 Hz), 130.4 (d, *J* = 9.6 Hz), 130.1, 129.0, 128.3, 125.3, 123.8, 120.8 (d, *J* = 26.1 Hz), 120.3 (d, *J* = 10.7 Hz), 116.1 (d, *J* = 22.8 Hz). IR (neat) cm$^{-1}$: 3127 (C-H stretch triazole). HR-MS (ESI) *m/z*: calculated mass 318.0037 $[M + H]^+$, found 318.0037.

### 1-(2-bromo-5-fluorophenyl)-4-phenyl-1*H*-1,2,3-triazole (3.5)

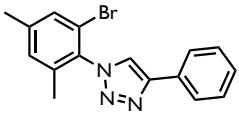


The general procedure was followed using 72 µL of phenylacetaldehyde (98 wt%, 0.60 mmol, 1.0 equiv) and 156 mg of 2-azido-1-bromo-4-fluorobenzene (0.72 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (149 mg, 78%).

Melting point (°C): 87 – 88. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 9.06 (s, 1H), 8.00 (dd, *J* = 8.9, 5.5 Hz, 1H), 7.97 – 7.93 (m, 2H), 7.84 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.42 – 7.36 (m, 1H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 161.2 (d, *J* = 247.7 Hz), 146.5, 137.2 (d, *J* = 10.7 Hz), 135.1 (d, *J* = 8.9 Hz), 130.0, 129.1, 128.3, 125.3, 123.6, 119.3 (d, *J* = 22.3 Hz), 116.5 (d, *J* =

25.9 Hz), 114.0 (d, $J$ = 3.8 Hz). IR (neat) $cm^{-1}$: 3133 (C-H stretch triazole). HR-MS (ESI) *m/z*: calculated mass 318.0037 $[M + H]^+$, found 318.0036.

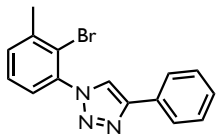
### 1-(2-bromo-4,6-dimethylphenyl)-4-phenyl-1*H*-1,2,3-triazole (3.6)




The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 190 mg of 2-azido-1-bromo-3,5-dimethylbenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a very viscous orange oil (223 mg, 97%).

$^1$H-NMR (400 MHz, DMSO-$d_6$): δ 8.89 (s, 1H), 7.99 – 7.92 (m, 2H), 7.58 (s, 1H), 7.53 – 7.45 (m, 2H), 7.41 – 7.35 (m, 1H), 7.33 (s, 1H), 2.39 (s, 3H), 2.01 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 146.5, 142.2, 137.3, 133.0, 131.0, 130.9, 130.3, 129.0, 128.2, 125.3, 123.6, 120.5, 20.4, 17.3. IR (neat) $cm^{-1}$: 3135 (C-H stretch triazole), 2922 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 328.0444 $[M + H]^+$, found 328.0442.

### 1-(2-bromo-3-methylphenyl)-4-phenyl-1*H*-1,2,3-triazole (3.7)

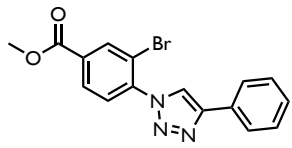



The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 178 mg of 1-azido-2-bromo-3-methylbenzene (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a white solid (213 mg, 97%).

Melting point (°C): 108 – 109. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.96 – 7.90 (m, 2H), 7.50 – 7.41 (m, 3H), 7.41 – 7.34 (m, 3H), 2.53 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 147.5, 140.7, 137.1, 132.3, 130.4, 129.0,

128.5, 127.8, 126.0, 125.9, 122.0, 121.9, 23.9. IR (neat) $cm^{-1}$: 3125 (C-H stretch triazole), 2949 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 314.0288 $[M + H]^+$, found 314.0282.

**Methyl 3-bromo-4-(4-phenyl)-1*H*-1,2,3-triazol-1-yl) benzoate (3.8)**




The general procedure was followed using 84 µL of phenylacetaldehyde (98 wt%, 0.70 mmol, 1.0 equiv) and 215 mg of methyl 4-azido-3-bromobenzoate (0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (65/35 heptane/ethyl acetate). The title compound was obtained as a yellowish solid (178 mg, 71%).

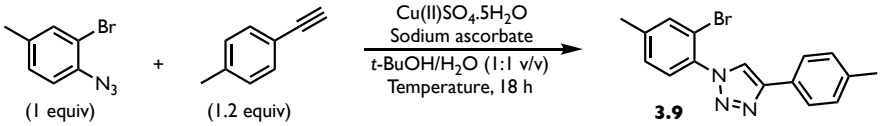
Melting point (°C): 130 – 131. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 9.12 (s, 1H), 8.38 (d, *J* = 1.8 Hz, 1H), 8.17 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.99 – 7.94 (m, 2H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.43 – 7.36 (m, 1H), 3.93 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 164.2, 146.7, 139.6, 134.1, 132.6, 130.0, 129.6, 129.0, 129.0, 128.4, 125.4, 123.5, 118.9, 52.9. IR (neat) $cm^{-1}$: 3137 (C-H stretch triazole), 2949 (C-H stretch methyl), 1720 (C=O stretch ester). HR-MS (ESI) *m/z*: calculated mass 358.0186 $[M + H]^+$, found 358.0187.

## 7.3.2. Triazole synthesis *via* copper-catalyzed azide-alkyne [3+2] cycloaddition

### *7.3.2.1. Optimization study*

The copper-catalyzed [3+2] cycloaddition of 2-bromo-4-methylphenyl azide with 4-ethynyltoluene was optimized since the original CuAAC conditions reported by Sharpless[261] only furnished the desired product (**3.9**) in 14%. The results are summarized in Table 7.1.

**Table 7.1** Optimization study of the copper-catalyzed [3+2] cycloaddition of 2-bromo-4-methylphenyl azide with 4-ethynyltoluene.



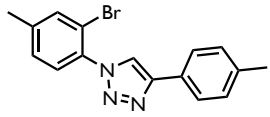

| Entry | $Cu(II)SO_4.5H_2O$ (mol%) | Sodium ascorbate (mol%) | Temperature (°C) | Yield (%) |
|---|---|---|---|---|
| 1 | 1 | 10 | 20 | 14 |
| 2 | 10 | 30 | 20 | 70 |
| 3 | 1 | 10 | 45 | 66 |
| 4 | 10 | 30 | 45 | 73 |
| 5 | 1 | 10 | 100 | 80 |

### *7.3.2.2. General procedure*

The azide (0.70 mmol, 1.0 equiv) and alkyne (0.84 mmol, 1.2 equiv) were suspended in a 1:1 (v/v) mixture of water and *tert*-butyl alcohol (3 mL). Sodium ascorbate (13.9 mg dissolved in 100 μL water, 0.07 mmol, 10 mol%) was added, followed by copper(II) sulfate pentahydrate (1.7 mg dissolved in 100 μL water, 7.00 μmol, 1 mol%). The heterogeneous mixture was stirred vigorously overnight at 100 °C in a sealed tube. Then, 20 mL of water was added to the crude mixture, which was extracted three times with dichloromethane (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The crude product was purified by flash column chromatography on silica gel. This procedure is based on reference [261].

*7.3.2.3. Reaction scope*

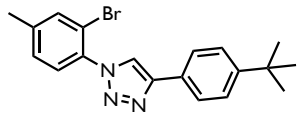
### 1-(2-bromo-4-methylphenyl)-4-(*p*-tolyl)-1*H*-1,2,3-triazole (3.9)



The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 109 µL of 4-ethynyltoluene (98 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a white solid (184 mg, 80%).

Melting point (°C): 114 – 115. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.90 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H), 2.35 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 146.4, 142.4, 137.5, 133.8, 133.7, 129.5, 129.4, 128.2, 127.5, 125.3, 123.2, 118.6, 20.9, 20.4. IR (neat) cm$^{-1}$: 3102 (C-H stretch triazole), 2918 (C-H stretch methyl), 2860 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 328.0444 $[M + H]^+$, found 328.0453.

### 1-(2-bromo-4-methylphenyl)-4-(4-(*tert*-butyl)phenyl)-1*H*-1,2,3-triazole (3.10)

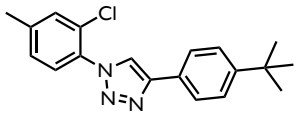


The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 158 µL of 4-*tert*-butylphenylacetylene (96 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a white solid (228 mg, 88%).

Melting point (°C): 128 – 129. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.92 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 0.9 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.44 (dd, *J* = 8.0, 0.9 Hz, 1H), 2.43 (s, 3H),

1.32 (s, 9H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 150.7, 146.3, 142.4, 133.8, 133.7, 129.4, 128.2, 127.5, 125.7, 125.1, 123.3, 118.6, 34.4, 31.1, 20.4. IR (neat) cm$^{-1}$: 3133 (C-H stretch triazole), 2958 (C-H stretch methyl), 2865 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 370.0914 $[M + H]^+$, found 370.0907.

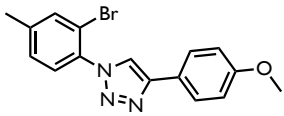
### 4-(4-(*tert*-butyl)phenyl)-1-(2-chloro-4-methylphenyl)-1*H*-1,2,3-triazole (3.11)




The general procedure was followed using 117 mg of 1-azido-2-chloro-4-methylbenzene (0.70 mmol, 1.0 equiv) and 158 μL of 4-*tert*-butylphenylacetylene (96 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a white solid (208 mg, 91%).

Melting point (°C): 147 – 148. $^1$H-NMR (400 MHz, DMSO-$d_6$): δ 8.94 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.60 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.39 (m, 1H), 2.43 (s, 3H), 1.31 (s, 9H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 150.7, 146.4, 142.1, 132.1, 130.7, 129.0, 128.2, 128.0, 127.4, 125.7, 125.2, 123.3, 34.4, 31.1, 20.5. IR (neat) cm$^{-1}$: 3133 (C-H stretch triazole), 2958 (C-H stretch methyl), 2866 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 326.1418 $[M + H]^+$, found 326.1412.

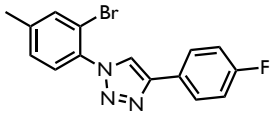
### 1-(2-bromo-4-methylphenyl)-4-(4-methoxyphenyl)-1*H*-1,2,3-triazole (3.12)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 112 μL of 4-ethynylanisole (97 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (75/25 heptane/ethyl acetate). The title compound was obtained as a white solid (210 mg, 87%).

Melting point (°C): 124 – 125. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.85 (s, 1H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 1.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.42 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 159.2, 146.3, 142.4, 133.8, 133.7, 129.4, 128.2, 126.7, 122.8, 122.6, 118.6, 114.4, 55.2, 20.4. IR (neat) cm$^{-1}$: 3142 (C-H stretch triazole), 2997 (C-H stretch methyl), 2945 (C-H stretch methyl), 1236 (aryl-O stretch). HR-MS (ESI) *m/z*: calculated mass 344.0393 $[M + H]^+$, found 344.0388.

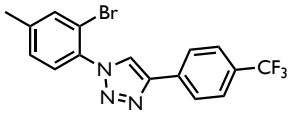
### 1-(2-bromo-4-methylphenyl)-4-(4-fluorophenyl)-1*H*-1,2,3-triazole (3.13)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 97 μL of 1-ethynyl-4-fluorobenzene (99 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a white solid (205 mg, 88%).

Melting point (°C): 146 – 147. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.97 (s, 1H), 7.99 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.78 (d, *J* = 0.8 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.34 (t, *J* = 8.8 Hz, 2H), 2.43 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 162.0 (d, *J* = 244.8 Hz), 145.5, 142.5, 133.7, 133.7, 129.4, 128.2, 127.4 (d, *J* = 8.3 Hz), 126.8 (d, *J* = 3.1 Hz), 123.5, 118.6, 116.0 (d, *J* = 21.7 Hz), 20.4. IR (neat) cm$^{-1}$: 3142 (C-H stretch triazole), 2925 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 332.0194 $[M + H]^+$, found 332.0183.

### 1-(2-bromo-4-methylphenyl)-4-(4-(trifluoromethyl) phenyl)-1*H*-1,2,3-triazole (3.14)

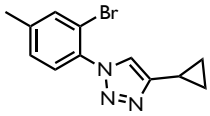



The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 141 μL of 4-ethynyl-α,α,α-

trifluorotoluene (97 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (75/25 heptane/ethyl acetate). The title compound was obtained as a white solid (233 mg, 87%).

Melting point (°C): 147 – 148. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 9.17 (s, 1H), 8.17 (d, $J$ = 8.2 Hz, 2H), 7.87 (d, $J$ = 8.2 Hz, 2H), 7.79 (d, $J$ = 0.9 Hz, 1H), 7.62 (d, $J$ = 8.0 Hz, 1H), 7.45 (dd, $J$ = 8.0, 0.9 Hz, 1H), 2.43 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 145.0, 142.6, 134.2, 133.7, 133.6, 129.5, 128.3 (q, $J$ = 31.9 Hz), 128.2, 126.0 (q, $J$ = 3.7 Hz), 125.8, 124.9, 124.2 (q, $J$ = 272.0 Hz), 118.6, 20.4. IR (neat) cm$^{-1}$: 3137 (C-H stretch triazole), 2931 (C-H stretch methyl), 1327 (C-$CF_3$ stretch). HR-MS (ESI) *m/z*: calculated mass 382.0162 [M + H]$^{+}$, found 382.0154.

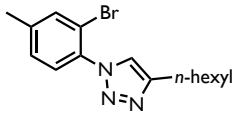
### 1-(2-bromo-4-methylphenyl)-4-cyclopropyl-1*H*-1,2,3-triazole (3.15)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 73 μL of cyclopropylacetylene (97 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a colorless viscous oil (150 mg, 77%).

$^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.18 (s, 1H), 7.72 (d, $J$ = 0.9 Hz, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.39 (dd, $J$ = 8.0, 0.9 Hz, 1H), 2.40 (s, 3H), 2.02 (tt, $J$ = 8.4, 5.0 Hz, 1H), 1.00 – 0.91 (m, 2H), 0.85 – 0.76 (m, 2H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 148.9, 142.0, 133.9, 133.6, 129.3, 128.1, 123.0, 118.4, 20.3, 7.8, 6.4. IR (neat) cm$^{-1}$: 3144 (C-H stretch triazole), 3088 (C-H stretch cyclopropyl), 3005 (C-H stretch cyclopropyl), 2923 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 278.0288 [M + H]$^{+}$, found 278.0294.

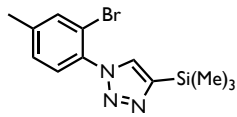
### 1-(2-bromo-4-methylphenyl)-4-hexyl-1*H*-1,2,3-triazole (3.16)



The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 128 µL of 1-octyne (97 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a colorless viscous oil (199 mg, 88%).

$^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.19 (s, 1H), 7.72 (d, $J$ = 1.0 Hz, 1H), 7.47 (d, $J$ = 8.0 Hz, 1H), 7.39 (dd, $J$ = 8.0, 1.0 Hz, 1H), 2.70 (t, $J$ = 7.6 Hz, 2H), 2.41 (s, 3H), 1.72 – 1.60 (m, 2H), 1.40 – 1.25 (m, 6H), 0.86 (t, $J$ = 7.0 Hz, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 146.9, 142.0, 134.0, 133.6, 129.3, 128.1, 124.0, 118.4, 31.0, 28.8, 28.2, 24.9, 22.0, 20.3, 13.9. IR (neat) cm$^{-1}$: 3135 (C-H stretch triazole), 2954 (C-H stretch), 2925 (C-H stretch), 2856 (C-H strecth). HR-MS (ESI) *m/z*: calculated mass 322.0914 [M + H]$^{+}$, found 322.0907.

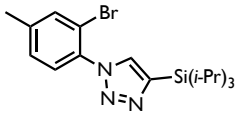
### 1-(2-bromo-4-methylphenyl)-4-(trimethylsilyl)-1*H*-1,2,3-triazole (3.17)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 396 µL of ethynyltrimethylsilane (98 wt%, 2.80 mmol, 4.0 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a pale white solid (156 mg, 72%).

Melting point (°C): 78 – 79. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.49 (s, 1H), 7.73 (d, $J$ = 0.9 Hz, 1H), 7.48 (d, $J$ = 8.0 Hz, 1H), 7.39 (dd, $J$ = 8.0, 0.9 Hz, 1H), 2.41 (s, 3H), 0.32 (s, 9H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 144.8, 142.0, 133.8, 133.6, 132.5, 129.3, 128.2, 118.5, 20.3, -1.0. IR (neat) cm$^{-1}$: 3111 (C-H stretch triazole), 2954 (C-H stretch methyl), 2856 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 310.0370 [M + H]$^{+}$, found 310.0369.

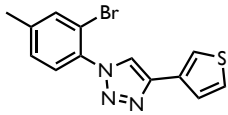
### 1-(2-bromo-4-methylphenyl)-4-(triisopropylsilyl)-1*H*-1,2,3-triazole (3.18)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 194 µL of (triisopropylsilyl)acetylene (97 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (9/1 heptane/ethyl acetate). The title compound was obtained as a white solid (237 mg, 86%).

Melting point (°C): 89 – 90. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.49 (s, 1H), 7.73 (d, $J$ = 0.9 Hz, 1H), 7.53 (d, $J$ = 8.0 Hz, 1H), 7.40 (dd, $J$ = 8.1, 0.9 Hz, 1H), 2.41 (s, 3H), 1.43 – 1.30 (m, 3H), 1.09 (d, $J$ = 7.4 Hz, 18H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 142.0, 140.0, 133.9, 133.6, 133.6, 129.3, 128.2, 118.7, 20.3, 18.4, 10.6. IR (neat) cm$^{-1}$: 3115 (C-H stretch triazole), 2939 (C-H stretch), 2887 (C-H stretch), 2863 (C-H stretch). HR-MS (ESI) *m/z*: calculated mass 394.1309 [M + H]$^{+}$, found 394.1304.

### 1-(2-bromo-4-methylphenyl)-4-(thiophen-3-yl)-1*H*-1,2,3-triazole (3.19)




The general procedure was followed using 148 mg of 1-azido-2-bromo-4-methylbenzene (0.70 mmol, 1.0 equiv) and 86 µL of 3-ethynylthiophene (96 wt%, 0.84 mmol, 1.2 equiv). The crude mixture was purified by flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a white solid (188 mg, 84%).

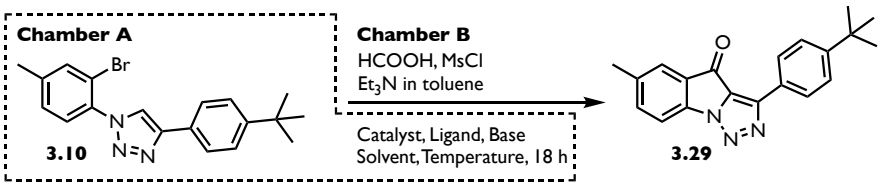
Melting point (°C): 92 – 93. $^{1}$H-NMR (400 MHz, DMSO-$d_6$): δ 8.83 (s, 1H), 7.95 (dd, $J$ = 2.9, 1.1 Hz, 1H), 7.77 (d, $J$ = 0.9 Hz, 1H), 7.69 (dd, $J$ = 5.0, 3.0 Hz, 1H), 7.62 – 7.56 (m, 2H), 7.43 (dd, $J$ = 8.0, 0.9 Hz, 1H), 2.43 (s, 3H). $^{13}$C-NMR (101 MHz, DMSO-$d_6$): δ 142.9, 142.4, 133.7, 133.7, 131.5, 129.4, 128.2, 127.4, 125.8, 123.3, 121.3, 118.5, 20.4. IR (neat) cm$^{-1}$: 3139 (C-H stretch triazole), 3100 (C-H stretch thiophene), 2918 (C-H stretch methyl). HR-MS (ESI) *m/z*: calculated mass 319.9852 [M + H]$^{+}$, found 319.9850.

## 7.3.3. Triazolo[1,5-*a*]indolone synthesis

### *7.3.3.1. Optimization study*

Different reaction conditions were screened for the intramolecular carbonylative C-H functionalization of substrate **3.10**. Full conversion was achieved in presence of 4 mol% $Pd(OAc)_2$, 8 mol% $P(Cy)_3$, carbon monoxide (1.5 equiv) and potassium carbonate (2.0 equiv) in toluene at 120 °C for 18 hours, yielding **3.29** in 80% (Table 7.2, entry 6). Remark that these reaction conditions (without CO) are identical to the ones reported by the Ackermann group for the direct arylation of triazoles with aryl chlorides.[228]

**Table 7.2** Optimization study of the intramolecular carbonylative C-H functionalization of 1-(2-bromophenyl)-1,2,3-triazole **3.10** for the synthesis of triazolo[1,5-*a*]indolone **3.29**.




| Entry | CO (equiv) | Catalyst (mol%) | Ligand (mol%) | Base (equiv) | Solvent | T (°C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 | 1.3 | $Pd(OAc)_2$ (5 mol%) | Xantphos (5 mol%) | KOAc (1.5 equiv) | Toluene | 100 | 0 |
| 2 | 1.3 | $Pd(PPh_3)_4$ (5 mol%) | | Cs Pivalate (2.0 equiv) | DMF | 140 | 0 |
| 3 | 1.5 | $Pd(PPh_3)_4$ (5 mol%) | | Cs Pivalate (2.0 equiv) | DMF | 140 | 0 |
| 4 | 1.5 | $Pd(OAc)_2$ (4 mol%) | $P(Cy)_3$ (8 mol%) | $K_2CO_3$ (2.0 equiv) | Toluene | 80 | 37 |
| 5 | 1.5 | $Pd(OAc)_2$ (4 mol%) | $P(Cy)_3$ (8 mol%) | $K_2CO_3$ (2.0 equiv) | Toluene | 100 | 65 |
| 6 | 1.5 | $Pd(OAc)_2$ (4 mol%) | $P(Cy)_3$ (8 mol%) | $K_2CO_3$ (2.0 equiv) | Toluene | 120 | 80 |
| 7 | 1.5 | $Pd(OAc)_2$ (2 mol%) | $P(Cy)_3$ (4 mol%) | $K_2CO_3$ (2.0 equiv) | Toluene | 120 | 62 |

### *7.3.3.2. General procedure*

Chamber A of a flame-dried two-chamber reactor (Figure 7.2) was filled with triazole (0.4 mmol, 1.0 equiv), palladium(II) acetate (3.6 mg, 0.016 mmol, 4 mol%), tricyclohexylphosphine (9.0 mg, 0.032 mmol, 8 mol%) and

potassium carbonate (111 mg, 0.80 mmol, 2.0 equiv). The reactor was brought under nitrogen atmosphere by two consecutive vacuum-nitrogen cycles. Next, chamber B was filled with 2 mL of dry degassed toluene, 23 μL formic acid (0.60 mmol, 1.5 equiv) and 47 μL mesyl chloride (0.60 mmol, 1.5 equiv). In chamber A, 2 mL of dried degassed toluene was added. Finally, 167 μL triethylamine (1.2 mmol, 3.0 equiv) was added by injection through the septum in chamber B and instant gas formation was observed. After 2 minutes, the reactor was immersed in an oil-bath at 120 °C.

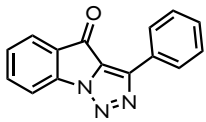
Remark: when the triazole was a viscous oil, it was first dissolved in 1 mL of dry degassed toluene and then added to chamber A right before the triethylamine was injected in chamber B.

Remark: 23 μL of $^{13}$C-HCOOH (95 wt. % in $H_2O$) was used for the synthesis of the $^{13}$C-isotope labeled compounds.

After 18 hours, the reactor was brought to room temperature and the residual pressure was released carefully by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was stirred at room temperature for another 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. Chamber A was rinsed five times with 2 mL of ethyl acetate and these fractions were added to the same flask. After the addition of 1 gram Celite®535, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel.

*7.3.3.3. Reaction scope*

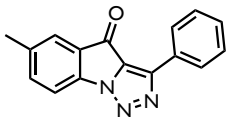
**3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.20)**



The general procedure was followed using 120 mg of compound **3.1** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellow solid (91 mg, 92%).

Melting point (°C): 241 – 242. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.43 – 8.33 (m, 2H), 7.88 – 7.78 (m, 2H), 7.74 – 7.66 (m, 1H), 7.55 – 7.42 (m, 4H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.1, 147.0, 140.6, 135.8, 130.9, 130.0, 129.9, 129.2, 128.9, 128.5, 127.8, 126.1, 113.1. IR (neat) cm$^{-1}$: 1707 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 248.0818 $[M + H]^+$, found 248.0823.

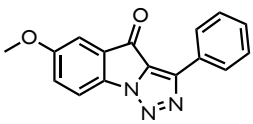
### 6-methyl-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.21)



The general procedure was followed using 126 mg of compound **3.2** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a yellow solid (94 mg, 90%).

Melting point (°C): 206 – 207. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.42 – 8.35 (m, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.56 – 7.45 (m, 4H), 2.46 (s, 3H). $^{13}$C-NMR (151 MHz, $CDCl_3$): δ 176.4, 146.9, 139.5, 138.6, 136.0, 130.8, 130.1, 130.1, 129.2, 128.6, 127.8, 126.5, 112.8, 21.5. IR (neat) cm$^{-1}$: 2914 (C-H stretch methyl), 1709 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 262.0975 $[M + H]^+$, found 262.0972.

### 6-methoxy-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.22)

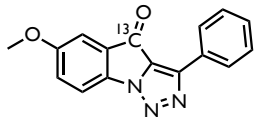


The general procedure was followed using 132 mg of compound **3.3** (0.40 mmol, 1.0 equiv.). The crude mixture was purified by solid-phase flash column chromatography on silica gel (7/3 heptane/ethyl acetate). The title compound was obtained as a yellow solid (101 mg, 91%).

Melting point (°C): 197 – 198. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.41 – 8.31 (m, 2H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.43 (m, 3H), 7.32 (d, *J* = 2.6 Hz, 1H), 7.14 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.89 (s, 3H). $^{13}$C-NMR (101 MHz,

$CDCl_3$): δ 176.0, 160.3, 147.2, 134.3, 131.4, 130.8, 130.2, 129.2, 128.6, 127.8, 120.7, 114.0, 111.0, 56.3. IR (neat) $cm^{-1}$: 3044 (C-H stretch methyl), 1709 (C=O stretch ketone), 1230 (aryl-O stretch). HR-MS (ESI) *m/z*: calculated mass 278.0924 $[M + H]^+$, found 278.0919.

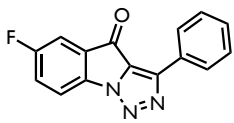
### 6-methoxy-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one-4-$^{13}$*C* ($^{13}$C-3.22)



The general procedure was followed using 132 mg of compound **3.3** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (7/3 heptane/ethyl acetate). The title compound was obtained as a yellow solid (102 mg, 92%).

Melting point (°C): 197 – 198. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.38 – 8.32 (m, 2H), 7.68 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.32 (dd, *J* = 3.8, 2.6 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.89 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.0, 160.3 (d, *J* = 5.1 Hz), 147.2 (d, *J* = 4.0 Hz), 134.2 (d, *J* = 2.6 Hz), 131.4 (d, *J* = 57.1 Hz), 130.8, 130.2 (d, *J* = 68.7 Hz), 129.2, 128.6, 127.8, 120.7, 114.0 (d, *J* = 3.2 Hz), 111.0 (d, *J* = 1.8 Hz), 56.3. IR (neat) $cm^{-1}$: 3044 (C-H stretch methyl), 1676 (C=O stretch ketone), 1230 (aryl-O stretch). HR-MS (ESI) *m/z*: calculated mass 279.0924 $[M + H]^+$, found 279.0956.

### 6-fluoro-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.23)

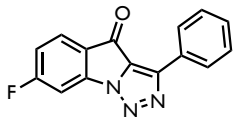


The general procedure was followed using 127 mg of compound **3.4** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (4/6 heptane/dichloromethane). The title compound was obtained as a yellow solid (81 mg, 76%).

Melting point (°C): 207 – 208. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.39 – 8.34 (m, 2H), 7.80 (dd, *J* = 8.5, 3.8 Hz, 1H), 7.57 – 7.47 (m, 4H), 7.39 (td, *J* = 8.5,

2.5 Hz, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 174.7, 162.5 (d, *J* = 252.1 Hz), 147.6, 136.7, 131.8 (d, *J* = 7.9 Hz), 131.2, 130.3, 129.2, 128.3, 127.9, 122.1 (d, *J* = 24.9 Hz), 114.5 (d, *J* = 8.2 Hz), 113.8 (d, *J* = 25.2 Hz). IR (neat) $cm^{-1}$: 1715 (C=O stretch ketone). HR-MS (ESI) *m*/*z*: calculated mass 266.0724 $[M + H]^+$, found 266.0726.

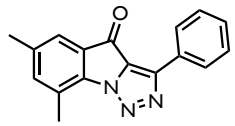
### 7-fluoro-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.24)



The general procedure was followed using 127 mg of compound **3.5** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellow solid (68 mg, 64%).

Melting point (°C): 205 – 206. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.40 – 8.33 (m, 2H), 7.84 (dd, *J* = 8.5, 5.0 Hz, 1H), 7.57 – 7.44 (m, 4H), 7.12 (td, *J* = 8.5, 2.2 Hz, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 174.6, 167.3 (d, *J* = 259.6 Hz), 147.0, 142.1 (d, *J* = 12.7 Hz), 131.1, 130.5, 129.2, 128.3, 128.2 (d, *J* = 6.0 Hz), 127.9, 126.0 (d, *J* = 3.1 Hz), 115.7 (d, *J* = 23.4 Hz), 102.4 (d, *J* = 28.7 Hz). IR (neat) $cm^{-1}$: 1711 (C=O stretch ketone). HR-MS (ESI) *m*/*z*: calculated mass 266.0724 $[M + H]^+$, found 266.0729.

### 6,8-dimethyl-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.25)

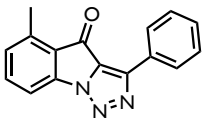


The general procedure was followed using 131 mg of compound **3.6** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (2/8 heptane/dichloromethane). The title compound was obtained as a yellow solid (91 mg, 83%).

Melting point (°C): 208 – 209. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.39 – 8.31 (m, 2H), 7.54 – 7.43 (m, 3H), 7.38 (s, 1H), 7.20 (s, 1H), 2.69 (s, 3H), 2.35 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.5, 146.1, 138.9, 138.4, 137.1,

130.7, 130.3, 130.2, 129.1, 128.6, 127.7, 125.5, 123.9, 21.2, 17.3. IR (neat) $cm^{-1}$: 2925 (C-H stretch methyl), 1713 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 276.1131 $[M + H]^+$, found 276.1127.

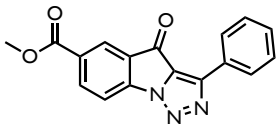
### 5-methyl-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.26)



The general procedure was followed using 126 mg of compound **3.7** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (7/3 heptane/ethyl acetate). The title compound was obtained as an orange solid (92 mg, 88%).

Melting point (°C): 217 – 218. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.44 – 8.36 (m, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.46 (m, 4H), 7.19 (d, *J* = 7.8 Hz, 1H), 2.70 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 177.4, 146.6, 141.9, 140.8, 135.1, 131.5, 130.8, 129.9, 129.1, 128.7, 127.7, 126.9, 110.6, 17.8. IR (neat) $cm^{-1}$: 2921 (C-H stretch methyl), 1701 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 262.0975 $[M + H]^+$, found 262.0975.

### Methyl 4-oxo-3-phenyl-4*H*-[1,2,3]triazolo[1,5-*a*]indole-6-carboxylate (3.27)

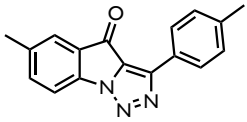


The general procedure was followed using 143 mg of compound **3.8** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (75/25 heptane/ethyl acetate). The title compound was obtained as an orange solid (60 mg, 49%).

Melting point (°C): 182 – 183. $^1$H-NMR (600 MHz, DMSO-$d_6$): δ 8.38 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.28 – 8.23 (m, 2H), 8.22 (d, *J* = 1.3 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.63 – 7.52 (m, 3H), 3.93 (s, 3H). $^{13}$C-NMR (151 MHz, DMSO-$d_6$): δ 174.5, 164.3, 145.1, 142.2, 136.9, 130.6, 130.0, 129.9, 128.9, 127.8, 127.4, 126.7, 125.4, 113.0, 52.4. IR (neat) $cm^{-1}$: 2951 (C-H stretch

methyl), 1715 (C=O stretch ester), 1701 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 306.0873 $[M + H]^+$, found 306.0872.

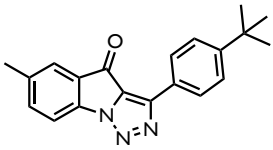
### 6-methyl-3-(*p*-tolyl)-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.28)



The general procedure was followed using 131 mg of compound **3.9** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (1/9 heptane/dichloromethane). The title compound was obtained as a yellow solid (91 mg, 83%).

Melting point (°C): 231 – 232. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.1 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 0.9 Hz 1H), 7.47 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H), 2.43 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.4, 147.1, 141.3, 139.3, 138.5, 135.9, 130.2, 129.9, 129.7, 127.8, 126.4, 125.9, 112.7, 21.8, 21.5. IR (neat) $cm^{-1}$: 2919 (C-H stretch methyl), 2861 (C-H stretch methyl), 1707 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 276.1131 $[M + H]^+$, found 276.1136.

### 3-(4-(*tert*-butyl)phenyl)-6-methyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.29)

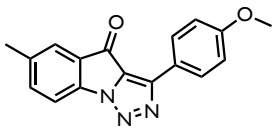


The general procedure was followed using 148 mg of compound **3.10** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellow solid (102 mg, 80%).

Melting point (°C): 171 – 172. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 2.41 (s, 3H), 1.37 (s, 9H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.2, 154.3, 146.8, 139.3, 138.5, 135.8, 130.1, 129.7, 127.6, 126.4, 126.1, 125.8, 112.7, 35.1, 31.3, 21.4. IR (neat) $cm^{-1}$: 2954 (C-H

stretch methyl), 2865 (C-H stretch methyl), 1711 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 318.1601 $[M + H]^+$, found 318.1604.

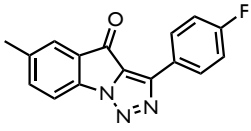
### 3-(4-methoxyphenyl)-6-methyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.30)



The general procedure was followed using 138 mg of compound **3.12** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (100% ethyl acetate). The title compound was obtained as a yellow solid (108 mg, 93%).

Melting point (°C): 233 – 234. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H), 2.46 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.4, 161.8, 146.9, 139.3, 138.5, 135.8, 130.3, 129.6, 129.2, 126.4, 121.4, 114.6, 112.7, 55.6, 21.5. IR (neat) $cm^{-1}$: 2918 (C-H stretch methyl), 2842 (C-H stretch methyl), 1707 (C=O stretch ketone), 1255 (aryl-O stretch). HR-MS (ESI) *m/z*: calculated mass 292.1080 $[M + H]^+$, found 292.1074.

### 3-(4-fluorophenyl)-6-methyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.31)

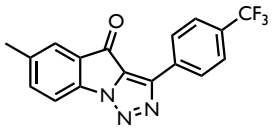


The general procedure was followed using 133 mg of compound **3.13** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (100% dichloromethane). The title compound was obtained as a yellow solid (76 mg, 68%).

Melting point (°C): 219 – 220. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.38 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.63 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.21 (t, *J* = 8.7 Hz, 2H), 2.46 (s, 3H). $^{13}$C-NMR (151 MHz, $CDCl_3$): δ 176.3, 164.4 (d, *J* = 251.6 Hz), 146.0, 139.6, 138.8, 136.0, 130.3, 130.0 (d, *J*

= 8.6 Hz), 129.9, 126.5, 125.1 (d, *J* = 3.2 Hz), 116.3 (d, *J* = 21.9 Hz), 112.8, 21.4. IR (neat) $cm^{-1}$: 2927 (C-H stretch methyl), 1713 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 280.0881 $[M + H]^+$, found 280.0880.

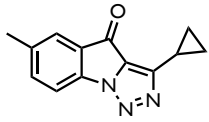
### 6-methyl-3-(4-(trifluoromethyl)phenyl)-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.32)



The general procedure was followed using 153 mg of compound **3.14** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (6/4 heptane/ethyl acetate). The title compound was obtained as a yellow solid (105 mg, 80%).

Melting point (°C): 212 – 213. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 7.9 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 2.46 (s, 3H). $^{13}$C-NMR (151 MHz, $CDCl_3$): δ 176.2, 145.1, 139.8, 138.7, 136.3, 132.3 (q, *J* = 32.6 Hz), 131.9, 130.7, 129.8, 127.9, 126.7, 126.1 (q, *J* = 3.7 Hz), 123.1 (q, *J* = 272.3 Hz), 113.0, 21.5. IR (neat) $cm^{-1}$: 2927 (CH stretch methyl), 1713 (C=O stretch ketone), 1325 (C-$CF_3$ stretch). HR-MS (ESI) *m/z*: calculated mass 330.0849 $[M + H]^+$, found 330.0848.

### 3-cyclopropyl-6-methyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.33)

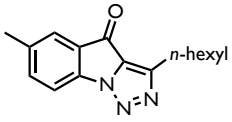


The general procedure was followed using 111 mg of compound **3.15** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellow solid (82 mg, 91%).

Melting point (°C): 157 – 158. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.51 (s, 1H), 7.41 (d, *J* = 7.9 Hz, 1H), 2.42 (s, 3H), 2.24 – 2.15 (m, 1H), 1.29 – 1.23 (m, 2H), 1.21 – 1.13 (m, 2H). $^{13}$C-NMR (101 MHz,

$CDCl_3$): δ 176.5, 152.5, 139.2, 138.6, 135.8, 130.3, 129.8, 126.2, 112.5, 21.4, 9.9, 8.3. IR (neat) $cm^{-1}$: 3082 (C-H stretch cyclopropyl), 3005 (C-H stretch cyclopropyl), 2920 (C-H stretch methyl), 1703 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 226.0975 $[M + H]^+$, found 226.0974.

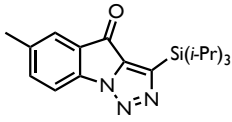
### 3-hexyl-6-methyl-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.34)




The general procedure was followed using 129 mg of compound **3.16** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (85/15 heptane/ethyl acetate). The title compound was obtained as a yellow solid (99 mg, 92%).

Melting point (°C): 79 – 80. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.53 (s, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 2.90 – 2.85 (m, 2H), 2.42 (s, 3H), 1.88 – 1.77 (m, 2H), 1.42 – 1.26 (m, 6H), 0.87 (t, *J* = 7.0 Hz, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.8, 148.8, 139.3, 138.8, 135.9, 131.4, 130.3, 126.3, 112.6, 31.6, 29.0, 28.4, 26.1, 22.7, 21.4, 14.2. IR (neat) $cm^{-1}$: 2943 (C-H stretch), 2923 (C-H stretch), 2852 (C-H stretch), 1707 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 270.1601 $[M + H]^+$, found 270.1605.

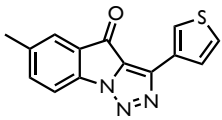
### 6-methyl-3-(triisopropylsilyl)-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.36)




The general procedure was followed using 158 mg of compound **3.18** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (9/1 heptane/ethyl acetate). Purification yielded 90 mg of an inseparable mixture of starting material **3.18** and the desired compound **3.36**. Based on $^1$H-NMR, 34% of the desired product was formed.

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 2.42 (s, 3H), 1.66 – 1.57 (m, 3H), 1.12 (d, *J* = 7.5 Hz, 18H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 177.3, 145.1, 141.0, 139.1, 138.8, 136.0, 130.3, 126.5, 112.8, 21.4, 18.6, 11.3. IR (neat) $cm^{-1}$: 2941 (C-H stretch), 2889 (C-H stretch), 2865 (C-H stretch), 1718 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 342.1996 $[M + H]^+$, found 342.1995.

### 6-methyl-3-(thiophen-3-yl)-4*H*-[1,2,3]triazolo[1,5-*a*]indol-4-one (3.37)



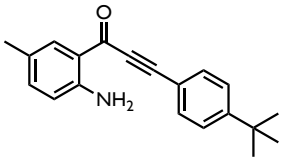

The general procedure was followed using 128 mg of compound **3.19** (0.40 mmol, 1.0 equiv). The crude mixture was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a yellow solid (91 mg, 85%).

Melting point (°C): 200 – 201. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.31 (t, *J* = 1.9 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.63 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 2.39 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.0, 140.5, 139.2, 138.0, 136.0, 130.2, 129.8, 129.4, 128.3, 126.5, 126.1, 126.0, 112.7, 20.7. IR (neat) $cm^{-1}$: 3080 (C-H stretch thiophene), 2920 (C-H stretch methyl), 1707 (C=O stretch ketone). HRMS (ESI) *m/z*: calculated mass 268.0539 $[M + H]^+$, found 268.0546.

## 7.3.4. A complementary pathway for the synthesis of triazolo[1,5-*a*]indolones

### *7.3.4.1. Carbonylative Sonogashira coupling*

**1-(2-amino-5-methylphenyl)-3-(4-(*tert*-butyl)phenyl)prop-2-yn-1-one (3.38)**

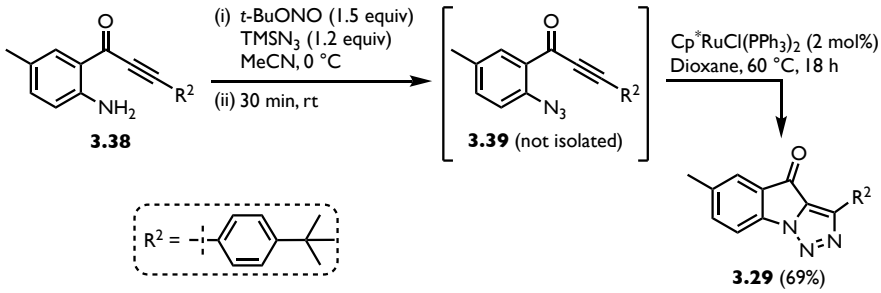



Chamber A of a flame-dried two-chamber reactor (Figure 7.2) was filled with palladium(II) chloride (8.9 mg, 0.05 mmol, 5 mol%) and Xantphos (29.0 mg, 0.05 mmol, 5 mol%). The reactor was brought under nitrogen atmosphere by two consecutive vacuum-nitrogen cycles. Next, chamber B was filled with 2 mL of dry degassed toluene, 58 μL formic acid (1.5 mmol, 1.5 equiv) and 117 μL mesyl chloride (1.5 mmol, 1.5 equiv). In chamber A, 2 mL of dried degassed dioxane was added, followed by 127 μL of 2-bromo-4-methylaniline (98 wt%, 1.0 mmol, 1.0 equiv), 376 μL of 4-*tert*-butylphenylacetylene (96 wt%, 2.0 mmol, 2.0 equiv) and 418 μL of triethylamine (3.0 mmol, 3.0 equiv). Finally, 418 μL triethylamine (3.0 mmol, 3.0 equiv) was added by injection through the septum in chamber B and instant gas formation was observed. After 2 minutes, the reactor was immersed in an oil-bath at 100 °C.

After 18 hours, the reactor was brought to room temperature and the residual pressure was released carefully by removing one of the caps. As carbon monoxide is a highly toxic gas, the reaction was stirred at room temperature for another 15 minutes to ensure that all carbon monoxide gas was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. Chamber A was rinsed five times with 2 mL of ethyl acetate and these fractions were added to the same flask. After the addition of 1 gram Celite®535, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The title compound was obtained as a deep red viscous oil (224 mg, 77%). This procedure is based on reference [265].

$^1$H-NMR (400 MHz, $CDCl_3$): δ 7.96 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 6.25 (brd, 2H), 2.30 (s, 3H), 1.35 (s, 9H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 179.6, 154.1, 149.2, 136.7, 133.9, 132.7, 125.8, 125.2, 119.0, 117.7, 117.0, 92.8, 87.1, 35.2, 31.2, 20.5. IR (neat) cm$^{-1}$: 3445 (N-H stretch amine), 2962 (C-H stretch methyl), 2867 (C-H stretch methyl), 2191 (C≡C stretch alkyne), 1629 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 292.1696 $[M + H]^+$, found 292.1690.

*7.3.4.2. Two-step, one-pot azidation/cycloaddition procedure*




**Scheme 7.1** Two-step one-pot azidation/cycloaddition procedure: conversion of aniline **3.38** into azide **3.39**, followed by a ruthenium-catalyzed [3+2] cycloaddition.

Compound **3.38** (117 mg, 0.40 mmol, 1.0 equiv) was dissolved in MeCN (5 mL) in a 10 mL round-bottomed flask and cooled to 0 °C in an ice bath. Then, *t*-BuONO (79 µL, 90 wt%, 0.60 mmol, 1.5 equiv) was added to this mixture, followed by a dropwise addition of $TMSN_3$ (67 µL, 95 wt%, 0.48 mmol, 1.2 equiv). The resulting solution was stirred at room temperature for 30 minutes. Next, the solvent was removed under reduced pressure. The concentrate was dissolved in dry degassed 1,4-dioxane (3 mL) and was added to a solution of $Cp^*RuCl(PPh_3)_2$ (6.37 mg, 8 µmol, 2 mol%) in 5 mL of the same solvent. The reaction vessel was sealed with a septum and subsequently purged with $N_2$. The reaction was allowed to stir at 60 °C for 18 hours. After addition of Celite®535 (1 gram) to the reaction mixture, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel (8/2 heptane/ethyl acetate). The desired compound **3.29** was obtained as a yellow solid (88 mg, 69%). This procedure is based on reference [254, 266].

Melting point (°C): 171 – 172. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 7.9 Hz, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 1H), 2.41 (s, 3H), 1.37 (s, 9H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 176.2, 154.3, 146.8, 139.3, 138.5, 135.8, 130.1, 129.7, 127.6, 126.4, 126.1, 125.8, 112.7, 35.1, 31.3, 21.4. IR (neat) $cm^{-1}$: 2954 (C-H stretch methyl), 2865 (C-H stretch methyl), 1711 (C=O stretch ketone). HR-MS (ESI) *m/z*: calculated mass 318.1601 $[M + H]^+$, found 318.1604.

## 7.3.5. X-ray structure of compound 3.29

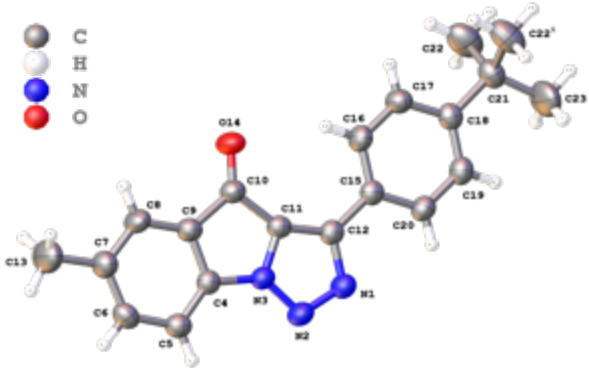


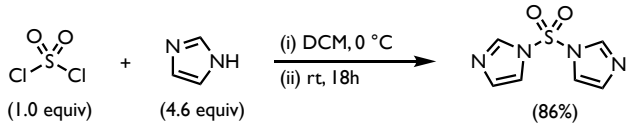

**Figure 7.3** Molecular structure of compound **3.29** with ellipsoids drawn at the 50% probability level. Symmetry code: (i) x, 1/2 – y, z.

**Table 7.3** Crystal data and structure refinement of compound **3.29**

| | |
|---|---|
| Empirical formula | $C_{20}H_{19}N_3O$ |
| Formula weight | 317.38 |
| Temperature/K | 293(1) |
| Crystal system | orthorhombic |
| Space group | Pnma |
| a/Å | 22.7454(19) |
| b/Å | 6.7360(5) |
| c/Å | 10.8129(7) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 90 |
| Volume/Å$^3$ | 1656.7(2) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.272 |
| μ/mm$^{-1}$ | 0.080 |
| F(000) | 672.0 |
| Crystal size/mm$^3$ | 0.4 × 0.1 × 0.1 |
| Radiation | MoKα (λ = 0.71073 Å) |
| 2Θ range for data collection/° | 5.198 to 52.74 |
| Index ranges | $-28 \leq h \leq 28$, $-8 \leq k \leq 7$, $-13 \leq l \leq 13$ |
| Reflections collected | 9675 |
| Independent reflections | 1838 [$R_{int}$ = 0.0273, $R_{sigma}$ = 0.0250] |
| Data/restraints/parameters | 1838/0/143 |
| Goodness-of-fit on $F^2$ | 1.071 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0530, $wR_2$ = 0.1303 |
| Final R indexes [all data] | $R_1$ = 0.0723, $wR_2$ = 0.1430 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.16/-0.18 |

## 7.4. Experimental details of chapter 4

### 7.4.1. 1,1'-sulfonyldiimidazole synthesis




**Scheme 7.2** Synthesis of 1,1'-sulfonyldiimidazole from sulfuryl chloride and imidazole

To a suspension of imidazole (15.82 g, 99 wt%, 230 mmol, 4.6 equiv) in DCM (100 mL) at 0 °C, a solution of sulfuryl chloride (4.13 mL, 98.5 wt%, 50 mmol, 1.0 equiv) in DCM (25 mL) was added dropwise. The reaction mixture was allowed to gradually warm to room temperature while stirring for 18 hours. Next, the straw-colored solution was filtered and washed excessively with DCM. The resulting filtrate was evaporated under reduced pressure. The crystalline material was recrystallized from boiling isopropyl alcohol (75 mL). After washing with cold isopropyl alcohol and drying under reduced pressure, 8.53 g (86%) of analytically pure 1,1'-sulfonyldiimidazole was obtained in the form of thick colorless needles. This procedure is based on reference [368].

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.30 (s, 1H), 7.14 (s, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 136.7, 132.5, 117.5.

### 7.4.2. Aryl fluorosulfate synthesis

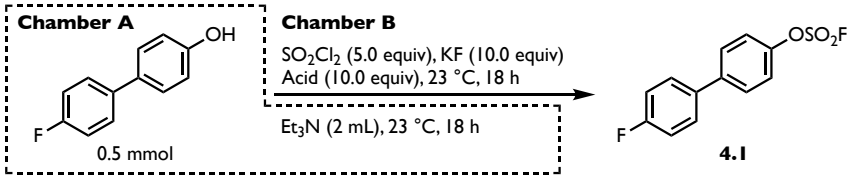
#### *7.4.2.1. Optimization study*

**Sulfuryl chloride as precursor**

*(1) Acid screening in chamber B*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride (337 mg, 2.5 mmol, 5.0 equiv) and potassium fluoride (290 mg, 5.0 mmol, 10.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv) and triethylamine (2 mL). Finally, 10 equivalents of the appropriate acid were added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.4)

**Table 7.4** Acid screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.



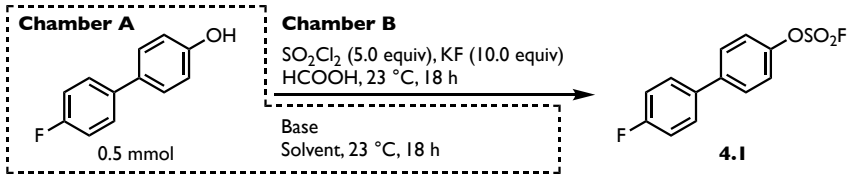

| Entry | Acid | Yield (%)[a] |
|---|---|---|
| 1 | Acetic acid | 16 |
| 2 | Lactic acid | 6 |
| 3 | Formic acid | 34 |
| 4 | Pyruvic acid | 4 |
| 5 | Trifluoroacetic acid | 7 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard.

*(2) Base and solvent screening in chamber A*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride (337 mg, 2.5 mmol, 5.0 equiv) and potassium fluoride (290 mg, 5.0 mmol, 10.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), the appropriate base and solvent. Finally, 0.2 mL (= 10 equiv) or 1 mL formic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.5)

**Table 7.5** Base and solvent screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.




| Entry | HCOOH (mL) | Base (equiv) | Solvent (mL) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 0.2 | $Et_3N$ (15.0) | MeCN, 1 | 75 |
| 2 | 0.2 | $Et_3N$ (15.0) | DCM, 1 | 75 |
| 3 | 0.2 | DMAP (5.0) | MeCN, 4 | 77 |
| 4 | 1.0 | DMAP (5.0) | MeCN, 4 | >99 |
| 5 | 1.0 | DMAP (3.0) | MeCN, 4 | 82 |
| 6 | 1.0 | DABCO (3.0) | MeCN, 4 | 51 |

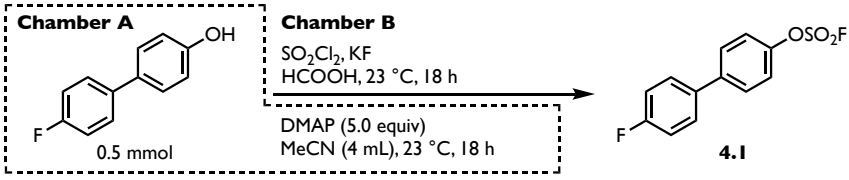
| | | | | |
|---|---|---|---|---|
| 7 | 1.0 | TMG (3.0) | MeCN, 4 | 48 |
| 8 | 1.0 | TMEDA (3.0) | MeCN, 4 | 47 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard. DMAP = 4-dimethyl aminopyridine, DABCO = 1,4-diazabicyclo[2.2.2]octane, TMG = 1,1,3,3-tetramethyl guanidine, TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine, MeCN = acetonitrile, DCM = dichloromethane.

*(3) Optimization of the amount of $SO_2Cl_2$, KF and HCOOH in chamber B*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride and potassium fluoride. Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), 4-dimethylaminopyridine (305 mg, 2.5 mmol, 5.0 equiv) and acetonitrile (4 mL). Finally, formic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.6)

**Table 7.6** Optimization of the amount of $SO_2Cl_2$, KF and HCOOH for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.




| Entry | $SO_2Cl_2$ (equiv) | KF (equiv) | HCOOH (mL) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 5.0 | 10.0 | 1.0 | >99 |
| 2 | 4.0 | 8.0 | 0.8 | >99 |
| 3 | 4.0 | 6.0 | 0.6 | 95 |
| 4 | 3.0 | 6.0 | 0.6 | 93 |
| 5 | 3.2 | 2.0 | 0.4 | 87 |
| 6 | 2.0 | 4.0 | 0.4 | 84 |

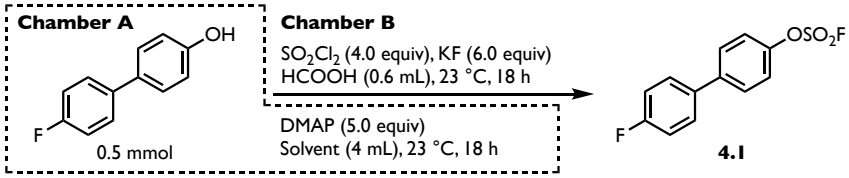
[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard.

*(4) Solvent screening in chamber A*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride (270 mg, 2.0 mmol, 4.0 equiv) and potassium fluoride (174 mg, 3.0 mmol, 6.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), 4-dimethyl aminopyridine (305 mg, 2.5 mmol, 5.0 equiv) and solvent (4 mL). Finally,

0.6 mL formic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.7)

**Table 7.7** Solvent screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.



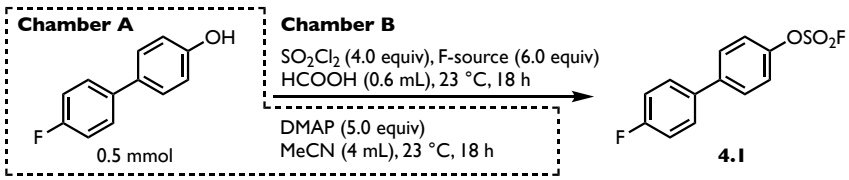

| Entry | Solvent | Yield (%)[a] |
|---|---|---|
| 1 | DMSO | Traces |
| 2 | MEK | 11 |
| 3 | EtOAc | 10 |
| 4 | DMC | 38 |
| 5 | MeCN | 95 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard. DMSO = dimethyl sulfoxide, MEK = methyl ethyl ketone, EtOAc = ethyl acetate, DMC = dimethyl carbonate, MeCN = acetonitrile.

*(5) Fluoride source screening in chamber B*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride (270 mg, 2.0 mmol, 4.0 equiv) and the appropriate fluoride source (3.0 mmol, 6.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), 4-dimethylaminopyridine (305 mg, 2.5 mmol, 5.0 eq.) and acetonitrile (4 mL). Finally, 0.6 mL formic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.8)

**Table 7.8** Fluoride source screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.



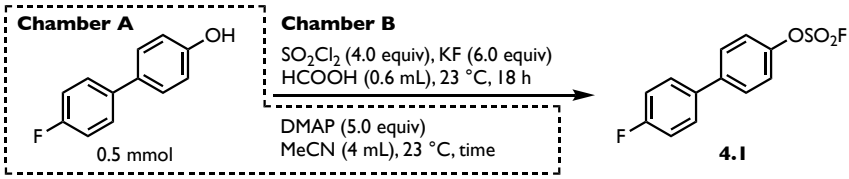
| Entry | F-source | Yield (%)[a] |
|---|---|---|
| 1 | KF | 95 |
| 2 | NaF | 86 |
| 3 | $NH_4F$ | 84 |
| 4 | $ZnF_2$ | Traces |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard.

*(6) Reaction time screening*

Chamber B of a flame-dried small two-chamber reactor was filled with sulfuryl chloride (270 mg, 2.0 mmol, 4.0 equiv) and potassium fluoride (174 mg, 3.0 mmol, 6.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), 4-dimethylaminopyridine (305 mg, 2.5 mmol, 5.0 equiv) and acetonitrile (4 mL). Finally, 0.6 mL formic acid was added by injection through the septum in chamber B. The reaction was stirred for the appropriate amount of time at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.9)

**Table 7.9** Reaction time screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with sulfuryl chloride as precursor.




| Entry | Time (h) | Yield (%)[a] |
|---|---|---|
| 1 | 1 | 55 |
| 2 | 2 | 86 |
| 3 | 5 | 92 |
| 4 | 18 | 95 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard.

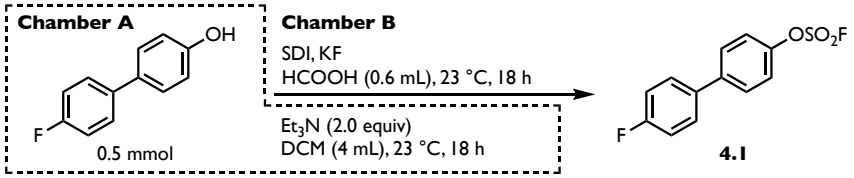
## 1,1'-Sulfonyldiimidazole as precursor

*(1) Optimization of the amount of SDI and KF in chamber B*

Chamber B of a flame-dried small two-chamber reactor was filled with 1,1'-sulfonyldiimidazole and potassium fluoride. Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), triethylamine (139 μL, 1.0 mmol, 2.0 equiv) and dichloromethane

(4 mL). Finally, 0.6 mL formic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.10)

**Table 7.10** Optimization of the amount of SDI and KF for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with 1,1'-sulfonyldiimidazole as precursor.



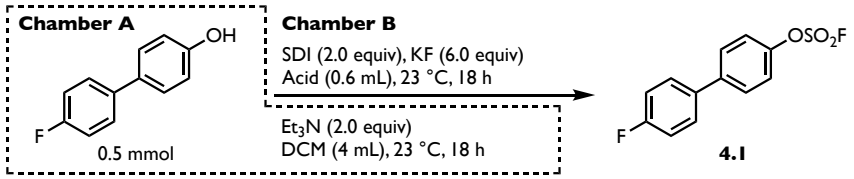

| Entry | SDI (equiv) | KF (equiv) | Yield (%)[a] |
|---|---|---|---|
| 1 | 4.0 | 6.0 | >99 |
| 2 | 3.0 | 6.0 | >99 |
| 3 | 2.0 | 6.0 | 81 |
| 4 | 2.0 | 4.0 | 73 |
| 5 | 1.5 | 6.0 | 76 |
| 6 | 1.5 | 3.0 | 61 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard.

*(2) Acid screening in chamber B*

Chamber B of a flame-dried small two-chamber reactor was filled with 1,1'-sulfonyldiimidazole (198 mg, 1.0 mmol, 2.0 equiv) and potassium fluoride (174 mg, 3.0 mmol, 6.0 equiv). Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), triethylamine (139 µL, 1.0 mmol, 2.0 equiv) and dichloromethane (4 mL). Finally, 0.6 mL of the appropriate acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.11)

**Table 7.11** Acid screening for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with 1,1'-sulfonyldiimidazole as precursor.



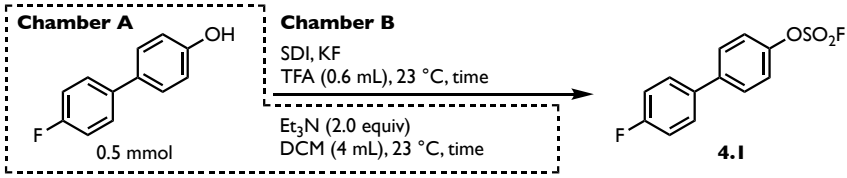
| Entry | Acid | Yield (%)[a] |
|---|---|---|
| 1 | Formic acid | 81 |
| 2 | Formic acid | 82[b] |
| 3 | Formic acid | 89[c] |
| 4 | Methanesulfonic acid | 35 |
| 5 | Trifluoroacetic acid | >99 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard. [b]The reaction was performed at 40 °C. [c]8 equivalents of KF were used.

*(3) Optimization of the amount of SDI and KF in chamber B and screening of the reaction time*

Chamber B of a flame-dried small two-chamber reactor was filled with the appropriate amount of 1,1'-sulfonyldiimidazole and potassium fluoride. Next, chamber A was charged with 96 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 0.5 mmol, 1.0 equiv), triethylamine (139 µL, 1.0 mmol, 2.0 equiv) and dichloromethane (4 mL). Finally, 0.6 mL the trifluoroacetic acid was added by injection through the septum in chamber B. The reaction was stirred for 18 hours at room temperature. Trifluorotoluene was added as an internal standard and the reaction mixture was analyzed by $^{19}$F-NMR. (Table 7.12)

**Table 7.12** Optimization of the amount of SDI and KF, and screening of the reaction time for the fluorosulfation of 4-fluoro-4'-hydroxybiphenyl with 1,1'-sulfonyldiimidazole as precursor.




| Entry | SDI (equiv) | KF (equiv) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|
| 1 | 2.0 | 6.0 | 18 | >99 |
| 2 | 2.0 | 4.0 | 18 | >99 |
| 3 | 1.5 | 4.5 | 18 | >99 |
| 4 | 1.5 | 4.0 | 18 | >99(96)[b] |
| 5 | 1.5 | 3.0 | 18 | 93 |
| 6 | 1.3 | 6.0 | 18 | 89 |
| 7 | 1.5 | 4.0 | 2 | 84 |
| 8 | 1.5 | 4.0 | 6 | 94 |

[a]Determined by $^{19}$F-NMR using trifluorotoluene as an internal standard. [b]Isolated yield.

*7.4.2.2. General procedures*

**Procedure A**

Chamber B of a flame-dried small two-chamber reactor (Figure 7.2) was filled with 1,1'-sulfonyldiimidazole (SDI, 297 mg, 1.5 mmol, 1.5 equiv) and potassium fluoride (KF, 232 mg, 4.0 mmol, 4.0 equiv). Next, chamber A was charged with the appropriate (hetero)aryl alcohol (1.0 mmol), triethylamine (279 μL, 2.0 mmol, 2.0 equiv) and dichloromethane (DCM, 4 mL). Finally, 1 mL trifluoroacetic acid (TFA) was added by injection through the septum in chamber B and instant gas formation was observed.

After 18 hours stirring at room temperature, one of the caps was carefully removed to release the residual pressure. The reaction was stirred for another 15 minutes to ensure that all sulfuryl fluoride was extracted out of the fume hood. Next, the content of chamber A was transferred to a 100 mL round-bottomed flask. Chamber A was rinsed five times with 2 mL of dichloromethane and these fractions were added to the same flask. After the addition of 1 gram Celite®545, the solvent was removed under reduced pressure. The crude product was purified by solid-phase flash column chromatography on silica gel.

An instructional video of this procedure is available on https://doi.org/10.1021/acs.orglett.7b02522

**Procedure B**

Identical to procedure A, except that *N*,*N*-diisopropylethylamine (DIPEA, 524 μL, 3.0 mmol, 3.0 equiv) was used as base and acetonitrile (MeCN, 4 mL) as solvent in chamber A.

**Large scale synthesis of 2-bromophenyl fluorosulfate**

Chamber B of a flame-dried large two-chamber reactor (Figure 7.4) was filled with 1,1'-sulfonyldiimidazole (5.95 g, 30.0 mmol, 1.5 equiv) and potassium fluoride (4.65 g, 80.0 mmol, 4.0 equiv). Next, chamber A was charged with 2-bromophenol (98 wt%, 3.53 g, 20.0 mmol, 1.0 equiv), triethylamine (5.58 mL, 40.0 mmol, 2.0 equiv) and dichloromethane (80 mL). Finally, 20 mL trifluoroacetic acid was added by injection through the septum in chamber B and instant gas formation was observed.

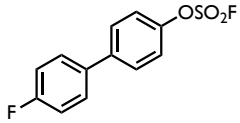
After 18 hours stirring at room temperature, one of the caps was carefully removed to release the residual pressure. The reaction was stirred for another 15 minutes to ensure that all sulfuryl fluoride was extracted out of the fume hood. Next, the content of chamber A was transferred to a 250 mL round-bottomed flask. Chamber A was rinsed five times with 10 mL of dichloromethane and these fractions were added to the same flask. The solvent was removed under reduced pressure. The residue was dissolved in 50 mL of ethyl acetate and washed successively with 1M HCl (3 x 50 mL), saturated $NaHCO_3$ (3 x 50 mL), and brine (1 x 50 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo to give analytically pure 2-bromophenyl fluorosulfate (4.92 g, 96%).

**Figure 7.4** Large two-chamber reactor[43-44] with an inner volume of approximately 400 mL

**Caution!** After reaction, chamber B was quenched with NaOH (1M) to neutralize trifluoroacetic acid and the *in situ* formed HF. The alkaline solution was discarded in basic waste. Etching of the glassware was seen after multiple experiments.

*7.4.2.3. Reaction scope*

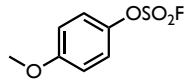
**4-fluoro-[1,1'-biphenyl]-4-yl sulfurofluoridate (4.1)**



General procedure A was followed using 192 mg of 4-fluoro-4'-hydroxybiphenyl (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (heptane, 100%). The title compound was obtained as a white solid (258 mg, 96%).

$R_f$ = 0.39 (heptane/ethyl acetate, 9/1). Melting point = 47 – 49 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.52 (dd, *J* = 8.1, 5.5 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.16 (t, *J* = 8.5 Hz, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 163.1 (d, *J* = 247.9 Hz), 149.5, 141.2, 135.6 (d, *J* = 3.3 Hz), 129.1, 129.0, 121.4, 116.1 (d, *J* = 21.6 Hz). $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.2, -114.7 (m). IR (neat) cm$^{-1}$: 1437, 1232, 921, 815. CHN: calculated for $C_{12}H_8F_2O_3S$: C 53.33%, H 2.98%, N 0.00%; found: C 53.43%, H 3.26%, N 0.00%.

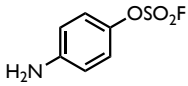
**4-methoxyphenyl sulfurofluoridate (4.2)**



General procedure A was followed using 125 mg of 4-methoxyphenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether, 100%). The title compound was obtained as a colorless oil (188 mg, 91%).

$R_f$ = 0.57 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 9.2 Hz, 2H), 3.83 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 159.4, 143.7, 122.1, 115.3, 55.9. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 35.9. These data are in agreement with literature data.[278]

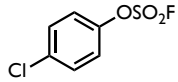
**4-aminophenyl sulfurofluoridate (4.3)**



General procedure A was followed using 110 mg of 4-aminophenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (heptane/ethyl acetate, 7/3). The title compound was obtained as a brown solid (171 mg, 89%).

$R_f$ = 0.48 (heptane/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 3.84 (brd, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 146.9, 142.2, 121.8, 115.6. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 35.5. These data are in agreement with literature data.[201]

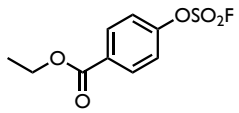
**4-chlorophenyl sulfurofluoridate (4.4)**



General procedure A was followed using 130 mg of 4-chlorophenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether, 100%). The title compound was obtained as a colorless oil (183 mg, 87%).

$R_f$ = 0.81 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 148.5, 134.8, 130.7, 122.5. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.2. These data are in agreement with literature data.[287]

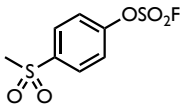
**ethyl 4-((fluorosulfonyl)oxy)benzoate (4.5)**



General procedure A was followed using 168 mg of ethyl 4-hydroxybenzoate (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (heptane/ethyl acetate, 99/1). The title compound was obtained as a colorless oil (236 mg, 95%).

$R_f$ = 0.37 (heptane/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 165.0, 152.9, 132.1, 131.1, 121.0, 61.7, 14.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 38.2. These data are in agreement with literature data.[278]

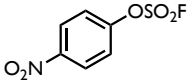
### 4-(methylsulfonyl)phenyl sulfurofluoridate (4.6)



General procedure A was followed using 178 mg of 4-(methylsulfonyl)phenol (97 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 5/5). The title compound was obtained as a white solid (238 mg, 94%).

$R_f$ = 0.39 (petroleum ether/diethyl ether, 3/7). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 3.09 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 153.1, 141.2, 130.4, 122.3, 44.6. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 38.7. These data are in agreement with literature data.[278]

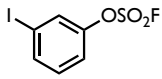
### 4-nitrophenyl sulfurofluoridate (4.7)



General procedure A was followed using 141 mg of 4-nitrophenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 95/5). The title compound was obtained as a yellowish oil (188 mg, 85%).

$R_f$ = 0.45 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 8.9 Hz, 2H), 7.56 (d, *J* = 8.9 Hz, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 153.5, 147.5, 126.3, 122.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 39.0. These data are in agreement with literature data.[201]

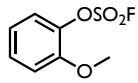
### 3-iodophenyl sulfurofluoridate (4.8)



General procedure A was followed using 222 mg of 3-iodophenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether, 100%). The title compound was obtained as a colorless oil (281 mg, 93%).

$R_f$ = 0.74 (petroleum ether/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.74 (m, 1H), 7.73 – 7.68 (m, 1H), 7.38 – 7.31 (m, 1H), 7.25 – 7.18 (m, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 149.8, 138.1, 131.7, 130.2, 120.5, 94.1. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.7. These data are in agreement with literature data.[287]

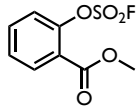
### 2-methoxyphenyl sulfurofluoridate (4.9)



General procedure A was followed using 125 mg of 2-methoxyphenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/ethyl acetate, 95/5). The title compound was obtained as a light yellowish oil (190 mg, 92%).

$R_f$ = 0.47 (petroleum ether/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.29 (m, 2H), 7.09 – 7.03 (m, 1H), 7.03 – 6.96 (m, 1H), 3.92 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 151.4, 139.2, 129.7, 122.5, 121.0, 113.6, 56.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 39.1. These data are in agreement with literature data.[278]

### methyl 2-((fluorosulfonyl)oxy)benzoate (4.10)

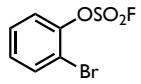


General procedure B was followed using 154 mg of methyl 2-hydroxybenzoate (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica

gel (heptane/ethyl acetate, 95/5). The title compound was obtained as a light yellowish oil (220 mg, 94%).

$R_f$ = 0.22 (heptane/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.14 – 8.07 (m, 1H), 7.70 – 7.62 (m, 1H), 7.54 – 7.47 (m, 1H), 7.44 – 7.39 (m, 1H), 3.97 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 164.0, 148.7, 134.5, 133.1, 128.9, 124.0, 122.6, 52.9. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 41.1. IR (neat) cm$^{-1}$: 2957, 1727, 1447, 1231, 1139, 911, 806. CHN: calculated for $C_8H_7FO_5S$: C 41.04%, H 3.01%, N 0.00%; found: C 41.21%, H 3.10%, N 0.00%.

### 2-bromophenyl sulfurofluoridate (4.11)

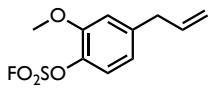



General procedure A was followed using 177 mg of 2-bromophenol (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether, 100%). The title compound was obtained as a light yellowish oil (237 mg, 93%).

The large scale procedure was followed using 3.53 g of 2-bromophenol (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by aqueous workup. The title compound was obtained as a light yellowish oil (4.92 g, 96%).

$R_f$ = 0.72 (petroleum ether/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.66 (m, 1H), 7.50 – 7.39 (m, 2H), 7.34 – 7.27 (m, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 147.4, 134.8, 130.1, 129.3, 122.8, 115.7. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 40.9. IR (neat) cm$^{-1}$: 1449, 1233, 908, 812. CHN: calculated for $C_6H_4BrFO_3S$: C 28.25%, H 1.58%, N 0.00%; found: C 28.72%, H 1.72%, N 0.00%.

### 4-allyl-2-methoxyphenyl sulfurofluoridate (4.12)

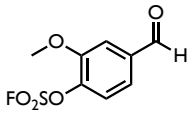



General procedure A was followed using 166 mg of eugenol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase

flash column chromatography on silica gel (petroleum ether/diethyl ether, 98/2). The title compound was obtained as a colorless oil (235 mg, 95%).

$R_f$ = 0.60 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.3 Hz, 1H), 6.88 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 6.02 – 5.88 (m, 1H), 5.18 – 5.14 (m, 1H), 5.14 – 5.07 (m, 1H), 3.90 (s, 3H), 3.41 (d, *J* = 6.7 Hz, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 151.1, 142.3, 137.5, 136.4, 122.2, 120.9, 117.0, 113.7, 56.2, 40.1. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 38.9. These data are in agreement with literature data.[201]

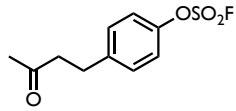
### 4-formyl-2-methoxyphenyl sulfurofluoridate (4.13)



General procedure A was followed using 154 mg of vanillin (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 7/3). The title compound was obtained as a white solid (230 mg, 98%).

$R_f$ = 0.13 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.57 (s, 1H), 7.54 – 7.48 (m, 2H), 3.99 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 190.5, 152.1, 142.9, 137.2, 124.1, 123.2, 112.3, 56.6. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 40.5. These data are in agreement with literature data.[201]

### 4-(3-oxobutyl)phenyl sulfurofluoridate (4.14)

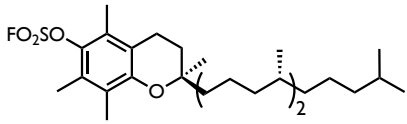


General procedure A was followed using 166 mg of raspberry ketone (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 7/3). The title compound was obtained as a colorless oil (238 mg, 97%).

$R_f$ = 0.13 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.30 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 2.79 (t, *J* = 7.3 Hz, 2H), 2.16 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 207.2,

148.5, 142.2, 130.4, 120.9, 44.7, 30.1, 28.9. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.8. IR (neat) cm$^{-1}$: 2935, 1716, 1445, 1232, 1138, 912, 815. CHN: calculated for $C_{10}H_{11}FO_4S$: C 48.78%, H 4.50%, N 0.00%; found: C 48.83%, H 4.68%, N 0.00%.

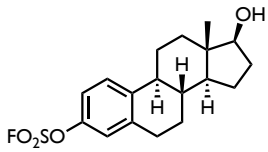
### (*R*)-2,5,7,8-tetramethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl sulfurofluoridate (4.15)



General procedure B was followed using 444 mg of D-α-tocopherol (97 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 98/2). The title compound was obtained as a colorless oil (507 mg, 99%).

$R_f$ = 0.70 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 2.61 (t, *J* = 6.7 Hz, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H), 1.91 – 1.73 (m, 2H), 1.60 – 1.03 (m, 24H), 0.91 – 0.82 (m, 12H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 151.2, 142.1, 127.6, 126.2, 124.5, 118.6, 75.9, 40.1, 39.5, 37.6, 37.5, 37.4, 33.0, 32.8, 31.0, 28.1, 25.0, 24.6, 24.0, 22.9, 22.8, 21.1, 20.8, 19.9, 19.8, 13.7 (d, *J* = 2.7 Hz), 12.8 (d, *J* = 2.6 Hz), 12.1. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 40.8. These data are in agreement with literature data.[201]

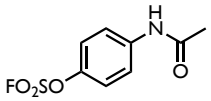
### (8*R*,9*S*,13*S*,14*S*,17*S*)-17-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl sulfurofluoridate (4.16)



General procedure B was followed using 281 mg of β-estradiol (97 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 5/5). The title compound was obtained as a white solid (342 mg, 96%).

$R_f$ = 0.29 (petroleum ether/diethyl ether, 5/5). Melting point = 103 – 105 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.7 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 7.03 (s, 1H), 3.74 (t, *J* = 8.3 Hz, 1H), 2.95 – 2.77 (m, 2H), 2.39 – 2.29 (m, 1H), 2.29 – 2.20 (m, 1H), 2.17 – 2.07 (m, 1H), 2.01 – 1.89 (m, 2H), 1.77 – 1.67 (m, 1H), 1.55 – 1.18 (m, 8H), 1.03 – 0.87 (m, 1H), 0.79 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 148.1, 141.3, 139.8, 127.4, 120.7, 117.7, 81.9, 50.2, 44.2, 43.3, 38.4, 36.7, 30.7, 29.7, 26.9, 26.2, 23.2, 11.1. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.8. IR (neat) cm$^{-1}$: 3599, 3287, 2920, 1444, 1231, 909, 797. CHN: calculated for $C_{18}H_{23}FO_4S$: C 61.00%, H 6.54%, N 0.00%; found: C 60.10%, H 6.55%, N 0.00%.

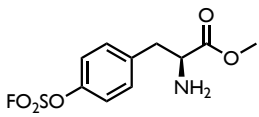
**4-acetamidophenyl sulfurofluoridate (4.17)**




General procedure B was followed using 154 mg of paracetamol (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 2/8). The title compound was obtained as a white solid (229 mg, 98%).

$R_f$ = 0.56 (diethyl ether, 100%). Melting point = 152 – 154 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.7 Hz, 2H), 7.45 (brd, 1H), 7.29 (d, *J* = 8.7 Hz, 2H), 2.20 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 168.6, 145.9, 138.3, 121.7, 121.3, 24.7. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.7. IR (neat) cm$^{-1}$: 3268, 3092, 1666, 1435, 1233, 1138, 906, 799. CHN: calculated for $C_8H_8FNO_4S$: C 41.20%, H 3.46%, N 6.01%; found: C 41.42%, H 3.57%, N 5.78%.

**methyl (*S*)-2-amino-3-(4-((fluorosulfonyl)oxy)phenyl) propanoate (4.18)**

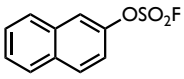



General procedure B was followed using 236 mg of L-tyrosine methyl ester hydrochloride (98 wt%, 1.0 mmol, 1.0 equiv) and 699 µL of *N*,*N*-diisopropylethylamine (4.0 mmol, 4.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (ethyl

acetate, 100%). The title compound was obtained as a yellow oil (274 mg, 99%).

$R_f$ = 0.49 (ethyl acetate, 100%). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.23 (m, 4H), 3.76 – 3.67 (m, 4H), 3.10 (dd, *J* = 13.7, 5.3 Hz, 1H), 2.89 (dd, *J* = 13.7, 7.9 Hz, 1H), 1.58 (brd, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 175.1, 149.0, 138.5, 131.3, 120.9, 55.6, 52.2, 40.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.9. IR (neat) cm$^{-1}$: 2956, 1739, 1443, 1230, 1139, 912, 804. CHN: calculated for $C_{10}H_{12}FNO_5S$: C 43.32%, H 4.36%, N 5.05%; found: C 42.86%, H 4.42%, N 4.84%.

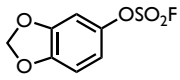
**naphthalen-2-yl sulfurofluoridate (4.19)**




General procedure A was followed using 146 mg of 2-naphthol (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 9/1). The title compound was obtained as a white solid (219 mg, 97%).

$R_f$ = 0.54 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.93 (m, 1H), 7.93 – 7.86 (m, 2H), 7.82 (m, 1H), 7.64 – 7.55 (m, 2H), 7.48 – 7.40 (m, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 147.7, 133.5, 132.6, 131.0, 128.2, 128.1, 127.8, 127.5, 119.1, 119.0. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.2. These data are in agreement with literature data.[201]

**benzo[*d*][1,3]dioxol-5-yl sulfurofluoridate (4.20)**

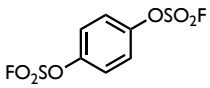



General procedure A was followed using 141 mg of sesamol (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 98/2). The title compound was obtained as a colorless oil (210 mg, 95%).

$R_f$ = 0.50 (petroleum ether/diethyl ether, 95/5). $^1$H-NMR (400 MHz, $CDCl_3$): δ 6.88 – 6.76 (m, 3H), 6.05 (s, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$):

δ 148.8, 147.8, 144.2, 114.1, 108.4, 103.1, 102.7. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.0. These data are in agreement with literature data.[201]

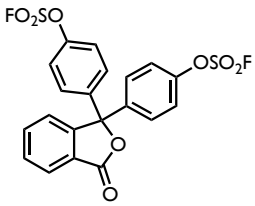
### 1,4-phenylene bis(sulfurofluoridate) (4.21)



General procedure A was followed using 55.6 mg of hydroquinone (99 wt%, 0.5 mmol, 0.5 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 95/5). The title compound was obtained as a white (126 mg, 92%).

$R_f$ = 0.52 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 4H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 149.1, 123.5. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.8. These data are in agreement with literature data.[201]

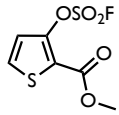
### (3-oxo-1,3-dihydroisobenzofuran-1,1-diyl)bis(4,1-phenylene) bis(sulfurofluoridate) (4.22)



General procedure A was followed using 161 mg of phenolphthalein (99 wt%, 0.5 mmol, 0.5 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 5/5). The title compound was obtained as a white solid (237 mg, 98%).

$R_f$ = 0.40 (petroleum ether/diethyl ether, 5/5). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.05 – 7.95 (m, 1H), 7.84 – 7.75 (m, 1H), 7.68 – 7.62 (m, 1H), 7.60 – 7.55 (m, 1H), 7.50 – 7.42 (m, 4H), 7.39 – 7.31 (m, 4H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 168.7, 150.4, 150.2, 141.1, 135.0, 130.4, 129.4, 126.8, 125.4, 124.0, 121.5, 89.7. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 37.7. These data are in agreement with literature data.[201]

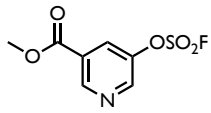
**methyl 3-((fluorosulfonyl)oxy)thiophene-2-carboxylate (4.23)**



General procedure A was followed using 163 mg of methyl 3-hydroxythiophene-2-carboxylate (97 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 95/5). The title compound was obtained as a colorless oil (226 mg, 94%).

$R_f$ = 0.30 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 5.5 Hz, 1H), 7.11 (d, *J* = 5.5 Hz, 1H), 3.92 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 159.9, 145.7, 130.9, 122.5, 122.0, 52.8. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 39.6. These data are in agreement with literature data.[279]

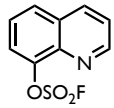
**methyl 5-((fluorosulfonyl)oxy)nicotinate (4.24)**



General procedure A was followed using 156 mg of methyl 5-hydroxynicotinate (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 9/1). The title compound was obtained as a white solid (207 mg, 88%).

$R_f$ = 0.70 (petroleum ether/diethyl ether, 5/5). Melting point = 54 – 56 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.84 (s, 1H), 8.29 (s, 1H), 4.00 (s, 3H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 163.9, 150.8, 146.8, 146.4, 129.7, 127.9, 53.2. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 38.8. IR (neat) cm$^{-1}$: 3064, 1723, 1447, 1229, 917, 809. CHN: calculated for $C_7H_6FNO_5S$: C 35.75%, H 2.57%, N 5.96%; found: C 35.72%, H 2.60%, N 5.74%.

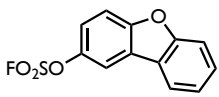
**quinolin-8-yl sulfurofluoridate (4.25)**



General procedure A was followed using 147 mg of 8-hydroxyquinoline (99 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (heptane/ethyl acetate, 98/2). The title compound was obtained as a white solid (220 mg, 97%).

$R_f$ = 0.09 (heptane/ethyl acetate, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 9.09 – 8.99 (m, 1H), 8.26 – 8.17 (m, 1H), 7.92 – 7.83 (m, 1H), 7.78 – 7.70 (m, 1H), 7.63 – 7.48 (m, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 151.9, 145.9, 140.5, 136.0, 130.1, 128.8, 126.0, 122.8, 121.4. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 40.1. These data are in agreement with literature data.[279]

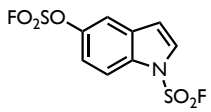
**dibenzo[*b*,*d*]furan-2-yl sulfurofluoridate (4.26)**




General procedure A was followed using 188 mg of 2-hydroxydibenzofuran (98 wt%, 1.0 mmol, 1.0 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum ether/diethyl ether, 98/2). The title compound was obtained as a white solid (260 mg, 98%).

$R_f$ = 0.69 (petroleum ether/diethyl ether, 9/1). Melting point = 94 – 95 °C. $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.88 (m, 2H), 7.67 – 7.58 (m, 2H), 7.57 – 7.50 (m, 1H), 7.46 – 7.36 (m, 2H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 157.4, 155.0, 145.7, 128.8, 125.9, 123.5, 123.4, 121.3, 119.8, 113.5, 113.2, 112.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 36.2. IR (neat) cm$^{-1}$: 1443, 1228, 923, 801. CHN: calculated for $C_{12}H_7FO_4S$: C 54.14%, H 2.65%, N 0.00%; found: C 54.27%, H 2.70%, N 0.00%.

**1-(fluorosulfonyl)-1*H*-indol-5-yl sulfurofluoridate (4.27)**




General procedure B was followed using 68.6 mg of 5-hydroxyindole (97 wt%, 0.5 mmol, 0.5 equiv). The crude reaction mixture was purified by solid-phase flash column chromatography on silica gel (petroleum

ether/diethyl ether, 95/5). The title compound was obtained as a colorless oil (145 mg, 97%).

$R_f$ = 0.68 (petroleum ether/diethyl ether, 9/1). $^1$H-NMR (400 MHz, $CDCl_3$): δ 8.06 – 7.95 (m, 1H), 7.72 – 7.63 (m, 1H), 7.62 – 7.55 (m, 1H), 7.48 – 7.38 (m, 1H), 6.93 – 6.83 (m, 1H). $^{13}$C-NMR (101 MHz, $CDCl_3$): δ 147.2, 133.9, 131.6, 128.7 (d, *J* = 1.6 Hz), 118.8, 115.3, 114.6, 110.8 (d, *J* = 1.3 Hz). $^{19}$F-NMR (376 MHz, $CDCl_3$): δ 55.3, 36.8. These data are in agreement with literature data.[279]

*7.4.2.4. Pressure profile of a typical fluorosulfation reaction*

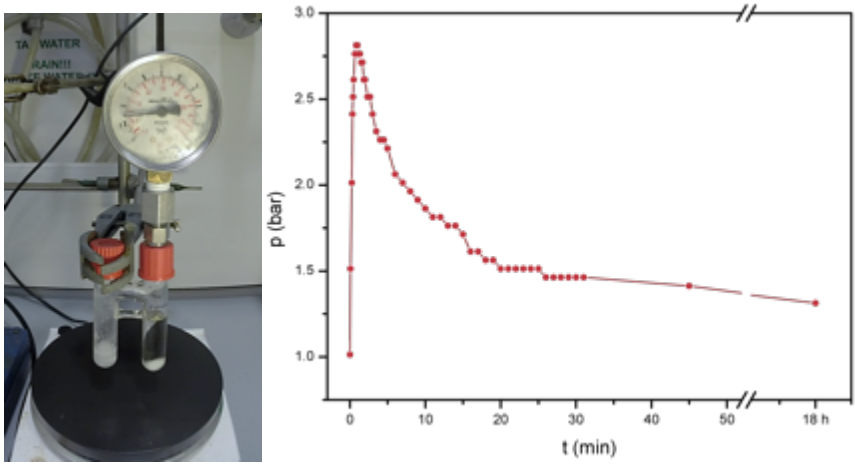



**Figure 7.5** A manometer attached to a two-chamber reactor (left). Pressure profile of a typical fluorosulfation reaction (right).

A study of the pressure was conducted in order to verify that safety measures concerning the glassware were met. It has been described that the two-chamber vessels can minimally resist 5 bar, hence we ensure that we never surpass this limit.

A calculation was done to determine the theoretical pressure generated inside. The ideal gas law was first used to know the amount of air already inside the vessel. The remaining volume amounts to 15 mL, since 5 mL solvent is already present.

$$n = \frac{pV}{RT} = \frac{1\ \text{atm x}\ 0.015\ \text{L}}{0.082\ \frac{\text{L x atm}}{\text{K x mol}}\ \text{x}\ 298\ \text{K}} = 0.61\ \text{x}\ 10^{-3}\ \text{mol}$$

The amount of air is 0.61 mmol. Next, we know the amount of generated $SO_2F_2$ gas since it is equal to the amount of SDI added, 1.50 mmol. The total amount of gas after generation is then 2.11 mmol. The pressure can then be calculated as follows:

$$p = \frac{nRT}{V} = \frac{0.00211 \text{ mol x } 0.082 \frac{\text{L x atm}}{\text{K x mol}} \text{ x } 298 \text{ K}}{0.015 \text{ L}} = 3.44 \text{ atm}$$

The theoretical pressure is thus 3.44 atm or 3.49 bar. When we measure this using a manometer (range: 1-10 bar), we notice a rapid increase of the pressure from the moment of addition to 60 s thereafter (Figure 7.5). At this point, we measure the maximum pressure of 2.8 bar.

In this way, we are certain that all the applicable safety measures are met, and no danger of explosion is present.

## 7.5. Experimental details of chapter 5

### 7.5.1. Bis(trifluoromethyl)carbinol synthesis by employing COgen as a CO source.

#### *7.5.1.1. General procedures*

**Procedure A**

In a glovebox filled with argon, chamber A of a two-chamber system (Figure 7.2) was charged with aryl bromide (0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (122.0 mg, 3.5 equiv) and DMF (3 mL) in that order. The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. To chamber B was added 9-methyl-9*H*-fluorene-9-carbonyl chloride (174.4 mg, 0.72 mmol), $HBF_4P(t\text{-}Bu)_3$ (2.1 mg, 1 mol%), $Pd(cod)Cl_2$ (2.1 mg, 1 mol%), DMF (3 mL) and $Cy_2NMe$ (308 μL, 2.0 equiv). The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. The two-chamber system was removed from the glovebox and placed in a preheated heating block and left under stirring at 80 °C for 18 hours. The reaction mixture was cooled to room temperature and $TMSCF_3$ (196 μL, 2.2 equiv) was added under argon atmosphere. The two-chamber was sealed and left under stirring at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (10 mL), filtered through a plug of celite, washed with water (3 x 10 mL) and brine (2 x 10 mL). The water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography.

**Procedure B**

In a glovebox filled with argon, chamber A of a two-chamber system (Figure 7.2) was charged with aryl bromide (0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (52.3 mg, 1.5 equiv) and DMF (3 mL) in that order. The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. To chamber B was added 9-methyl-9*H*-fluorene-9-carbonyl chloride (174.4 mg, 0.72 mmol), $HBF_4P(t\text{-}Bu)_3$ (2.1 mg, 1 mol%), $Pd(cod)Cl_2$ (2.1 mg, 1 mol%), DMF (3 mL) and $Cy_2NMe$ (308 μL, 2.0 equiv). The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. The two-chamber system was removed from the glovebox and placed in a

preheated heating block and left under stirring at 80 °C for 18 hours. The reaction mixture was cooled to room temperature and KF (87.2 mg, 2.5 equiv) and $TMSCF_3$ (196 µL, 2.2 equiv) was added under argon atmosphere. The two-chamber was sealed and left under stirring at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (10 mL), filtered through a plug of celite, washed with water (3 x 10 mL) and brine (2 x 10 mL). The water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, concentrated under reduced pressure and purified by flash column chromatography.

**Procedure C**

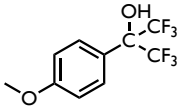
Identical to Procedure B, except the reaction mixture was washed with 1M HCl (1 x 10 mL) and $NaHCO_3$ (3 x 10 mL) instead of water (3 x 10 mL) and brine (2 x 10 mL).

**Procedure D**

Identical to procedure C, except using aryl fluorosulfates (0.6 mmol) instead of aryl bromides. Furthermore, 1.0 M TBAF in THF (0.6 mL, 0.6 mmol) was added before filtration of the reaction mixture through a plug of celite.

*7.5.1.2. Reaction scope*

### 1,1,1,3,3,3-Hexafluoro-2-(4-methoxyphenyl)propan-2-ol (5.1)

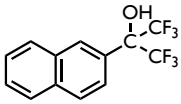



The title compound was prepared according to procedure A, starting from 4-bromoanisole (112.2 mg, 0.6 mmol). The product was isolated by flash column chromatography (diethyl ether/formic acid/pentane 2:2:96) as a colorless solid (133.2 mg, 81%). The isolated yield reported in chapter 5 is an average of two runs (78% and 81%).

Melting point (°C): 99 – 101. $^1$H-NMR (400 MHz, $CD_3OD$): δ 7.63 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 3.82 (s, 3H). $^{13}$C-NMR (101 MHz,

$CD_3OD$): δ 162.3, 129.5-129.4 (m), 124.6 (q, *J* = 287.7 Hz), 124.3, 114.7, 78.3 (apparent sep, *J* = 29.6 Hz), 55.8. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -78.2. HRMS $C_{10}H_8F_6O_2$ [M-H$^+$]; calculated: 273.0356, found: 273.0357.

### 1,1,1,3,3,3-Hexafluoro-2-(naphthalen-2-yl)propan-2-ol (5.2)

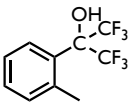


The title compound was prepared according to procedure A, starting from 2-bromonaphthalene (124.2 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/formic acid/pentane 10:2:88) as a colorless solid (138.5 mg, 78%). The isolated yield reported in chapter 5 is an average of two runs (74% and 78%).

Melting point (°C): 78 – 81. $^1$H-NMR (400 MHz, $CD_3OD$): δ 8.30 (s, 1H), 7.91-7.84 (m, 3H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.54-7.48 (m, 2H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 135.1, 134.0, 129.9, 129.6, 129.1, 128.5 (m), 128.4, 127.7, 124.7 (q, *J* = 287.9 Hz) 124.6-124.5 (m), 78.7 (apparent sep, *J* = 29.6 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.0. HRMS $C_{13}H_8F_6O$ [M-H$^+$]; calculated: 293.0407, found: 293.0410.

When the title compound was prepared according to procedure D, starting from naphthalen-2-yl sulfurofluoridate (135.7 mg, 0.6 mmol), the product was isolated in 82% (144.2 mg) as a colorless solid. The isolated yield reported in chapter 5 is an average of two runs (81% and 82%).

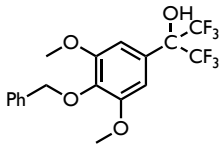
### 1,1,1,3,3,3-Hexafluoro-2-(o-tolyl)propan-2-ol (5.3)



The title compound was prepared according to procedure A, starting from 2-bromotoluene (103.6 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 15:85) as a colorless oil (134.4 mg, 87%). The isolated yield reported in chapter 5 is an average of two runs (74% and 87%).

$^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.33-7.19 (m, 3H), 2.62 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 140.9, 134.9, 130.6, 130.2, 129.0-128.9 (m), 126.5, 126.0 (q, *J* = 286.6 Hz), 81.8 (apparent sep, *J* = 29.3 Hz), 23.2. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -75.0. HRMS $C_{10}H_8F_6O$ [M-H$^+$]; calculated: 257.0407, found: 257.0409.

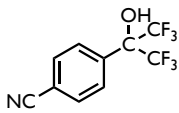
### 2-(4-(Benzyloxy)-3,5-dimethoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.4)



The title compound was prepared according to procedure B, starting from 2-benzyl-5-bromo-1,3-dimethoxybenzene (194.0 mg, 0.6 mmol). The product was isolated by flash column chromatography (diethyl ether/pentane/formic acid 2:98:2) as colorless crystals (169.8 mg, 69%). The isolated yield reported in chapter 5 is an average of two runs (65% and 69%).

Melting point (°C): 106 – 107. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.46 (d, *J* = 7.0 Hz, 2H), 7.35-7.26 (m, 3H), 7.04 (s, 2H), 4.98 (s, 2H), 3.82 (s, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 154.6, 139.3, 138.9, 129.5, 129.1, 129.0, 128.2, 125.2 (q, *J* = 287.1 Hz), 105.8, 78.3 (apparent sep, *J* = 29.6 Hz), 76.0, 56.7. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.3. HRMS $C_{18}H_{16}F_6NO_3$ [M+Na$^+$]; calculated: 433.0845 found: 433.0846.

### 4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)benzonitrile (5.5)

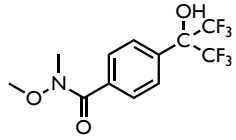


The title compound was prepared according to procedure A, starting from 4-bromobenzonitrile (109.2 mg, 0.6 mmol). The product was isolated by flash column chromatography (diethyl ether/formic acid/pentane 3:2:95 to 5:2:93) as a yellow solid (128.7 mg, 80%). The isolated yield reported in chapter 5 is an average of two runs (78% and 80%).

Melting point (°C): 117 – 121. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.93 (d, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 8.6 Hz, 2H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 137.6, 133.3, 129.3-129.2 (m), 124.1 (q, *J* = 287.9 Hz), 118.9, 115.2, 78.3 (apparent sep, *J* = 29.9 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.2. HRMS $C_{10}H_5F_6NO$ [M+H$^+$]; calculated: 270.0348, found: 270.0350.

The title compound was additionally synthesized according to procedure B, except using 4-chlorobenzonitrile (82.5 mg, 0.6 mmol) at 120 °C instead of 4-bromobenzonitrile at 80 °C. The product was isolated by flash column chromatography (diethyl ether/formic acid/pentane 4:2:94 to 5:2:93) as a yellow solid (105.9 mg, 66%).

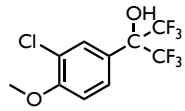
### 4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-*N*-methoxy-*N*-methylbenzamide (5.6)



The title compound was prepared according to procedure B, starting from 4-bromo-*N*-methoxy-*N*-methylbenzamide (146.5 mg, 0.6 mmol). The product was isolated by flash column chromatography (ethyl acetate/pentane 25:75) as a white solid (161.1 mg, 81%). The isolated yield reported in chapter 5 is an average of two runs (79% and 81%).

Melting point (°C): 141 – 143. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.84 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 3.59 (s, 3H), 3.36 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 170.8, 137.0, 135.1, 129.0, 128.2-128.1 (m), 124.4 (q, *J* = 287.9 Hz), 78.4 (apparent sep, *J* = 29.7 Hz), 61.7, 34.0 (brd s). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.3. HRMS $C_{12}H_{11}F_6NO_3$ [M+Na$^+$]; calculated: 354.0535, found: 354.0539.

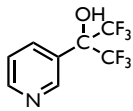
### 2-(3-Chloro-4-methoxyphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.7)



The title compound was prepared according to procedure B, starting from 4-bromo-2-chloroanisole (132.7 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 30:70) as a colorless oil (131.2 mg, 71%). The isolated yield reported in chapter 5 is an average of two runs (70% and 71%).

$^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.70 (s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 3.93 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 157.7, 129.9, 128.0, 125.3, 124.9 (q, *J* = 286.8 Hz), 123.5, 113.0, 77.9 (apparent sep, *J* = 30.0 Hz), 56.7. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.7. HRMS $C_{10}H_6ClF_6O_2$ [M+H$^+$]; calculated: 309.0112, found: 309.0112.

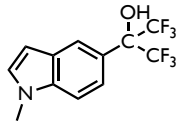
### 1,1,1,3,3,3-Hexafluoro-2-(pyridin-3-yl)propan-2-ol (5.8)



The title compound was prepared according to procedure A, starting from 3-bromopyridine (94.8 mg, 0.6 mmol). The product was isolated by flash column chromatography (ethyl acetate/pentane 30:70) as a colorless solid (128.6 mg, 91%). The isolated yield reported in chapter 5 is an average of two runs (87% and 91%).

Melting point (°C): 190 – 194. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 8.82 (s, 1H), 8.60 (dd, *J* = 5.0, 1.6 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.49 (dd, *J* = 8.2, 4.9 Hz, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 150.2, 147.4-147.3 (m), 135.7-135.6 (m), 128.1, 123.6, 122.8 (q, *J* = 287.9 Hz), 76.4 (apparent sep, *J* = 30.3 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.6. HRMS $C_8H_5F_6NO$ [M-H$^+$]; calculated: 244.0203, found: 244.0211.

### 1,1,1,3,3,3-Hexafluoro-2-(1-methyl-1*H*-indol-5-yl)propan-2-ol (5.9)

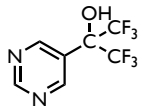


The title compound was prepared according to procedure B, starting from 5-bromo-1-methyl-1*H*-indole (126.0 mg, 0.6 mmol). After work-up, 1.0 M TBAF in THF (0.6 mL, 0.6 mmol) was added to the reaction mixture. The

product was isolated by flash column chromatography (ethyl acetate/pentane 10:90 to 50:50) as a yellow oil (145.5 mg, 82%). The isolated yield reported in chapter 5 is an average of two runs (75% and 82%).

$^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.98 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 1H), 7.11 (d, *J* = 3.1 Hz, 1H), 6.47 (d, *J* = 3.1 Hz, 1H), 3.68 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 138.5, 131.2, 129.6, 124.8 (q, *J* = 287.6 Hz), 122.9, 120.9, 120.7, 109.9, 102.3, 78.9 (apparent sep, *J* = 29.4 Hz), 32.8. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.2. HRMS $C_{12}H_9F_6NO$ [M+H$^+$]; calculated: 298.0661, found: 298.0665.

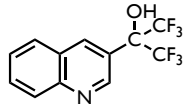
### 1,1,1,3,3,3-Hexafluoro-2-(pyrimidin-5-yl)propan-2-ol (5.10)



The title compound was prepared according to procedure B, starting from 5-bromopyrimidine (95.4 mg, 0.6 mmol). The product was isolated by flash column chromatography (diethyl ether/formic acid/pentane 10:2:88) as a colorless solid (109.5 mg, 74%). The isolated yield reported in chapter 5 is an average of two runs (70% and 74%).

Melting point (°C): 107 – 109. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 9.31 (s, 1H), 9.16 (s, 2H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 160.7, 157.0-156.9 (m), 127.6, 124.0 (q, *J* = 288.2 Hz), 77.1 (apparent sep, *J* = 30.8 Hz). $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.5. HRMS $C_7H_4F_6N_2O$ [M+H$^+$]; calculated: 247.0301, found: 247.0300.

### 1,1,1,3,3,3-Hexafluoro-2-(quinoline-3-yl)propan-2-ol (5.11)

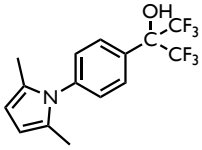


The title compound was prepared according to procedure B, starting from 3-bromoquinoline (124.8 mg, 0.6 mmol). The product was isolated by flash column chromatography (ethyl acetate/pentane 15:85 to 20:80) as a yellow

solid (144.1 mg, 81%). The isolated yield reported chapter 5 is an average of two runs (81% and 81%).

Melting point (°C): 250 – 256. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 9.12 (s, 1H), 8.74 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.89 (t, *J* = 7.7 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 148.9, 148.8-148.7 (m), 137.9, 132.8, 129.9, 129.1, 129.1, 128.4, 126.2, 123.0 (q, *J* = 288.2 Hz), 78.0 (apparent sep, *J* = 30.3 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.4. HRMS $C_{12}H_7F_6NO$ [M-H$^+$]; calculated: 294.0359, found: 294.0361.

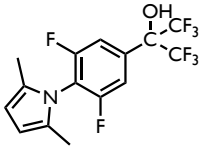
### 2-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.12)



The title compound was prepared according to procedure B, starting from 1-(4-bromophenyl)-2,5-dimethyl-1*H*-pyrrole (1.250 g, 5.0 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 15:85) as a colorless solid (1.240 g, 74%).

Melting point (°C): 153 – 155. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 5.82 (s, 2H), 2.00 (s, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 142.1, 132.0, 129.3, 129.3, 129.2-129.1 (m), 124.9 (q, *J* = 287.4 Hz), 107.3, 78.4 (apparent sep, *J* = 29.7 Hz), 13.1. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.34. HRMS $C_{15}H_{13}F_6NO$ [M+H$^+$]; calculated: 338.0974 found: 338.0974.

### 2-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)-3,5-difluorophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.13)

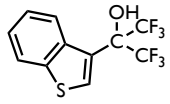


The title compound was prepared according to procedure B, starting from 1-(4-bromo-2,6-difluorophenyl)-2,5-dimethyl-1*H*-pyrrole (171.1 mg, 0.6 mmol). The product was isolated by flash column chromatography (diethyl

ether/pentane/formic acid 2:98:2) as white crystals (186.0 mg, 83%). The isolated yield reported in chapter 5 is an average of two runs (80% and 83%).

Melting point (°C): 107 – 108. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.55 (d, *J* = 8.6 Hz, 2H), 5.88 (s, 2H), 1.95 (s, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 160.4 (dd, *J* = 251.5, 4.5 Hz), 135.6 (t, *J* = 9.3 Hz), 130.0, 124.2 (q, *J* = 286.4 Hz), 119.0 (t, *J* = 17.0 Hz), 112.6 (d, *J* = 26.0 Hz), 108.1, 78.0 (apparent sep, *J* = 30.2 Hz), 12.1. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.4, -118.6. HRMS $C_{15}H_{11}F_8NO$ [M+H$^+$]; calculated: 374.0786 found: 374.0784.

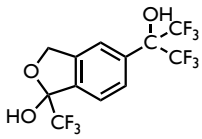
### 2-(Benzo[*b*]thiophen-3-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.14)




The title compound was prepared according to procedure B, starting from 3-bromothianaphtene (127.9 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 10:90 to 20:80) as a yellow oil (62.4 mg, 35%). The isolated yield reported in chapter 5 is an average of two runs (35% and 32%).

$^{1}$H-NMR (400 MHz, $CD_3OD$): δ 8.42 (d, *J* = 8.9 Hz, 1H), 7.91-7.89 (m, 2H), 7.41-7.35 (m, 2H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 141.4, 139.0, 129.3-129.2 (m), 126.6, 126.6, 125.7, 125.3, 124.6 (q, *J* = 288.4 Hz), 123.5, 79.7 (apparent sep, *J* = 30.3 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.2. HRMS $C_{11}H_6F_6OS$ [M-H$^+$]; calculated: 298.9971, found: 298.9982.

### 5-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-1-(trifluoromethyl)-1,3-dihydroisobenzofuran-1-ol (5.15)

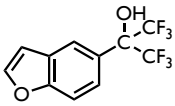



The title compound was prepared according to procedure B, starting from 5-bromoisobenzofuran-1(3*H*)-one (128.1 mg, 0.6 mmol), with the exception that 3.2 equiv $TMSCF_3$ was added (285 µL). The product was isolated by flash column chromatography (diethyl ether/pentane/formic

acid 2:98:2) as colorless crystals (186.0 mg, 58%). The isolated yield reported in chapter 5 is an average of two runs (51% and 58%).

Melting point (°C): 112 – 113. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.82 (d, *J* = 8.7 Hz, 1H), 7.80 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 1H), 5.30 (d, *J* = 13.0 Hz, 1H), 5.16 (d, *J* = 13.0 Hz, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 142.4, 138.4, 135.5, 128.3, 124.8, 124.4 (q, *J* = 286.0 Hz), 124.3 (q, *J* = 283.4 Hz), 121.6, 105.9 (q, *J* = 33.9 Hz), 78.5 (apparent sep, *J* = 29.6 Hz), 73.6. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.3, -85.0. HRMS $C_{12}H_7F_9O_3$ [M-H+]; calculated: 369.0179 found: 369.0183.

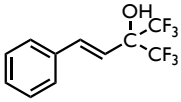
### 2-(Benzofuran-5-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.16)




The title compound was prepared according to procedure B, starting from 5-bromobenzofuran (118.2 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 25:75 to 30:70) as a colorless solid (130.5 mg, 77%). The isolated yield reported in chapter 5 is an average of two runs (71% and 77%).

Melting point (°C): 72 – 76. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 8.04 (s, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 156.8, 147.6, 128.9, 127.2, 124.5 (q, *J* = 287.7 Hz), 124.1, 121.6, 111.9, 107.8, 78.7 (apparent sep, *J* = 29.6 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.3. HRMS $C_{11}H_6F_6O_2$ [M-H+]; calculated: 283.0199, found: 283.0201.

### (*E*)-1,1,1-Trifluoro-4-phenyl-2-(trifluoromethyl)but-3-en-2-ol (5.17)



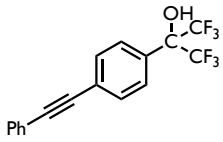

The title compound was prepared according to procedure B, starting from β-bromostyrene (E:Z 82:18) (109.8 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 20:80)

as a yellow oil (121.5 mg, 75%). The isolated yield reported in chapter 5 is an average of two runs (71% and 75%).

$^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.49 (d, *J* = 7.2 Hz, 2H), 7.39-7.31 (m, 3H), 7.17 (d, *J* = 16.0 Hz, 1H), 6.31 (d, *J* = 16.0 Hz, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 138.4, 136.3, 130.1, 129.9, 128.1, 125.1 (q, *J* = 287.6 Hz), 118.4, 77.7 (apparent sep, *J* = 29.7 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -78.5. HRMS $C_{11}H_8F_6O$ [M-H$^+$]; calculated: 269.0407, found: 269.0409.

The title compound was additionally prepared according to procedure B, starting from (Z)-β-bromostyrene (109.8 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 20:80) as a yellow oil (66.1 mg, 41%).

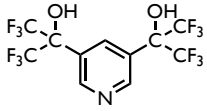
### 1,1,1,3,3,3-Hexafluoro-2-(4-(phenylethynyl)phenyl) propan-2-ol (5.18)




The title compound was prepared according to procedure B, starting from 1-bromo-4-(phenylethynyl)benzene (154.3 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 50:50) as a yellow solid (171.8 mg, 83%). The isolated yield reported in chapter 5 is an average of two runs (81% and 83%).

Melting point (°C): 66 – 72. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.60-7.57 (m, 2H), 7.39-7.36 (m, 3H), 4.83 (s, 1H). $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$): δ 132.2, 132.2, 131.4, 129.5, 129.2, 127.8, 125.8, 123.7 (q, *J* = 286.2 Hz), 123.3, 91.5, 88.6, 77.9 (apparent sep, *J* = 29.8 Hz). $^{19}$F-NMR (376 MHz, $(CD_3)_2CO$): δ -75.4. HRMS $C_{17}H_{10}F_6O$ [M+H$^+$]; calculated: 345.0709, found: 345.0704.

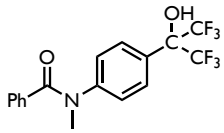
### 2,2'-(Pyridine-3,5-diyl)bis(1,1,1,3,3,3-hexafluoropropan-2-ol) (5.19)



The title compound was prepared according to procedure B, starting from 3,5-dibromopyridine (71.1 mg, 0.3 mmol, 0.5 equiv). The product was isolated by flash column chromatography (ethyl acetate/pentane 20:80) as a colorless solid (64.7 mg, 52%). The isolated yield reported in chapter 5 is an average of two runs (47% and 52%).

Melting point (°C): 153 – 159. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 9.02 (s, 2H), 8.52 (s, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 150.4, 135.9, 129.4, 124.2 (q, *J* = 287.9 Hz), 77.7 (apparent sep, *J* = 30.4 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.7. HRMS $C_{11}H_5F_{12}NO_2$ [M+H$^+$]; calculated: 412.0201, found: 412.0210.

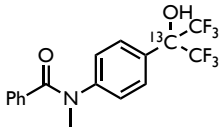
### *N*-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylbenzamide (5.20)




The title compound was prepared according to procedure C, starting from *N*-(4-bromophenyl)-*N*-methylbenzamide (174.1 mg, 0.6 mmol). The product was isolated by flash column chromatography (ethyl acetate/formic acid/pentane 16:4:80) as a colorless solid (178.5 mg, 79%). The isolated yield reported in chapter 5 is an average of two runs (75% and 79%).

Melting point (°C): 171 – 174. $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$): δ 7.67 (d, *J* = 8.5 Hz, 2H), 7.33-7.28 (m, 5H), 7.23-7.19 (m, 2H), 3.46 (s, 3H). $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$): δ 170.6, 147.5, 137.0, 130.4, 129.3, 129.1, 128.4-128.4 (m), 127.6, 123.8 (q, *J* = 287.9 Hz), 77.8 (apparent sep, *J* = 29.7 Hz), 38.1. $^{19}$F-NMR (376 MHz, $(CD_3)_2CO$): δ -75.6. HRMS $C_{17}H_{13}F_6NO_2$ [M+H$^+$]; calculated: 378.0923, found: 378.0928.

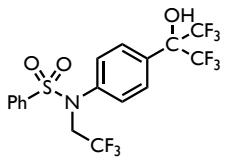
### [$^{13}$*C*]-*N*-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-methylbenzamide ($^{13}$C-5.20)



The title compound was prepared according to procedure C, starting from *N*-(4-bromophenyl)-*N*-methylbenzamide (174.1 mg, 0.6 mmol). 9-methyl-9*H*-fluorene-9-carbonyl-$^{13}$C chloride (175.5 mg, 0.72 mmol) was used to generate $^{13}$CO. The product was isolated by flash column chromatography (ethyl acetate/pentane 20:80) as a colorless solid (177.9 mg, 78%).

Melting point (°C): 171 – 174. $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$): δ 7.69-7.67 (m, 2H), 7.56 (s, 1H), 7.33-7.28 (m, 5H), 7.23-7.19 (m, 2H), 3.46 (s, 3H). $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$): δ 170.6, 147.5, 137.0, 130.3, 129.3, 129.1 (d, *J* = 49.0 Hz), 128.4-128.4 (m), 127.6 (d, *J* = 3.7 Hz), 123.8 (dq, *J* = 287.9 Hz, 66.6 Hz), 77.8 (sep, *J* = 29.7 Hz), 38.1. $^{19}$F-NMR (376 MHz, $(CD_3)_2CO$): δ -75.6 (d, *J* = 29.8 Hz). HRMS $C_{16}{}^{13}CH_{13}F_6NO_2$ [M+H$^+$]; calculated: 379.0957, found: 379.0953.

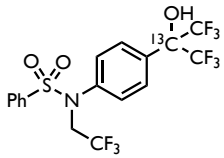
### *N*-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide (5.21)




The title compound was prepared according to procedure C, starting from *N*-(4-bromophenyl)-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide (236.5 mg, 0.6 mmol). The product was isolated by flash column chromatography (ethyl acetate/formic acid/pentane 10:2:88) as a colorless solid (202.2 mg, 70%). The isolated yield reported in chapter 5 is an average of two runs (69% and 70%).

Melting point (°C): 115 – 118. $^{1}$H-NMR (400 MHz, $(CD_3)_2CO$): δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.72-7.63 (m, 4H), 7.56 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.8 Hz, 2H), 4.59 (q, *J* = 8.6 Hz, 2H). $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$): δ 141.8, 138.5, 134.2, 131.6, 129.8, 129.6, 128.5-128.5 (m), 128.2, 124.9 (q, *J* = 277.6 Hz), 123.6 (q, *J* = 286.1 Hz), 77.7 (apparent sep, *J* = 29.8 Hz), 52.2 (q, *J* = 34.4 Hz). $^{19}$F-NMR (376 MHz, $(CD_3)_2CO$): δ -71.4, -75.5. HRMS $C_{17}H_{12}F_9NO_3S$ [M+H$^+$]; calculated: 482.0467, found: 482.0469.

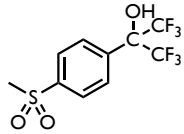
### [$^{13}C$]-*N*-(4-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)phenyl)-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide ($^{13}$C-5.21)



The title compound was prepared according to procedure C, starting from *N*-(4-bromophenyl)-*N*-(2,2,2-trifluoroethyl)benzenesulfonamide (236.5 mg, 0.6 mmol). 9-methyl-9*H*fluorene-9-carbonyl-$^{13}$C chloride (175.5 mg, 0.72 mmol) was used to generate $^{13}$CO. The product was isolated by flash column chromatography (ethyl acetate/pentane 1:8) as a colorless solid (214.5 mg, 74%).

Melting point (°C): 115 – 118. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 8.5, 2.4 Hz, 2H), 7.63-7.56 (m, 3H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 4.24 (q, *J* = 8.2 Hz, 2H). $^{13}$C-NMR (101 MHz, $(CD_3)_2CO$): δ 142.0, 138.8, 134.4, 131.7 (d, *J* = 48.8 Hz), 130.0, 129.8 (d, *J* = 3.7 Hz), 128.7-128.7 (m), 128.4, 125.1 (q, *J* = 279.3 Hz), 123.8 (dq, *J* = 287.9 Hz, 66.7 Hz), 77.9 (sep, *J* = 29.8 Hz), 52.4 (q, *J* = 34.4 Hz). $^{19}$F-NMR (376 MHz, $(CD_3)_2CO$): δ -71.4 (t, *J* = 8.6 Hz), -75.6 (d, *J* = 29.8 Hz). HRMS $C_{16}{}^{13}CH_{12}F_9NO_3S$ [M+H$^+$]; calculated: 483.0500, found: 483.0497.

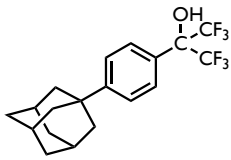
### 1,1,1,3,3,3-Hexafluoro-2-(4-(methylsulfonyl)phenyl) propan-2-ol (5.22)



The title compound was prepared from 4-(methylsulfonyl)phenyl sulfurofluoridate (152.5 mg, 0.6 mmol) according to procedure D. The product was isolated by flash column chromatography (pentane/diethyl ether/formic acid 70:28:2 to 60:38:2) as a colorless solid (106.5 mg, 55%). The isolated yield reported in chapter 5 is an average of two runs (55% and 62%).

Melting point (°C): 80 – 83. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 8.3 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H), 3.74 (s, 1H), 3.10 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 143.8, 138.4, 129.5-129.4 (m), 128.6, 124.2 (q, *J* = 287.9 Hz), 78.4 (apparent sep, *J* = 29.9 Hz), 44.1. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.3. HRMS $C_{10}H_8F_6O_3S$ [M+H$^+$]; calculated: 323.0171, found: 323.0173.

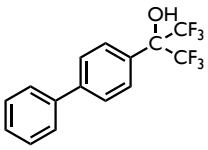
### 2-(4-((3*r*,5*r*,7*r*)-Adamantan-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.23)




The title compound was prepared according to procedure D, starting from 4-((3*r*,5*r*,7*r*)-adamantan-1-yl)phenyl sulfurofluoridate (186.2 mg, 0.6 mmol). The product was isolated by flash column chromatography (dichloromethane/pentane 20:80) as colorless crystals (187.7 mg, 83%). The isolated yield reported in chapter 5 is an average of two runs (79% and 83%).

Melting point (°C): 148 – 150. $^{1}$H-NMR (400 MHz, $CD_3OD$) δ 7.67 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.7 Hz, 2H), 2.08 (s, 3H), 1.95 (s, 6H), 1.85-1.77 (m, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 154.3, 129.6, 127.8, 126.0, 125.3 (q, *J* = 286.0 Hz), 78.4 (sep, *J* = 29.7 Hz), 44.1, 37.8, 37.3, 30.3. $^{19}$F-NMR (376 MHz, $CD_3OD$) δ -76.3. HRMS $C_{29}H_{20}F_6O$ [M-H$^+$]; calculated: 377.1346, found: 377.1357.

### 2-([1,1'-Biphenyl]-4-yl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.24)

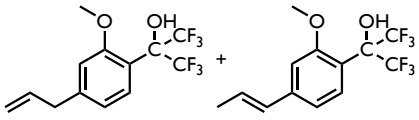



The title compound was prepared from [1,1'-biphenyl]-4-yl sulfurofluoridate (151.4, 0.6 mmol) according to procedure D. The product was isolated by flash column chromatography (diethyl ether/pentane 3:97

to 5:95) as a colorless solid (148.1 mg, 77%). The isolated yield reported in chapter 5 is an average of two runs (77% and 77%).

Melting point (°C): 108 – 111. $^{1}$H-NMR (400 MHz, $CD_3OD$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.35-7.31 (m, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 144.0, 141.2, 131.5, 129.9, 128.9, 128.6-128.6 (m), 128.1, 127.9, 124.5 (q, *J* = 287.8 Hz), 78.5 (apparent sep, *J* = 29.6 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$) δ -76.3. HRMS $C_{15}H_{10}F_6O$ [M+H$^+$]; calculated: 321.0709, found: 321.0704.

### 2-(4-Allyl-2-methoxyphenyl)-1,1,1,3,3,3-hexafluoro propan-2-ol and (*E*)-1,1,1,3,3,3-Hexafluoro-2-(2-methoxy-4-(prop-1-en-1-yl)phenyl)propan-2-ol (5.25)

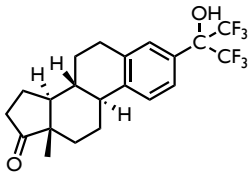


(1:1.5)

The title compounds were prepared from 4-allyl-2-methoxyphenyl sulfurofluoridate (147.8 mg, 0.6 mmol) according to procedure D. The products were isolated as an inseparable mixture by flash column chromatography (pentane/ethyl acetate/formic acid 96:3:1) as a light yellowish oil (156.3 mg, 83%, ratio 1:1). The isolated yield reported in chapter 5 is an average of two runs (83%, 1:1 ratio and 84%, 1:2 ratio).

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.9 Hz, 1H) 7.39 (d, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.90 (d, *J* = 1.7 Hz, 1H), 6.86 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H), 6.34-6.23 (m, 2H), 5.95-5.80 (m, 1H), 5.09-5.08 (m, 1H), 5.07-5.04 (m, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.34 (d, *J* = 6.7 Hz, 2H), 1.84 (d, *J* = 5.4 Hz, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 159.8, 159.7, 145.8, 143.0, 137.9, 131.1, 130.5-130.3 (m), 129.2, 124.5 (q, *J* = 287.7 Hz), 122.4, 119.6, 117.8, 117.5, 116.8, 114.2, 111.2, 80.3 (apparent sep, *J* = 30.4 Hz), 56.7, 40.8, 18.6. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.5, -75.6. HRMS $C_{13}H_{12}F_6O_2$ [M+H$^+$]; calculated: 315.0814, found: 315.0814.

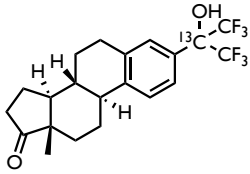
### (8*R*,9*S*,13*S*,14*S*)-3-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (5.26)



The title compound was prepared from (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl sulfurofluoridate (211.5 mg, 0.6 mmol) according to procedure D, with the exception that 3.2 equiv $TMSCF_3$ (285 µL) was added. The product was isolated by flash column chromatography (dichloromethane/ethyl acetate 100:0 to 95:5) as a colorless solid (179.3 mg, 71%). The isolated yield reported in chapter 5 is an average of two runs (71% and 72%).

Melting point (°C): 146 – 149. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.5 Hz, 1H), 7.43 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 3.35 (s, 1H), 2.98-2.96 (m, 2H), 2.52 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.45-2.41 (m, 1H), 2.36-2.29 (m, 1H), 2.21-1.96 (m, 4H), 1.70-1.42 (m, 6H), 0.92 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3CN$): δ 220.9, 143.5, 138.4, 128.5, 128.2, 126.8, 124.9-124.7 (m), 124.1 (q, *J* = 286.9 Hz), 78.1 (apparent sep, *J* = 29.7 Hz), 51.2, 48.7, 45.1, 38.7, 36.3, 32.5, 30.2, 27.0, 26.4, 22.2, 14.2. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.6. HRMS $C_{21}H_{22}F_6O_2$ [M+H$^+$]; calculated: 421.1597, found: 421.1600.

### (8*R*,9*S*,13*S*,14*S*)-3-(1,1,1,3,3,3-Hexafluoro-2-hydroxy propan-2-yl-2-$^{13}$*C*)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one ($^{13}$C-5.26)

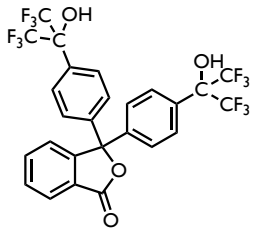


The title compound was prepared from (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene 3-yl sulfurofluoridate (211.5 mg, 0.6 mmol) according to procedure D, with the exception that 3.2 equiv $TMSCF_3$ (285 µL) was added. 9-methyl-9*H*-fluorene-9-carbonyl-$^{13}$C chloride (175.5 mg, 0.72 mmol) was used to generate $^{13}$CO. The product was isolated by flash column chromatography

(dichloromethane/ethyl acetate 100:0 to 95:5) as a colorless solid (180.6 mg, 72%).

Melting point (°C): 146 – 149. $^{1}$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.7 Hz, 1H), 7.43 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 3.32 (s, 1H), 2.99-2.95 (m, 2H), 2.52 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.47-2.40 (m, 1H), 2.37-2.29 (m, 1H), 2.21-1.96 (m, 4H), 1.71-1.42 (m, 6H), 0.92 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3CN$): δ 221.0, 143.5, 138.4 (d, *J* = 3.4 Hz), 128.6 (d, *J* = 48.4 Hz), 128.2, 126.8 (d, *J* = 3.6 Hz), 125.0-124.8 (m), 124.1 (dq, *J* = 287.2, 66.6 Hz), 78.1 (sep, *J* = 29.7 Hz), 51.3, 48.7, 45.1, 38.8, 36.3, 32.6, 30.2, 27.1, 26.4, 22.2, 14.3. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.6 (d, *J* = 30.4 Hz). HRMS $C_{20}{}^{13}CH_{22}F_6O_2$ [M+H$^+$]; calculated: 422.1630, found: 422.1634.

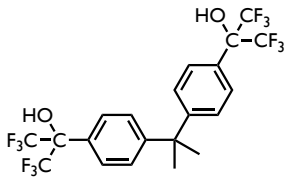
### 3,3-Bis(4-(1,1,1,3,3,3-hexafluoro-2-hydroxypropan-2-yl)phenyl)isobenzofuran-1(3*H*)-one (5.27)



The title compound was prepared from (3-oxo-1,3-dihydroisobenzofuran-1,1-diyl)bis(4,1-phenylene) bis(sulfurofluoridate) (144.7 mg, 0.3 mmol, 0.5 equiv) according to procedure D, with the exception that 3.2 equiv $TMSCF_3$ (285 µL) was added. The product was isolated by flash column chromatography (pentane/diethyl ether/formic acid 80:18:2) as a colorless solid (89.6 mg, 48%). The isolated yield reported in chapter 5 is an average of two runs (48% and 55%).

Melting point (°C): 231 – 236. $^{1}$H-NMR (400 MHz, $CD_3OD$) δ 7.97 (d, *J* = 7.7 Hz, 1H), 7.87-7.82 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 4H), 7.71-7.65 (m, 1H), 7.48 (d, *J* = 8.6 Hz, 4H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 170.9, 152.6, 143.8, 136.2, 133.4, 131.2, 128.8-128.6 (m), 128.1, 127.0, 126.2, 125.7, 124.4 (q, *J* = 287.7 Hz), 92.0, 78.3 (apparent sep, *J* = 29.9 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$) δ -76.3. HRMS $C_{26}H_{14}F_{12}O_4$ [M+H$^+$]; calculated: 619.0773, found: 619.0779.

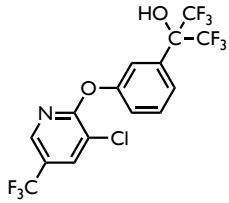
## 2,2'-(Propane-2,2-diylbis(4,1-phenylene))bis(1,1,1,3,3,3-hexafluoropropan-2-ol) (5.28)



The title compound was prepared from propane-2,2-diylbis(4,1-phenylene) bis(sulfurofluoridate) (117.7 mg, 0.3 mmol, 0.5 equiv) according to procedure D. The product was isolated by flash column chromatography (pentane/diethyl ether 98:2 to 80:20) as a colorless solid (101.4 mg, 64%). The isolated yield reported in chapter 5 is an average of two runs (64% and 69%).

Melting point (°C): 99 – 104. $^{1}$H-NMR (400 MHz, $CD_3OD$) δ 7.64 (d, *J* = 8.5 Hz, 4H), 7.34 (d, *J* = 8.5 Hz, 4H), 1.72 (s, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 153.4, 130.2, 128.0-127.9 (m), 124.6 (q, *J* = 287.6 Hz), 78.4 (apparent sep, *J* = 29.7 Hz), 43.9, 30.9. $^{19}$F-NMR (376 MHz, $CD_3OD$) δ -76.4. HRMS $C_{21}H_{16}F_{12}O_2$ [M-H$^+$]; calculated: 527.0886, found: 527.0888.

## 2-(3-((3-Chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.29)

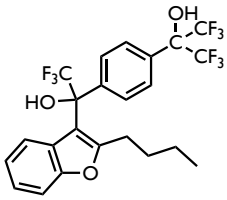


The title compound was prepared from 3-((3-chloro-5-(trifluoromethyl)pyridin-2-yl)oxy)phenyl sulfurofluoridate (223.0 mg, 0.6 mmol) according to procedure D. The product was isolated by flash column chromatography (pentane/diethyl ether 97:3) as a colorless oil (138.7 mg, 53%). The isolated yield reported in chapter 5 is an average of two runs (39% and 53%).

$^{1}$H-NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.59-7.51 (m, 2H), 7.33 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.46 (s, 1H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 162.3, 154.4, 143.8 (q, *J* = 4.5 Hz),

138.0 (q, *J* = 3.4 Hz), 134.6, 130.8, 125.4-125.2 (m), 124.5, 124.4 (q, *J* = 271.4 Hz), 124.4 (q, *J* = 287.9 Hz), 124.0 (q, *J* = 33.7 Hz), 121.8-121.7 (m), 120.6, 78.3 (apparent sep, *J* = 29.7 Hz). Traces of dibutylhydroxytoluene (BHT) are observed in the carbon-NMR. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -61.6, -75.5. HRMS $C_{15}H_7ClF_9NO_2$ [M+Na$^+$]; calculated: 461.9914, found: 461.9915.

### 2-(4-(1-(2-Butylbenzofuran-3-yl)-2,2,2-trifluoro-1-hydroxyethyl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (5.30)

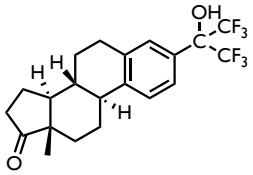



The title compound was prepared according to procedure D, starting from 4-(2-butylbenzofuran-3-carbonyl)phenyl sulfurofluoridate (225.8 mg, 0.6 mmol), with the exception that 3.2 equiv $TMSCF_3$ (285 μL) was added. The product was isolated by flash column chromatography (dichloromethane/pentane 40:60) as a colorless oil (187.7 mg, 73%). The isolated yield reported in chapter 5 is an average of two runs (68% and 73%).

$^1$HNMR (400 MHz, $CD_3OD$) δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.71 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 2.72-2.55 (m, 2H), 1.61-1.45 (m, 2H), 1.22 (sext, *J* = 8.5 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 159.8, 155.0, 143.4, 133.1, 129.0, 128.9, 128.1, 127.3 (q, *J* = 285.2 Hz), 124.4, 123.3, 123.1, 115.2, 111.3, 78.4 (app sep, *J* = 29.6 Hz), 78.2 (q, *J* = 30.1 Hz), 31.1, 28.7, 23.6, 14.0. $^{19}$F-NMR (376 MHz, $CD_3OD$) δ -76.0, -76.4. HRMS $C_{23}H_{19}F_9O_3$ [M+H$^+$]; calculated: 515.1263, found 515.1269.

7.5.2. Bis(trifluoromethyl)carbinol synthesis by employing $CO_2$ as a CO source

**(8*R*,9*S*,13*S*,14*S*)-3-(1,1,1,3,3,3-Hexafluoro-2-hydroxypropan-2-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (5.26)**



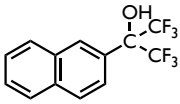
In a glovebox filled with argon, chamber A of a two-chamber system (Figure 7.2) was charged with (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*cyclopenta[*a*]phenanthren-3-yl sulfurofluoridate (211.5 mg, 0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (52.3 mg, 1.5 equiv) and DMF (3 mL) in that order. The chamber was tightly sealed with a screwcap fitted with a PTFE/silicone seal. To chamber B was added CsF (13.2 mg, 0.09 mmol), diphenyltetramethyldisilane (242.4 mg, 0.9 mmol) and DMSO (3.6 mL). The second chamber was sealed using a screwcap fitted with a PTFE/silicone seal. As the last reagent, $CO_2$ (25.2 mL, 1.02 mmol) was injected with a syringe through the septum outside the glovebox. The reaction mixture in chamber B was stirred at 23 °C, while chamber A was stirred at 80 °C for 18 hours. The reaction mixture was cooled to room temperature and KF (87.2 mg, 2.5 equiv) and $TMSCF_3$ (196 µL, 2.2 equiv) was added under argon atmosphere. The two-chamber was sealed and left under stirring at room temperature for 1 h. 1.0 M TBAF in THF (0.6 mL, 0.6 mmol) was added to the reaction mixture. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a plug of celite, washed with 1M HCl (1 x 10 mL) and saturated $NaHCO_3$ (3 x 10 mL). The water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was isolated by flash column chromatography (dichloromethane/ethyl acetate 100:0 to 95:5) as a colorless solid (171.5 mg, 68%).

Melting point (°C): 146 – 149. $^1$H-NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.5 Hz, 1H), 7.43 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 3.35 (s, 1H), 2.98-2.96

(m, 2H), 2.52 (dd, *J* = 18.8, 8.7 Hz, 1H), 2.45-2.41 (m, 1H), 2.36-2.29 (m, 1H), 2.21-1.96 (m, 4H), 1.70-1.42 (m, 6H), 0.92 (s, 3H). $^{13}$C-NMR (101 MHz, $CD_3CN$): δ 220.9, 143.5, 138.4, 128.5, 128.2, 126.8, 124.9-124.7 (m), 124.1 (q, *J* = 286.9 Hz), 78.1 (apparent sep, *J* = 29.7 Hz), 51.2, 48.7, 45.1, 38.7, 36.3, 32.5, 30.2, 27.0, 26.4, 22.2, 14.2. $^{19}$F-NMR (376 MHz, $CDCl_3$): δ -75.6. HRMS $C_{21}H_{22}F_6O_2$ [M+H$^+$]; calculated: 421.1597, found: 421.1600.

7.5.3. Bis(trifluoromethyl)carbinol synthesis by employing CO from a balloon.

**1,1,1,3,3,3-Hexafluoro-2-(naphthalen-2-yl)propan-2-ol (5.2)**




**Preparation of CO balloon**

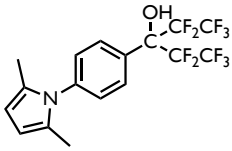
To a dry 50 mL flask was added *p*-toluenesulfonyl chloride (0.953 g, 5.0 mmol), toluene (10 mL) and $Cy_2NMe$ (2.14 mL, 10.0 mmol) under argon. The flask was fitted with septum with a balloon before formic acid (189 µL, 5.0 mmol) was added, upon which instant CO formation was observed.

In a glovebox filled with argon, a screw-capped vial was charged with 2-bromonaphtalene (124.2 mg, 0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (52.3 mg, 1.5 equiv) and DMF (3 mL) in that order. The vial was tightly sealed with a screwcap fitted with a Teflon® seal and removed from the glovebox. The CO balloon was moved to the screw-capped vial and the reaction mixture was heated to 80 °C for 18 h. The reaction mixture was cooled to room temperature and KF (87.2 mg, 2.5 equiv) and $TMSCF_3$ (196 µL, 2.2 equiv) was added under argon atmosphere. The screw-capped vial was sealed and left under stirring at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate (10 mL), filtered through a plug of celite, washed with water (3 x 10 mL) and brine (2 x 10 mL). The water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated. The product was isolated by flash column chromatography (dichloromethane/formic acid/pentane 10:2:88) as a colorless solid (9.8 mg, 6%).

Melting point (°C): 78 – 81. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 8.30 (s, 1H), 7.91-7.84 (m, 3H), 7.79 (d, *J* = 9.0 Hz, 1H), 7.54-7.48 (m, 2H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 135.1, 134.0, 129.9, 129.6, 129.1, 128.5 (m), 128.4, 127.7, 124.7 (q, *J* = 287.9 Hz) 124.6-124.5 (m), 78.7 (apparent sep, *J* = 29.6 Hz). $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -76.0. HRMS $C_{13}H_8F_6O$ [M-H$^+$]; calculated: 293.0407, found: 293.0410.

7.5.4. Bis(pentafluoroethyl)carbinol synthesis

**3-(4-(2,5-Dimethyl-1*H*-pyrrol-1-yl)phenyl)-1,1,1,2,2,4,4,5,5,5-decafluoropentan-3-ol (5.34)**

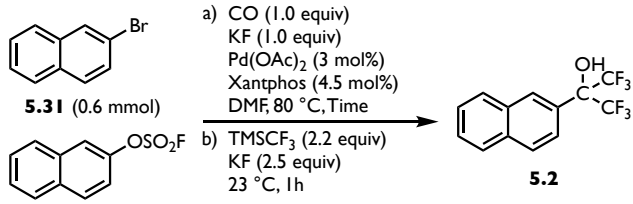



In a glovebox filled with argon, chamber A of a two-chamber system was charged with 1-(4-bromophenyl)-2,5-dimethyl-1*H*-pyrrole (150.1 mg, 0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (52.3 mg, 1.5 equiv) and DMF (3 mL) in that order. The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. To chamber B was added 9-methyl-9*H*-fluorene-9-carbonyl chloride (174.4 mg, 0.72 mmol), $HBF_4P(t\text{-}Bu)_3$ (2.1 mg, 1 mol%), $Pd(cod)Cl_2$ (2.1 mg, 1 mol%), DMF (3 mL) and $Cy_2NMe$ (308 µL, 2.0 equiv). The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. The two-chamber system was removed from the glovebox and placed in a preheated heating block and left under stirring at 80 °C for 18 hours. The reaction mixture was cooled to room temperature and KF (87.2 mg, 2.5 equiv) and $TMSCF_2CF_3$ (232 µL, 2.2 equiv) was added under argon atmosphere. The two-chamber was sealed and left under stirring at room temperature for 1 h. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a plug of celite, washed with water (3 x 10 mL) and brine (2 x 10 mL). The water phase was extracted with ethyl acetate (2 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered, concentrated under reduced pressure. The product was isolated by flash column chromatography (pentane/diethyl ether 97:3) as a colorless solid (215.4 mg, 82%). The isolated yield reported in chapter 5 is an average of two runs (82% and 84%).

Melting point (°C): 109 – 114. $^{1}$H-NMR (400 MHz, $CD_3OD$): δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 5.83 (s, 2H), 1.97 (s, 6H). $^{13}$C-NMR (101 MHz, $CD_3OD$): δ 142.2, 130.8, 129.6, 129.3, 129.2, 107.3, 77.1 (p, *J* = 21.0 Hz), 12.9. The peaks corresponding to the $CF_2CF_3$ group were poorly resolved and are in the region of 125-112 ppm. $^{19}$F-NMR (376 MHz, $CD_3OD$): δ -79.4, (-119.0)-(-120.8) (m). HRMS $C_{17}H_{13}F_{10}NO$ [M+H$^+$]; calculated: 438.0910, found: 438.0910.

## 7.5.5. Competition experiment

**Table 7.13** Competition experiment between aryl bromide **5.31** and aryl fluorosulfate **5.32**.




| Entry | Reaction time (h) | Conversion of **5.31** (%)[a] | Conversion of **5.32** (%)[a] | Yield of **5.2** (%)[a] |
|---|---|---|---|---|
| 1 | 1 | 2 | 74 | 68 |
| 2 | 18 | 14 | 90 | 79 |

All reactions were performed in a two-chamber setup. CO was released from a solid precursor in one chamber. [a]Determined by GC using dodecane as an internal standard.

In a glovebox filled with argon, chamber A of a two-chamber system (Figure 7.2) was charged with 2-bromonaphthalene **5.31** (124.2 mg, 0.6 mmol) and naphthalen-2-yl sulfurofluoridate **5.32** (135.7 mg, 0.6 mmol), $Pd(OAc)_2$ (4.0 mg, 3 mol%), Xantphos (15.6 mg, 4.5 mol%), KF (34.9 mg, 0.6 mmol, 1.0 equiv) and DMF (3 mL) in that order. The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. To chamber B was added 9-methyl-9*H*-fluorene-9-carbonyl chloride (145.6 mg, 0.6 mmol, 1.0 equiv), $HBF_4P(t\text{-}Bu)_3$ (2.1 mg, 1 mol%), $Pd(cod)Cl_2$ (2.1 mg, 1 mol%), DMF (3 mL) and $Cy_2NMe$ (308 μL, 2.0 equiv). The chamber was tightly sealed with a screwcap fitted with a Teflon® seal. The two-chamber system was removed from the glovebox and placed in a preheated heating block and left under stirring at 80 °C for 18 hours. The reaction mixture was cooled to room temperature and KF (87.2 mg, 2.5 equiv) and $TMSCF_3$ (196 μL, 2.2

equiv) was added under argon atmosphere. The two-chamber was sealed and left under stirring at room temperature for 1 h. 0.6 mL of a 1.0 M TBAF solution in THF (0.6 mmol) was added to the reaction mixture. The reaction mixture was diluted with 10 mL ethyl acetate, filtered through a plug of celite. Dodecane was added as internal standard and the crude reaction mixture was analyzed by GC.

The above-mentioned competition experiment was conducted to gain insight in the relative reactivity of the aryl bromides and the aryl fluorosulfates. As can be seen in Table 7.13, the conversion of 2-bromonaphthalene **5.31** and naphthalen-2-yl sulfurofluoridate **5.32** was 2% and 74% after one hour, respectively, and yielded 68% of the desired bis(trifluoromethyl)carbinol **5.2**. This result indicates that the relative reactivity in this coupling reaction follows OFs > Br as the bis(trifluoromethyl)carbinol was almost exclusively formed from naphthalen-2-yl sulfurofluoridate. A similar trend was observed after 18 hours.

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## Publication list (0000-0001-9076-3623)

[1] L. Balduyck, C. Veryser, K. Goiris, C. Bruneel, K. Muylaert and I. Foubert, 'Optimization of a Nile Red method for rapid lipid determination in autotrophic, marine microalgae is species dependent' *J. Microbiol. Methods* **2015**, *118*, 152-158, **DOI**: 10.1016/j.mimet.2015.09.009

[2] C. Veryser‡, S. Van Mileghem‡, B. Egle, P. Gilles, and W. M. De Borggraeve, 'Low-cost instant CO generation at room temperature using formic acid, mesyl chloride and triethylamine' *React. Chem. Eng.* **2016**, *1*, 142-146, **DOI**: 10.1039/C6RE00006A ‡Authors contributed equally

[3] S. Van Mileghem, B. Egle, P. Gilles, C. Veryser, L. Van Meervelt, and W. M. De Borggraeve, 'Carbonylation as Novel Method for the Assembly of Oligoamide Alpha-Helix Mimetics' *Org. Biomol. Chem.* **2017**, *15*, 373-378, **DOI**: 10.1039/C6OB02358D

[4] C. Veryser, G. Steurs, L. Van Meervelt, and W. M. De Borggraeve, 'Intramolecular Carbonylative C-H Functionalization of 1,2,3-Triazoles for the synthesis of Triazolo[1,5-*a*]indolones' *Adv. Synth. Catal.* **2017**, *359*, 1271-1276, **DOI**: 10.1002/adsc.201601388

[5] C. Veryser‡, J. Demaerel‡, V. Bieliūnas, P. Gilles, and W. M. De Borggraeve, '*Ex Situ* Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates' *Org. Lett.* **2017**, *19*, 5244-5247, **DOI:** 10.1021/acs.orglett.7b02522 ‡Authors contributed equally

[6] L. Van Puyvelde, M. Liu, C. Veryser, W. M. De Borggraeve, J. Mungarulire, M. J. Mukazayire, W. Luyten, 'Active principles of Tetradenia riparia. IV. Anthelmintic activity of 8(14),15-sandaracopimaradiene-7$\alpha$,18-diol' *J. Ethnopharmacol.* **2018**, *216*, 229-232, **DOI:** 10.1016/j.jep.2018.01.024

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[8] K. Domino‡, C. Veryser‡, B. A. Wahlqvist, C. Gaardbo, K. T. Neumann, K. Daasbjerg, W. M. De Borggraeve, T. Skrydstrup, 'Direct

Access to Aryl Bis(trifluoromethyl)carbinols from Aryl Bromides or Fluorosulfates: Palladium-Catalyzed Carbonylation' *Angew. Chem. Int. Ed.* **2018**, *57*, 6858-6862 **DOI:** 10.1002/anie.201802647 ‡Authors contributed equally

[9] P. Gilles, C. Veryser, S. Vangrunderbeeck, S. Ceusters, L. Van Meervelt, W. M. De Borggraeve, 'Synthesis of *N*-Acyl Sulfamates from Fluorosulfates and Amides' *J. Org. Chem.* **2019**, *84*, 1070-1078 **DOI:** 10.1021/acs.joc.8b02785

## Book chapter

S. Van Mileghem, C. Veryser, W. M. De Borggraeve, 'Flow-Assisted Synthesis of Heterocycles via Multicomponent Reactions' *Topics in Heterocyclic Chemistry*, Springer, Berlin, Heidelberg, **2018**, **DOI:** 10.1007/7081_2018_23

## International research stays

**08/2017 – 01/2018**

*UNIVERSITY OF AARHUS, Aarhus, Denmark*

Supervisor: Prof. Troels Skrydstrup

Topic: CO chemistry

Travel Grant: Scientific Prize Gustave Boël-Sofina Fellowship

**08/2018 – 12/2018**

*MASSACHUSETTS INSTITUTE OF TECHNOLOGY (MIT), Cambridge, USA*

Supervisor: Prof. Timothy F. Jamison

Topic: Flow chemistry

Travel Grant awarded by FWO

## Conference participations

[1] **Flow Chemistry Europe 2016**, *Cambridge, United Kingdom – February 2016*. Poster: Selective Debenzylation of *N*-Benzyloxypyrazinones in Flow.

[2] **Belgium Organic Synthesis Symposium BOSS 2016**, *Antwerp, Belgium – July 2016*. Poster: Low-cost Instant CO Generation at Room Temperature using Formic Acid, Mesyl Chloride and Triethylamine

[3] **Chemical Research in Flanders – CRF-1**, *Blankenberge, Belgium – October 2016*. Poster: Low-cost Instant CO Generation at Room Temperature using Formic Acid, Mesyl Chloride and Triethylamine

[4] **20th Sigma-Aldrich Symposium**, *Blankenberge, Belgium – December 2016*. Poster: Low-cost Instant CO Generation at Room Temperature using Formic Acid, Mesyl Chloride and Triethylamine

[5] **Træf for Organisk Kemi Studerende – TOKS XVI**, *Aarhus, Denmark – November 2017*. Presentation: *Ex Situ* Generation of Sulfuryl Fluoride for the Synthesis of Aryl Fluorosulfates

[6] **The Torkil Holm Symposium**, *Copenhagen, Denmark – January 2018*

[7] **Belgium Organic Synthesis Symposium BOSS 2018**, *Brussels, Belgium – July 2018*. Poster: Convenient Handling of Reactive Gases: Methods for Fluorosulfation and Carbonylation

[8] **256th ACS National Meeting & Exposition**, *Boston, MA, USA – August 2018*. Poster: Convenient Handling of Reactive Gases: Methods for Fluorosulfation and Carbonylation