# CHEMICAL REVIEWS

Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents

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CONTENTS

1. INTRODUCTION

This review article is concerned with the use of compounds **1** and **2** (Figure 1) as effective and very versatile reagents for
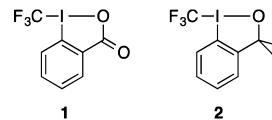
Figure 1. Two main hypervalent iodine reagents for electrophilic trifluoromethylation.

trifluoromethylation reactions of a variety of substrates. These two hypervalent iodine compounds, 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one (**1**) and trifluoromethyl-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole (**2**), were reported for the first time in 2006 from our laboratory.[1]

Since then, but in particular during the last three to four years, they have attracted the attention of numerous research groups worldwide, most prominently active in the area of organofluorine chemistry and homogeneous catalysis as directed toward the development of new synthetic methods. The growing interest that trifluoromethylation chemistry has enjoyed in recent years is quite remarkable. Advances in this area, in terms of both discovering new reactions and accessing new compounds, have been made possible also by the availability of reagents such as **1** and **2**. In fact, soon after the first report, several commercial suppliers of laboratory

chemicals started offering research quantities of these materials. Meanwhile, these compounds may be supplied even on a multikilogram scale. The fact that there is no patent pending on the original development surely facilitated the use of these reagents by industrial research and development laboratories. Moreover, their preparation is simple and easily accomplished from readily available starting materials (vide infra). Hence the body of publications describing successful applications of these reagents has reached an extent that warrants this specifically focused review as appropriate and timely. However, accounts detailing recent progresses in trifluoromethylation and perfluoroalkylation chemistry by various approaches have been accumulating in the literature since 2011, partly covering but not focusing on compounds **1** and **2**.[2]

Despite the undisputed significance of reagents **1** and **2** for modern trifluoromethylation chemistry—for organic synthesis the prototypical and most relevant perfluoroalkylation reaction—they represent but one of the most recent developments in this area. However, methods for trifluoromethylation of organic molecules by way of transferring an intact CF_3 group from a reagent to a target molecule have been known for more than half a century. Correspondingly, this topic has been reviewed previously. The first major comprehensive review article was published in 1992.[3] Still during the 1990s, important review articles were already specifically highlighting either nucleophilic,[4] radical,[5] or electrophilic trifluoromethylation reactions.[6] Further key references appeared in the new century have been emphasizing special aspects, for example, nucleophilic[7] or asymmetric trifluoromethylation[8] or the uses and properties of trifluoromethylated compounds,[9] thereby underscoring the multifaceted features of this chemistry.

Reagents **1** and **2** are so-called hypervalent iodine compounds. Because of the three bonding partners attached to the iodine atom they are λ^3-iodanes or 10-I-3 species.[10] Such iodanes are often described in the literature as having an I(III) center, though strictly speaking, this does not necessarily imply an oxidation state of +III for the iodine atom as one would derive by applying common rules and taking into account electronegativity differences between bonding partners, as would be true in the clear-cut case IF_3.
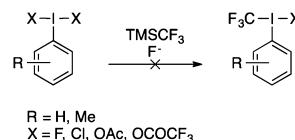
This review covers the literature dealing with the use of reagents **1** and **2** up to March 2014 and is subdivided into four main sections describing synthesis (section 2), structure and properties (section 3), activation (section 4), and applications (section 5). Section 4 reports what is known about the influence of additives and catalysts on the reactivity of the reagents and includes some still-unpublished material from our research group. Mechanistic aspects are also covered in this section, though thorough mechanistic studies are still scarce. The application section consists of two main parts. Section 5.1 is concerned with heteroatom nucleophiles as substrates for trifluoromethylation and largely reflects our own work. Carbon-centered nucleophiles (section 5.2), on the other hand, represent the vast majority of substrates that have been successfully trifluoromethylated by using **1** and/or **2** and mirror the interest of the synthetic community for reactions leading to a new C–CF_3 bond.

2. SYNTHESIS

The ability of hypervalent iodine compounds to perform atom or functional group-transfer reactions inspired our group to develop a new reagent based on a λ^3-iodane core, capable of transferring an electrophilic CF_3 unit.[10] The objective was to

prepare a stable trifluoromethyl λ^3-iodane as an electrophilic source of CF_3, analogous to Yagupolskii's perfluoroalkylation reagents.[11] The first synthetic attempts toward such a λ^3 I–CF_3 compound were done by subjecting an iodine(III) fragment to nucleophilic trifluoromethylation, in order to exchange the substituent at the iodine center (Scheme 1).[1] This approach
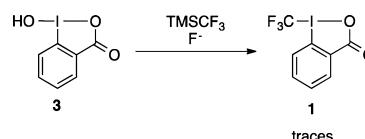
Scheme 1. Initial Attempts toward Formation of I–CF_3 Bond[1b]

$$R = H, Me$$
$$X = F, Cl, OAc, OCOCF_3$$

was chosen over other pathways involving aromatic substitution with CF_3–IX_2 or functional group interconversion of a CX_3 fragment already attached to iodine—mainly for safety considerations and availability of the reagents. However, attempts to introduce the trifluoromethyl group into different λ^3-iodane-based substrates such as iodosyltoluene, (dihalo)-iodotoluene, bis(acetoxy)iodotoluene, or bis(trifluoroacetoxy)-iodobenzene by use of the commercially available Ruppert–Prakash reagent (trifluoromethyltrimethylsilane, TMSCF$_3$) in the presence of a fluoride source failed. Several byproducts, in particular CF_3I, were observed, indicating that most likely ligand substitution took place but was followed by degradation of the desired product.
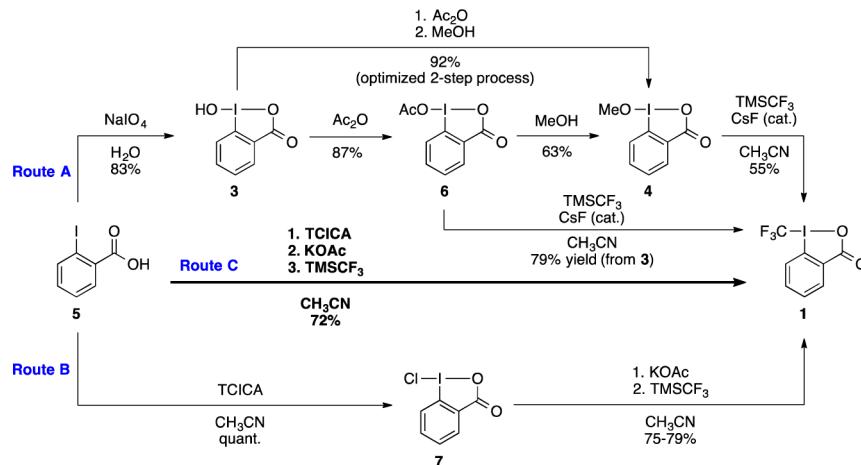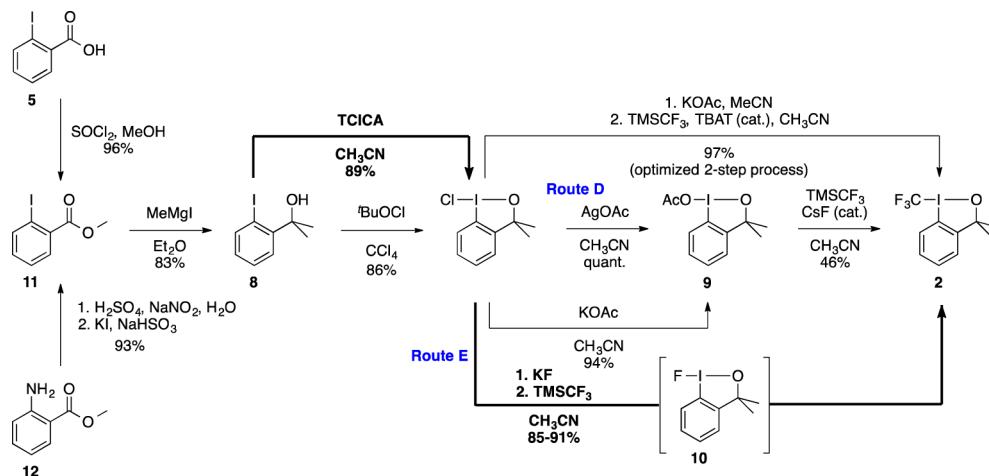
This led to the hypothesis that a more rigid backbone was needed to increase the stability of the desired product. A benziodoxolone-based core was chosen as precursor, with the premise that the rigidity provided by the additional 5-membered ring would increase the stability of the final CF_3-containing compound (Scheme 2). Indeed, when 2-iodosyl-

Scheme 2. First Synthesis of Benziodoxolone-based CF_3 Compounds[1b]

benzoic acid (**3**) was used as substrate and TMSCF$_3$ was added in the presence of catalytic amounts of fluoride, the formation of a compound containing a CF_3 group bound to a hypervalent iodine fragment was indicated by a ^{19}F NMR signal at −35.7 ppm.

At that point, we concluded that the lack of reactivity was to be attributed to the low solubility of the λ^3-iodane precursor and the low leaving-group ability of the hydroxyl group. When the more soluble methoxy analogue **4** was used, trifluoromethylbenziodoxolone **1** could be isolated in 55% yield (despite a cumbersome and inefficient purification procedure). Starting from commercially available 2-iodobenzoic acid (**5**), compound **1** could thus be prepared in four steps in satisfactory yields (Scheme 3, route A), consisting of an initial oxidation with NaIO$_4$, followed by two successive ligand exchange steps (OH$^-$ is replaced by AcO$^-$, which is finally displaced by MeO$^-$). An optimized two-step process improves the ligand exchange steps by combining them without the need to isolate an intermediate. Later on, it was found that intermediate **6** could also undergo

Scheme 3. Routes toward Trifluoromethylbenziodoxolone 1[1,12,13]

Scheme 4. Routes toward Trifluoromethylbenziodoxole 2[1,13,14]

ligand exchange and thereby reduce the total protocol to a three-step process.[12]

A thorough reassessment of the synthetic route has been performed more recently,[13] wherein chloroiodane **7** was identified as a privileged intermediate as it is readily available and reacts smoothly to yield the desired product via initial chloride/acetate exchange followed by the usual displacement of AcO⁻ for CF₃⁻ (Scheme 3, route B). The most remarkable features of this two-step process are the use of trichlorocyanuric acid (TCICA) as a cheap and safe Cl⁺ source, replacing NaIO₄ as oxidant, and that the reaction can be performed on a multigram scale in good yield, provided vigorous stirring is guaranteed. The scalability of the reaction is also supported by the ease of purification by simple filtration and the use of only a very small excess (1.1 equiv) of the relatively expensive Ruppert–Prakash reagent. The simplification of the synthesis of **1** culminated in the development of a one-pot, three-step process (Scheme 3, route C), even though a slightly larger excess of Ruppert–Prakash reagent is required for good yields (72% from 2-iodobenzoic acid).

Prompted by the fact that benziodoxole-based scaffolds are frequently encountered as stable λ^3-iodane structures, our group investigated the routes to the analogous product **2** for similar applications.[1a] The original route consisted of the synthesis of 2-iodophenylpropan-2-ol (**8**) by esterification of the commercially available 2-iodobenzoic acid (**5**) and

subsequent addition of methylmagnesium iodide. The oxidation to iodine(III) is performed by use of *tert*-butyl hypochlorite. The unstable nature of this oxidative chlorination agent requires its careful handling in dim light and thorough temperature control. The acetoxylation can be performed with either KOAc or AgOAc. Since AgOAc is appreciably more expensive and requires the absence of light, the use of KOAc is advised.[14] Trifluoromethylation is performed under similar conditions as previously described (Scheme 4, route D). Once again, intermediate **9** does not need to be isolated, thus rendering the entire procedure more convenient.

This synthesis has also been subjected to reevaluation for large-scale applications.[13] Most notable is the omission of the hazardous *tert*-butyl hypochlorite in the revised protocol. TCICA proved once again to be an exceptional chlorinating agent, leaving isocyanuric acid as byproduct, which precipitates and thus can easily be filtered off. Ligand exchange with KF (preferably spray-dried) leaves fluoroiodane **10**, which is directly transformed to product **2** by use of TMSCF₃ (Scheme 4, route E). Additionally, the route to methyl iodobenzoate **11** was modified, starting from the significantly cheaper methyl anthranilate (**12**), which undergoes iodination via Sandmeyer reaction with KI (Scheme 4).

In summary, convenient routes have been designed to access the two most popular hypervalent iodine CF₃ reagents **1** and **2**,

making them available in large quantities for synthetic applications.

3. STRUCTURE AND PROPERTIES

3.1. Reagents 1 and 2

Compounds **1** and **2** are air-stable crystalline solids; however, **2** decomposes over weeks at ambient temperature and should thus be stored in a fridge or freezer. It is furthermore relevant to note that hypervalent iodine compounds are usually energetic materials and can thus decompose exothermally. Corresponding safety considerations will be discussed below.

The crystalline nature of these compounds allowed the structural features of **1**[1a] and **2** to be analyzed by X-ray crystallography.[14a] These analyses show a typical distorted T-shape geometry around iodine arising from a pseudotrigonal-bipyramidal geometry where the two lone pairs at iodine occupy equatorial positions (Figure 2). The position of the lone
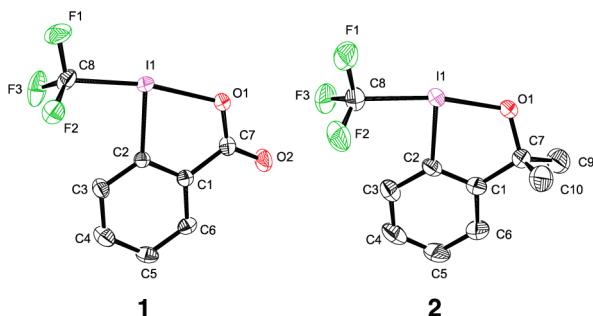

Figure 2. ORTEP views of the X-ray crystal structures of **1** (CCDC-239458) and **2** (CCDC-618737) and adopted numbering scheme (hydrogen atoms are omitted for clarity; thermal ellipsoids are set to 50% probability).[1a,14a]

pairs is due to their mutual repulsion as predicted by valence-shell electron-pair repulsion (VSEPR) theory for all 10-I-3 compounds.[10a] Indeed, for **1**, the bond angle C8–I–O1 is 170.43(12)°, which is significantly smaller than 180°. The quasi-linearity of the C8–I–O1 bond is a representation of the so-called 3c-4e bond (three-centers-four-electron bond), with four electrons participating in the hypervalent bonding interaction of the three atoms. The other bond angles [93.74(14)° for C8–I–C2 and 76.79(11)° for O1–I–C2] further support the notion of a distorted T-shape, deviating from a perfect 90° angle. The torsion angles O1–I1–C2–C1 and C8–I1–C2–C1 show only minimal deviation from the expected 0°, indicating coplanarity of these atoms. The situation for **2** is very similar and the expected distorted T-shape can also be found in this structure. However, the torsion angles show that replacement of the carbonyl oxygen atom O2 in structure **1** by two methyl groups in **2** causes the axis of the 3c-4e bond to twist out of the plane of the phenyl group by ca. 13°. Furthermore, it is interesting to observe the impact of electronic properties of the substituents at the iodine center. Namely, the electron-withdrawing carboxylate group in **1** leads to a longer I1–O1 bond [2.283(2) vs 2.1176(14) Å] and a shorter I1–C8 bond [2.219(4) vs 2.267(2) Å] when compared to the more electron-donating alkoxy substituent of **2**. We shall remark that the very T-shape geometry of **1** and **2** is often disregarded by many authors who draw these compounds as having equivalent bond angles around iodine, clearly ignoring

basic VSEPR theory and the resulting typical structure of λ^3-iodane compounds.

Heteronuclear NMR analysis of these I–CF$_3$ compounds further corroborates their intriguing characteristics. The ^{19}F NMR chemical shift (−33.8 ppm for **1** and −40.1 ppm for **2**) is shifted to lower fields/higher frequency as compared to classic organic CF$_3$ moieties (usually expected between −50 and −70 ppm), highlighting their more electron-poor nature. More fascinating are the following observations of the ^{1}H and ^{13}C NMR spectra of **1**; the signal of the proton bound to C3 (ortho to iodine) is shifted to higher frequencies, the ^{13}C-signal of C3 being additionally split into a quartet with a coupling constant of 3.1 Hz. This indicates a "through-lone-pair-coupling" (commonly referred to as "through-space coupling") between the fluorine atoms of the CF$_3$ group and the adjacent CH group.

Cyclic voltammetry studies have been performed on both **1** and **2**. Depending on the exact experimental conditions, values of the one-electron reduction potential ranging between −1.10 and −0.94 V versus standard calomel electrode (SCE) have been determined for **1**, while the values for **2** are found to be between −1.82 and −1.09 V (both vs SCE in CH$_3$CN).[15] The lower reduction potential of **2** indicates that this compound is less prone to undergo a one-electron reduction and hence to generate CF$_3$ radicals. Additionally, when these values are compared to previously reported reduction potentials of other commonly used CF$_3$ radical sources such as CF$_3$I and a series of trifluoromethylsulfonium salts, it appears that hypervalent iodine-based trifluoromethylation reagents are more reluctant than other trifluoromethyl sources to generate a CF$_3$ radical.[15a,16]
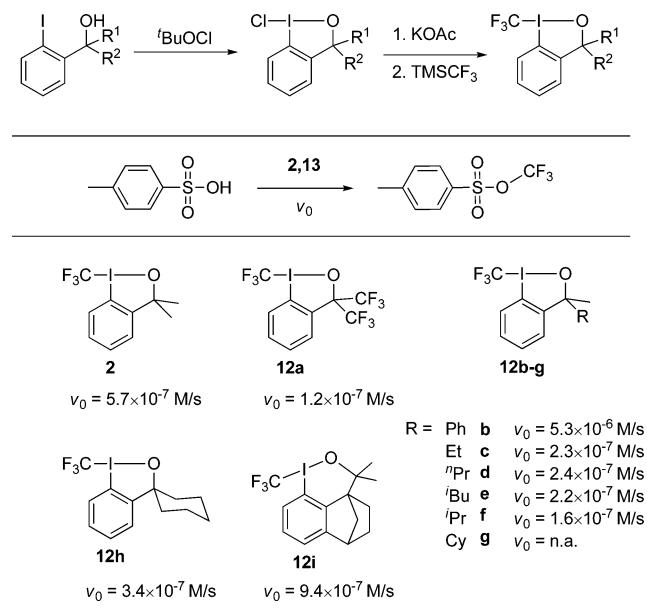
Recently, the thermal stability of **1** and **2** has been investigated by Novasep Synthesis.[17] The exothermic decomposition energies are 37.9 kcal/mol for **1** and 62.3 kcal/mol for **2**. These values are in good agreement with what has been previously found by our group (62.1 kcal/mol for **2**).[14b] Other safety tests carried out by the same company showed that none of the compounds is friction-sensitive and that some samples of CF$_3$-benziodoxole-based **1** were impact-sensitive. Presumably this difference in sensitivity between different samples of **1** stems from the amount and nature of impurities contained by the analyzed sample, which can influence impact sensitivity in both directions. Additionally, it was found that **1** is explosive by Koenen test and can be ignited by the flame of a match (while **2** has not been tested for these properties). In conclusion, the reagents are shelf-stable and nonexplosive under typical laboratory and reaction conditions. However, heating the reagents, especially as solids, to elevated temperatures may lead to a violent decomposition. Consequently, it must be said that **1** (and **2**) should be handled with sensible precautions by appropriately trained personnel without the need of exceptional safety measures. On a further note, no incident involving these hypervalent iodine-based reagents has ever been reported so far, even though they have been synthesized and applied on large scales by both undergraduate students and experienced chemists in academic as well as industrial laboratories.

3.2. Further Reagents

With the desire to develop new trifluoromethylation reagents that would show better selectivities in trifluoromethylation reactions or would allow the selective trifluoromethylation of different substrates, our group tried to relate the reactivity (and selectivity) of these hypervalent iodine-based reagents to their

structure. The synthesis of a series of 10-I-3 trifluoromethylation reagents was thus undertaken.[18] As a first approach, variation of the side chain of reagent **2** with different alkyl and phenyl substituents was investigated as shown in Scheme 5

Scheme 5. Synthesis of Derivatives of 2 and Evaluation of Initial Rate Constant v_0[1a,18a,20]
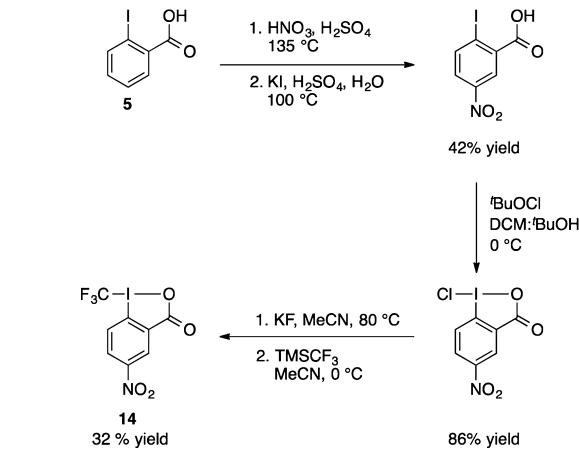

(**13a–i**). The synthesis of these compounds follows the synthetic pathways described above. On the basis of crystal structures, the correlation between I1–O1 and C8–I1 bond lengths and their reactivity in trifluoromethylation of *p*-toluenesulfonic acid was investigated (see section 5.1.3). Even though a certain trend indicated that lengthening of the I1–O1 bond (which is synonymous with shortening of the I–CF$_3$ bond) coincided with higher initial reaction rates, no strong correlations could be established. In fact, one could intuitively argue that a weaker I1–O1 bond would lead to increased reactivity. However, by the same argument, because a longer I1–O1 bond is concomitant with a shorter I1–CF$_3$ bond, decreased reactivity should be predicted. Furthermore, it is important to remember that bond lengths as revealed by X-ray crystallography might also be influenced by specific solid-state factors, such as crystal packing, and thus are not necessarily appropriate for the description of solution behavior. The fact that **13i**, which has an expanded ring size, is an outlier in this trend shows that presumably factors other than bond lengths affect reactivity. For instance, it could be hypothesized that electronic properties of the side chains induce variations in reactivity. One measure of electronic properties could be the ^{13}C chemical shift of carbon C7.[19] It appears that this correlation holds good for as long as only alkyl substituents are considered. Phenyl substitution cannot be assessed by these means.[20] It should also be noted at this point that reactivity can only be consistently defined for one substrate class, since several mechanisms are thought to be operational, depending on the substrate (see section 4). In conclusion, the fact that **1** outperforms **2** in studies of trifluoromethylation of *p*-toluenesulfonic acid is not necessarily transferable to other substrate classes.

Another approach to modulate the reactivity of hypervalent iodine-based trifluoromethylation reagents is to modify the electronic properties of the aromatic ring system. We hypothesized that rendering the hypervalent iodine center more electron-deficient should increase its propensity toward reduction, thus enhancing the reactivity. One way to achieve this is obviously the introduction of electron-withdrawing substituents, such as a nitro group, in para position. Scheme 6

Scheme 6. Synthesis of Nitrated Derivative 14 of Reagent 1[18b]

shows the synthesis of the nitro variant **14** of compound **1**. Compound **14** shows indeed very high reactivity when exposed to *p*-toluenesulfonic acid, as shown by its fast decay. Unfortunately, no formation of the desired trifluoromethylation product, *p*-TsOCF$_3$, could be observed. As it appears, reagent **14** rapidly degrades under acidic conditions without the expected trifluoromethylation of *p*-toluenesulfonic acid. Another limitation of **14** is its very poor solubility in common organic solvents, which makes it of scant use for regular synthetic applications.

4. ACTIVATION

4.1. Activation by Lewis Acids

Trifluoromethylation of acetylenes was explored in the early days of reagents **1** and **2** by our group (see section 5.2.4). In view of activating the triple bond of phenylacetylene, various metal salts have been used. In the case of Zn(OTf)$_2$, however, instead of the desired trifluoromethylated acetylene, trifluoromethyl triflate (TFMT) was formed from the reaction of reagent **1** and the anion of the zinc salt. Further experiments with other triflate salts such as NaOTf, KOTf, or Cu(OTf)$_2$, however, did not produce TFMT. On the other hand, when ZnBr$_2$ was added together with such simple triflates, TFMT was formed, thus hinting at the crucial role of the zinc(II) cation in this reaction. Furthermore, while investigating the trifluoromethylation of aliphatic alcohols (see section 5.1.3), we found that Zn(NTf$_2$)$_2$ was the Lewis acid of choice due to very low reactivity of the counterion and high solubility of the salt in organic solvents. However, it has to be noted that even NTf$_2^-$ can undergo trifluoromethylation with reagent **1** upon zinc(II) activation, thus indicating a potential extension of its reactivity. Therefore, we were very interested in the nature of the activated reagent and investigated the trifluoromethylating system of aliphatic alcohols by NMR spectroscopy (pulsed-field gradient spin echo, PGSE), electrospray ionization mass spectrometry (ESI MS), and single-crystal X-ray analysis. ^{19}F

NMR analysis of a reaction mixture consisting of reagent **1**, *p*-nitrobenzyl alcohol, and $Zn(NTf_2)_2$ showed a significant downfield shift of the CF_3 signal of reagent **1** from −33.0 to −26.9 ppm after a few minutes. Similarly, when reagent **1** and $Zn(OTf)_2$ were mixed in an equimolar ratio, a shift of $\Delta\delta = 8$ ppm to lower field was observed. This intermediate decayed over time concomitant with formation of the desired trifluoromethyl ether or TFMT, respectively. Since this decay was slow on the NMR time scale, it was possible to analyze the reaction intermediates by high-resolution mass spectroscopy. ESI MS analysis of a 2:1 mixture of **1** and $Zn(NTf_2)_2$ showed a mass peak indicating the presence of a $[Zn(\mathbf{1})_2(NTf_2)]^+$ ion. Single-crystal analysis revealed the bis(triflimide) salt $[Zn-(\mathbf{1})_2(p\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2\text{OH})_2(OH_2)_2]^{2+}$ in which the carbonyl group of the hypervalent iodine reagent **1**, 4-nitrobenzyl alcohol, and water coordinate to the zinc(II) center in an octahedral fashion, each as monodentate ligands (Figure 3).
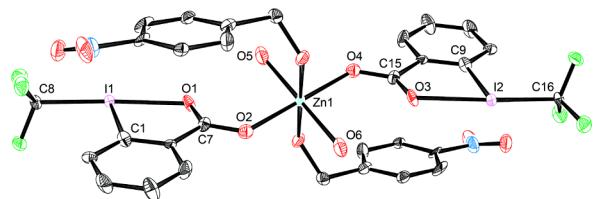

Figure 3. ORTEP view of the asymmetric unit of dication $[Zn(\mathbf{1})_2(p\text{-NO}_2\text{-C}_6\text{H}_4\text{-CH}_2\text{OH})_2(OH_2)_2]^{2+}$ (CCDC-720606; hydrogen atoms and counterion are omitted for clarity; thermal ellipsoids are set to 50% probability).[21]

It has always been speculated that activation of reagents **1** and **2** proceeds via weakening of the I−O bond, thus promoting the release of the CF_3 unit. The above crystal structure confirms a significant elongation of the iodine−oxygen bond from 2.283(2) Å in **1**[1a] to 2.403(12) Å in the Zn(II) complex. Additionally a larger $C2-I1-CF_3$ angle of 95.4(7)° versus 93.74(14)° in **1** was observed, which can be interpreted as distortion toward a reactive iodonium species.
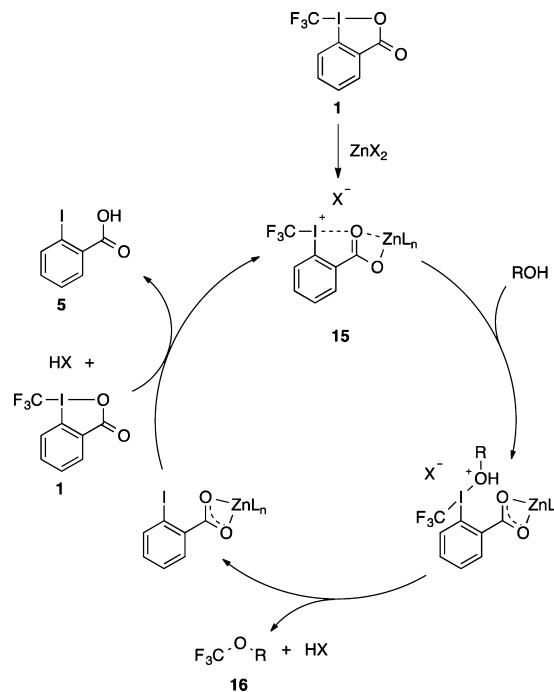
In our efforts to contribute to the mechanistic understanding of trifluoromethylation of alcohols, we measured PGSE diffusion NMR spectra of the reaction mixture. The spectra showed a 2:1 adduct of **1** with zinc(II), confirming the ratio observed by X-ray and ESI MS measurements. Similar diffusion constants were observed for the dicationic complex and NTf_2^-, indicating a strong interaction between the two. In contrast, 4-nitrobenzylic alcohol showed a different diffusion constant, which led to the conclusion that trifluoromethylation of the alcohol does not require substrate coordination to the zinc(II) center.

These results allow us to formulate a plausible reaction mechanism for the trifluoromethylation of alcohols under Zn(II) catalysis (Scheme 7). Reagent **1** reacts with the Zn(II) salt to form the carboxylate/iodonium complex **15**. Upon coordination, the I−O bond is weakened and the ligand exchange with the alcohol (ROH) is facilitated. Subsequent reductive elimination forms the desired trifluoromethyl ether **16** after deprotonation. The active species is then regenerated by ligand exchange of 2-iodobenzoic acid (**5**) with **1**.[22]

4.2. Activation by Brønsted Acids
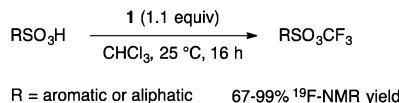
4.2.1. Sulfonic Acids.
Further investigation showed that **1** could also be activated by strong Brønsted acids. Sulfonic acids react with reagent **1** to give the corresponding trifluoromethyl

Scheme 7. Mechanistic Hypothesis for Trifluoromethylation of Alcohols[22]

sulfonates in good to excellent yields (Scheme 8; see also section 5.1.3).

Scheme 8. Trifluoromethylation of Sulfonic Acids[23]

$$RSO_3H \xrightarrow[\text{CHCl}_3,\ 25\ ^\circ\text{C},\ 16\ \text{h}]{\mathbf{1}\ (1.1\ \text{equiv})} RSO_3CF_3$$

R = aromatic or aliphatic   67-99% ^{19}F-NMR yield
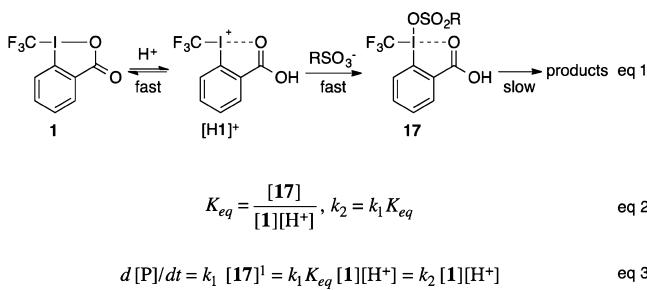
The reaction of **1** with sulfonic acids seemed to be an appropriate model system for mechanistic investigations due to the minimal amount of byproducts, convenient conditions in terms of time and temperature, and monitorability by ^{19}F NMR.

Initial rate studies showed that the reaction was first-order in both reagent and substrate but independent of the substitution pattern on the sulfonic acids.[23a] Also, it was found that the sulfonate anion is not engaged in the rate-determining step of the reaction.

The most plausible mechanistic hypothesis involves a rapid protonation−deprotonation of reagent **1** to $[H\mathbf{1}]^+$ in a pre-equilibrium, followed by the formation of a steady-state intermediate (**17**). This intermediate is then converted into the products in the rate-determining step as shown in Scheme 9 and described by eqs 2 and 3 therein.

This is also corroborated by the observation of an inverse kinetic isotope effect, $k_H/k_D = 0.65$. Reactions under general acid catalysis show a primary kinetic isotope effect due to the rate of a proton versus deuterium transfer, whereas reactions with a rapid pre-equilibrium (protonation/deprotonation) display an inverse kinetic isotope effect. The reason is that the deuterated intermediate is a weaker acid than the protonated intermediate. Therefore, the steady-state concentration of intermediate **17** is higher in the former case, leading to an overall higher reaction rate. Hence, we proposed that the reaction mechanism follows the pathway described in eq 1 with

Scheme 9. Plausible Reaction Mechanism for Formation of Trifluoromethyl Sulfonates[23b]

$$K_{eq} = \frac{[17]}{[1][H^+]}, \quad k_2 = k_1 K_{eq} \qquad \text{eq 2}$$

$$d[P]/dt = k_1 [17]^1 = k_1 K_{eq} [1][H^+] = k_2 [1][H^+] \qquad \text{eq 3}$$

the rate law described by eq 3 in Scheme 9. Rapid protonation of the carboxyl moiety causes a weakening of the I–O bond, thus freeing a coordination site at the iodine, which is occupied by the substrate to form intermediate **17**. In the last, rate-determining step, the trifluoromethyl group is transferred to the substrate to form the trifluoromethyl sulfonates and iodobenzoic acid by a reductive elimination-type process.

Not only was reagent **1** effective in the trifluoromethylation of sulfonic acids but also reagent **2** reacted in the same manner, albeit about one order of magnitude slower than **1**. Thus, we carried out rate studies for **2** to determine whether the two reaction mechanisms were comparable. Surprisingly, initial rate studies showed the reaction rate was independent of the concentration of **2**, whereas the mechanism indicated for **1** has a first-order dependence on the concentration of **1** (Scheme 9, eq 3). This observation suggested that reagent **2** is transformed into a stable intermediate under the reaction conditions. Closer inspection of ^{19}F NMR data showed a significant downfield shift of the CF₃ resonance of reagent **2** (−40.1 ppm) to −26 ppm, supporting the proposition of a stable intermediate. An NMR titration experiment was carried out with $[H(OEt_2)_2]$-$[(3,5\text{-}CF_3C_6H_3)_4B]$ (BArF₂₄) as acid, as shown in Figure 4. We
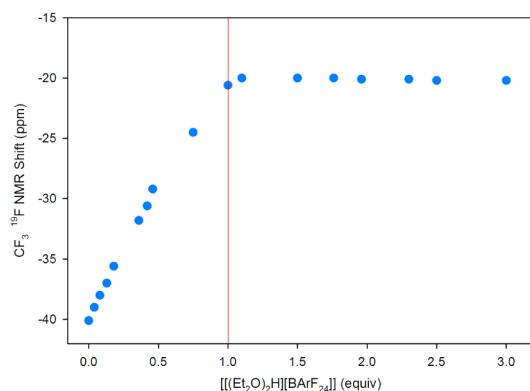
Figure 4. ^{19}F NMR titration curve of **2** with BArF₂₄ acid.

observed a linear dependence of the observed ^{19}F NMR chemical shift of the CF₃ group in the range 0−1 equiv of acid added, whereas beyond 1 equiv the position of the signal remained constant. This indicates the formation of a well-defined monoprotonated form of the reagent.

In addition, from the mixture corresponding to the addition of 0.5 equiv of acid, the crystalline product ($[H(\mathbf{2})_2][BArF_{24}]$) was obtained and subjected to X-ray analysis. The I–O bond lengths in the two nonequivalent molecules of **2** in the salt $[2.440(4)\ \text{Å for O1–I1 and } 2.257(3)\ \text{Å for O2–I2}]$ are substantially longer than for the unprotonated form of the

reagent [2.118(2) Å]. However, the I−O bond elongations are significantly different from one another and the distance between O1 and O2 (2.59 Å) is larger than that typically observed for a symmetric hydrogen bond (typically up to 2.45 Å). Therefore, the structure of this salt in the solid state may be described as consisting of the protonated form of **2** ($[H\mathbf{2}]^+$) forming a hydrogen bond to a second molecule of **2**, as shown in Figure 5.
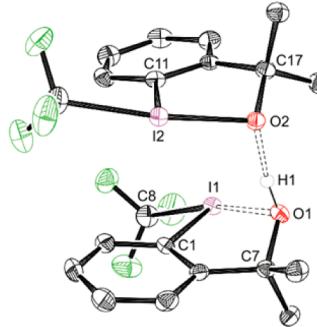
Figure 5. ORTEP view of the X-ray crystal structure of a 2:1 adduct of **2** and a proton ($[H\mathbf{2}]^+$) (hydrogen atoms, except for H1, and the counterion are omitted for clarity; thermal ellipsoids are set to 50% probability).[22]

These observations prompted us to revisit the initial experiments indicating that the rate of the reaction of **2** with sulfonic acids is independent of the concentration of reagent **2**. Not surprisingly, the reaction rate shows a clear first-order dependence on the concentration of $[H\mathbf{2}]^+$. Therefore, very similar mechanistic conclusions can be drawn for the trifluoromethylation of sulfonic acids with reagent **2** as already pointed out for reagent **1**.[23]

4.2.2. Protonated Reagent 2: Frontier Molecular Orbital Considerations. The electronic structures of reagent **2** and its protonated form $[H\mathbf{2}]^+$ were calculated by use of density functional theory at the B3LYP/aug-cc-pVTZ level. These theoretical considerations provided further insight into the mode of activation of **2** by protonation. The relevant molecular orbitals (MOs) are shown in Figure 6. In **2** the lowest unoccupied molecular orbital (LUMO) is an antibond-
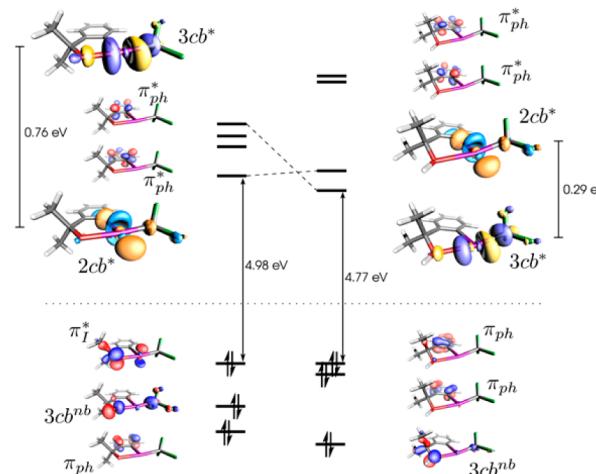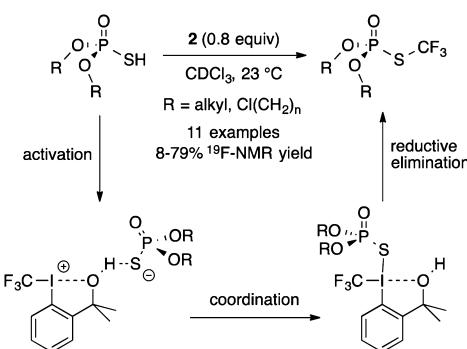
Figure 6. Comparison of frontier molecular orbitals (MOs) of **2** and $[H\mathbf{2}]^+$ (B3LYP/aug-cc-pVTZ).[20,24]

ing orbital aligned with the C_{phenyl}–I bond, whereas in the protonated form $[H2]^+$ the LUMO corresponds to the antibonding orbital of the hypervalent interaction. In addition, the energy of the LUMO is lowered with respect to the energy level of the highest occupied molecular orbital (HOMO), thus rendering $[H2]^+$ a stronger oxidant as compared to **2**. Moreover, there is a noticeable polarization toward the I–CF$_3$ bond, which indicates a considerable weakening of the 3c-4e interaction. These findings support the previous experimental data and further emphasize the importance of activation of reagents **1** and **2**.[20,24] It may be added that the LUMO of $[H2]^+$ displays a suited symmetry for interaction with a filled transition-metal d orbital, this possibly being required for oxidative addition processes.

4.2.3. Trifluoromethylation of *S*-Hydrogen Phosphorothioates and Hydrogen Phosphates.

Similarly to sulfonic acids (see section 4.2.1), a substrate that can act as proton donor can possibly activate reagents **1** and **2**. The reactivity of variously substituted *S*-hydrogen phosphorothioates toward **2** was tested. These compounds underwent trifluoromethylation in the presence of reagent **2** in moderate to good ^{19}F NMR yields. Product isolation, however, turned out to be difficult due to their sensitivity toward chromatographic purification. Nevertheless, this reaction allowed for further mechanistic investigations; competition experiments provided evidence for electronic effects heavily influencing the relative rates, while steric factors are generally much less significant. Thus, we propose that after protonation of **2** the substrate coordinates to the iodonium ion, followed by reductive elimination of the product. This assumption was further supported by the observation that substrates containing a donor for iodine(III) reacted more slowly due to stabilization of the intermediate (Scheme 10).[25]

Scheme 10. Trifluoromethylation of *S*-Hydrogen Phosphorothioates and Proposed Mechanism[25]
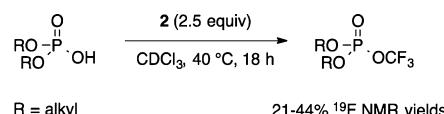
The behavior of hydrogen phosphates in the presence of reagent **2** gave very similar results. Several dialkyl hydrogen phosphates were synthesized and reacted with reagent **2** to form the corresponding trifluoromethylated products. The reaction proceeds in low to moderate yields and, once again, isolation was hardly possible (Scheme 11). Not surprisingly, mechanistic studies hint toward an analogous mechanism as was proposed for *S*-hydrogen phosphorothioates (see Scheme 10).[26]

## 4.3. Activation by Metals and Radical Trifluoromethylation
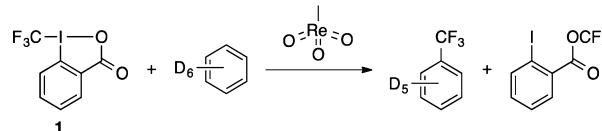
4.3.1. Rhenium-Catalyzed Trifluoromethylation of Arenes.

When we attempted to synthesize CF$_3$ derivatives of methyltrioxorhenium (MeReO$_3$, MTO), we found that

Scheme 11. Trifluoromethylation of Phosphates[26]

reagents **1** and **2** were able to trifluoromethylate benzene and other aromatic substrates in the presence of MTO (Scheme 12; see section 5.2.3).

Scheme 12. Trifluoromethylation of Benzene by Use of Methyltrioxorhenium as Lewis Acid[27]

To elucidate the mechanism of the transformation, the reaction was studied by NMR and electron paramagnetic resonance (EPR) spectroscopy. Time-dependent ^{19}F NMR showed a clear induction period of ca. 1 h, after which the reagent is rapidly consumed, forming the desired product along with byproducts within 20 min (Figure 7). The sigmoid curves hint toward an autocatalytic or radical process.[27]
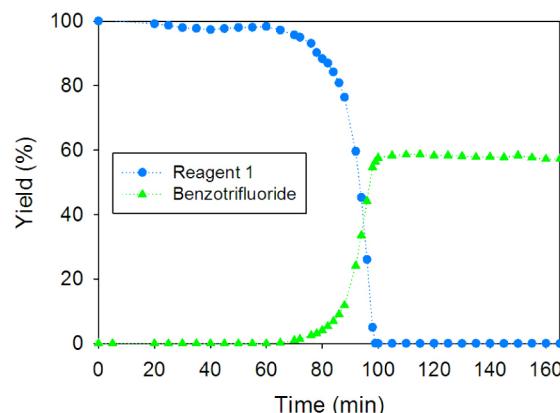
Figure 7. Reaction profile for trifluoromethylation of benzene (consumption of **1**, blue circles; formation of PhCF$_3$, green triangles).[27]

Therefore, EPR reaction monitoring was carried out to investigate whether radical species were involved in the reaction. Consonant with the ^{19}F NMR reaction profile, an induction period of ca. 1 h was observed, after which the concentration of radical species suddenly rose and decayed within ca. 30 min. It has to be noted that the shape of the EPR signal changes over time from a pseudodoublet to a singlet, indicating a change of radical composition in the reaction mixture (Figure 8).[27]

Based on these studies, a plausible reaction mechanism for the trifluoromethylation of arenes was proposed. We suggest that in a first step reagent **1** is activated by MTO via coordination of the metal center to the carboxyl group, as was shown for Zn(II) (see section 4.1). The activated species may form a CF$_3$ radical via a possible single-electron-transfer (SET) process with the substrate, thereby leading to formation of radical intermediate **18**. This first intermediate is then
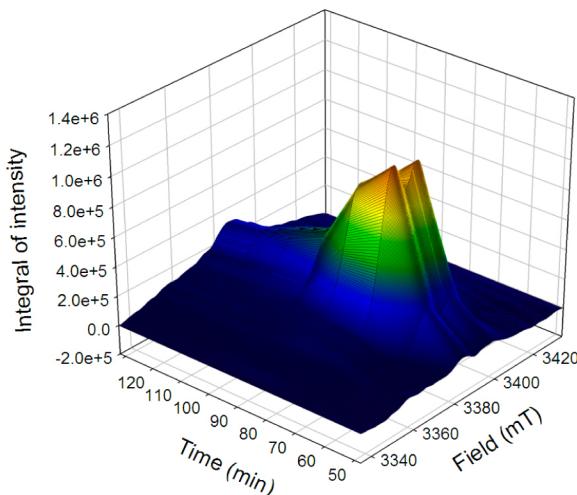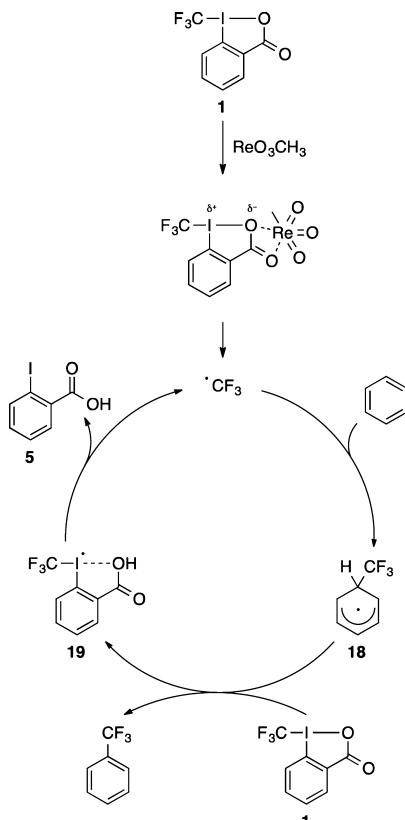
Figure 8. EPR reaction profile.[27]

deprotonated by reagent **1** to form the product and the reactive intermediate **19**, which is rapidly consumed by transfer of a CF_3 radical to the substrate, thus closing the cycle (Scheme 13).[27]

Scheme 13. Plausible Reaction Mechanism for Rhenium-Catalyzed Trifluoromethylation of Benzene[27]

4.3.2. Copper-Catalyzed Trifluoromethylation.
Between 2012 and 2013, no less than 35 contributions on copper-catalyzed[28] trifluoromethylations of carbon centers by use of reagents **1** and **2** were published (see section 5.2). In most cases reagent **1** is applied, which we presume to be due to the shorter synthesis, price, and commercial availability. Additionally, "standard conditions" for such transformations

emerged from several reports, consisting of reagent **1** and a substoichiometric amount of a copper(I) salt in acetonitrile. Usually, after a short optimization, suitable conditions for the corresponding transformation are found. In almost every report a possible reaction mechanism is presented, though in most cases detailed mechanistic investigations are scarce.

The most recurrent motif in these mechanistic proposals is the formation of iodonium ion **20** as shown in Figure 9.
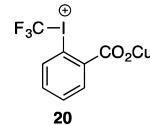
Figure 9. Postulated iodonium ion **20** supposedly formed in Cu-catalyzed trifluoromethylations.
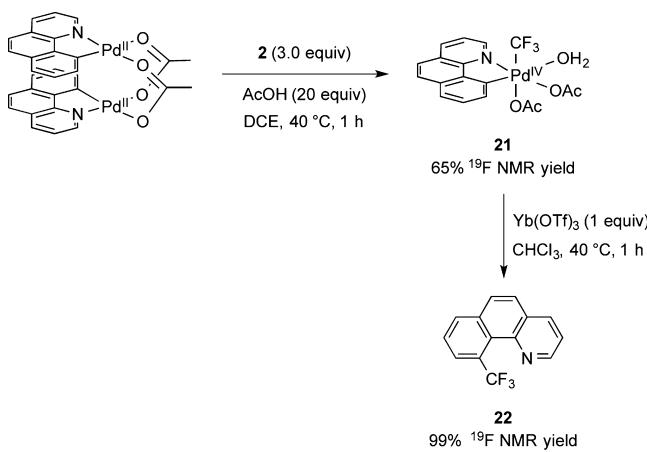
Originally, we also intuitively suspected such an intermediate; however, after we were able to obtain a crystal structure of a zinc(II) complex with **1** (see section 4.1), we abandoned this concept. The latter complex represents the only experimental evidence available so far describing the interaction of reagent **1** with a metal center from a structural point of view. Nevertheless, this evidence speaks strongly against the formation of iodonium ion **20** but merely indicates an I–O bond elongation. The formation of a real iodonium is actually even more unlikely in the case of copper(I), since Cu(I) has poor affinity for a κ^2 carboxylate group and the proximity of the large iodine atom to the carboxylate facilitates an even weaker I–O bonding interaction. It is well-known that interactions with iodine(III) are usually loose and bond distances are long, which further supports the view in favor of a mere elongation of the I–O bond rather than full cleavage.

Moreover, most reports suggest a radical/SET mechanism and thus "prove" this assumption by adding 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) to the reaction mixture. However, as shown recently by our group,[29] TEMPO itself can undergo trifluoromethylation with reagent **1** or **2** without the addition of a substrate. Thus, when trifluoromethylated TEMPO is formed, this does not necessarily indicate a radical-based mechanism but could indicate that TEMPO competes with the nucleophile present in the reaction mixture.[30] Similarly, the absence of a TEMPO–CF_3 adduct could be erroneously interpreted as disproof of a radical mechanism. So far, one of the few pieces of mechanistic evidence clearly speaking in favor of a radical mechanism has been reported by Zhang and co-workers[31] for the trifluoromethylation of allylic alcohols, where they observed products corresponding to a (radical) neophyl rearrangement rather than to a semipinacol rearrangement (see section 5.2.11).

4.3.3. Palladium-Mediated Trifluoromethylation.
A stand-alone report has been published by Sanford and co-workers[32] describing the oxidation of a dinuclear Pd[II] complex by use of reagent **1** to form the mononuclear Pd[IV]–CF_3 complex **21**. By choosing the right solvent and additive, it was possible to obtain the reductive elimination product 10-(trifluoromethyl)benzo[h]quinolone (**22**) in excellent yield (Scheme 14). Complex **21** is a potentially important intermediate in Pd-mediated C–CF_3 bond-forming reactions and could possibly be applied in Pd-catalyzed trifluoromethylations using reagent **1** or **2**.
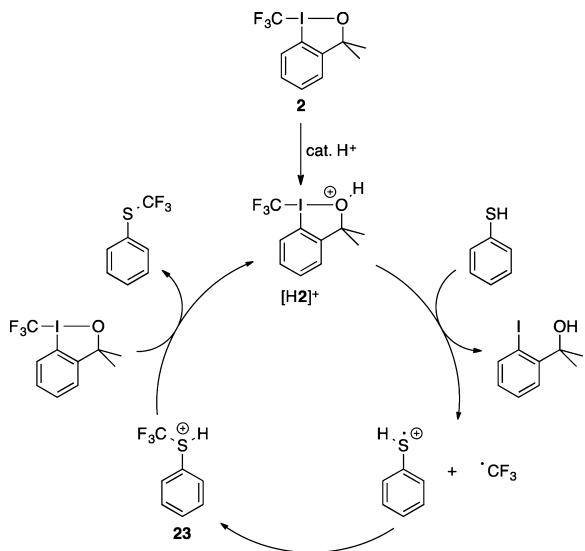
4.3.4. Trifluoromethylation of Thiols.
Thiols were among the first nucleophiles that were trifluoromethylated by

Scheme 14. Synthesis and Reductive Elimination of Pd[IV]–CF₃ Complex 21[32]

21
65% ¹⁹F NMR yield

Yb(OTf)₃ (1 equiv)
CHCl₃, 40 °C, 1 h

22
99% ¹⁹F NMR yield

use of reagent **1** or **2** (see section 5.1.1). They were found to react with both high yields and selectivity, and they feature an extensive substrate scope from simple thiophenol to cysteine side chains in peptides.[14a,33] The very short reaction times (the reaction is usually finished immediately after complete addition of the reagent) make the process inadequate for common ¹⁹F NMR monitoring experiments for mechanistic purposes. Therefore, a classical physicochemical approach was adopted. A Hammett plot was obtained through competition experiments between thiophenol and para-substituted thiophenols. The plot indicates the formation of a small negative charge on the substrate during the rate-determining step. The byproducts of the reaction, disulfide and CF₃H, however, hint toward a radical-based mechanism. Nitrone spin trapping followed by EPR detection confirmed this hypothesis. With these findings and the help of meta-dynamic calculations for the stability of intermediates,[34] a mechanistic proposal for the trifluoromethylation was formulated as shown in Scheme 15. After protonation of reagent **2** by either thiophenol or remaining H⁺ in dichloromethane, a CF₃ radical, from homolytic cleavage of the I–CF₃ bond, and simultaneously a thiyl radical are

Scheme 15. Mechanistic Proposal for Trifluoromethylation of Thiols[20]
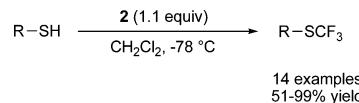
formed. After recombination, the highly acidic sulfonium intermediate **23** is formed, closing the catalytic cycle by protonation of another molecule of **2** and forming the desired product.[20]

5. APPLICATIONS

## 5.1. Trifluoromethylation of Non-Carbon-Centered Nucleophiles

5.1.1. Sulfur-Centered Nucleophiles. As mentioned above, thiols were among the first nucleophiles subjected to direct electrophilic trifluoromethylation conditions with reagent **1** or **2** (see section 4.3.4). Many aromatic and aliphatic mercaptans were trifluoromethylated in moderate to excellent yields. Biologically relevant compounds such as thiopyranose and cysteine were also readily trifluoromethylated with reagent **2** (Scheme 16). The transformation was shown to be highly
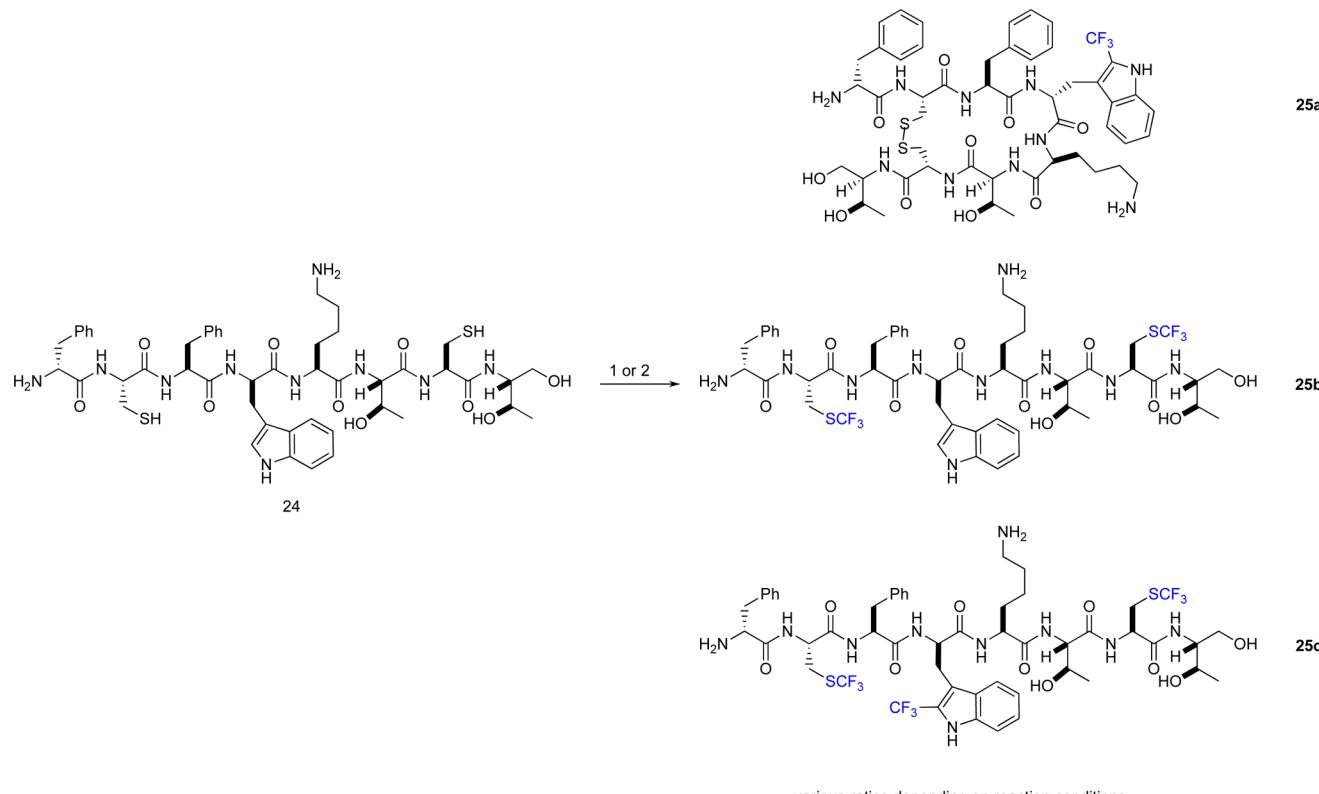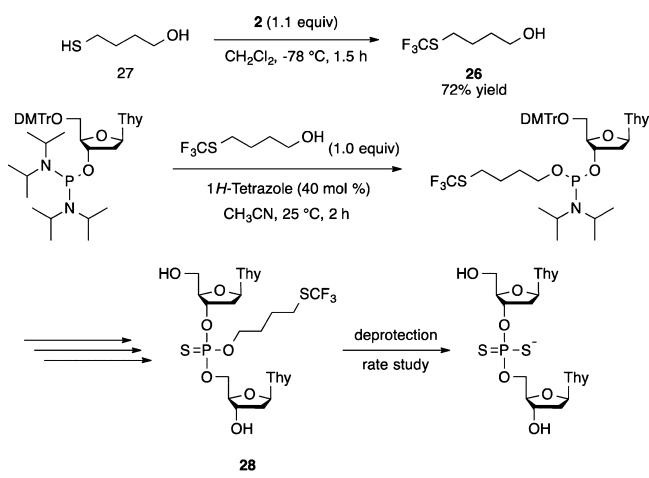
Scheme 16. Trifluoromethylation of Thiols[14a]

R–SH → R–SCF₃

2 (1.1 equiv)
CH₂Cl₂, -78 °C

14 examples
51–99% yield

tolerant toward a large number of functional groups. Amines, amides, carboxylic acids, thioacetals, alcohols, and alkynes did not interfere with the formation of the trifluoromethyl thioether, thus showing the possibility of forming the SCF₃ group in late stages of a synthesis. Trifluoromethylation of a thiol proceeds very quickly even at low temperatures, so that usually no competing side reactions are observed.[14a]
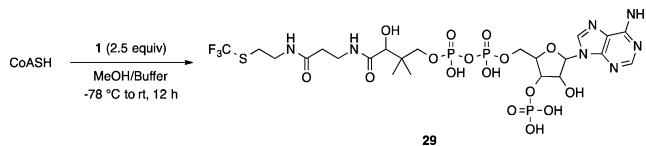
After the initial report concerning trifluoromethylation of thiols (Scheme 16) and the promising possible late-stage functionalization of biologically relevant molecules, the first corresponding practical application of reagent **1** or **2** was carried out by our group in collaboration with Seebach and co-workers.[33] The cysteine side chains of α- and β-peptides and of the reduced (ring-opened) form of the pharmaceutical Octreotide **24** were successfully trifluoromethylated. In the case of Octreotide, we were able to isolate three products in different ratios depending on the reaction conditions. Derivative **25a**, with a single CF₃ group in the 2-position of the indole moiety, is formed when the disulfide bond is still intact, whereas peptide **25b** is formed after cleavage and double trifluoromethylation, and derivative **25c**, bearing three CF₃ groups, is a byproduct (Scheme 17).[33,35]

In 2010, Beaucage and co-workers[36] investigated the deprotection rate of thiophosphate groups in oligonucleotide prodrugs. One of the protecting groups tested was 4-(trifluoromethylthio)but-1-yl (**26**), which was synthesized from 4-mercaptobutanol (**27**). This compound was trifluoromethylated by use of **2** and subsequently reacted with a deoxyribonucleoside phosphoramidite, which was then added to 2′-deoxythymidine. After oxidation, deprotection, and purification, the removal of the protecting groups of **28** under thermolytic conditions was investigated. Cleavage of the 4-(trifluoromethylthio)but-1-yl moiety took more than a day at 90 °C [compared to less than an hour for the best-performing protecting group N-(2-hydroxyethyl)acetamide]. This fact is accounted for by the strong electron-withdrawing properties of the trifluoromethyl group, which ultimately led the authors to conclude that this group is not a suitable protecting group for phosphoramidites (Scheme 18).[36]

Scheme 17. Trifluoromethylation of Octreotide[33]

25a

24 → (1 or 2) → 25b

25c

various ratios depending on reaction conditions

Scheme 18. Trifluoromethylation of 4-Mercaptobutanol (27) and Subsequent Use in a Deprotection-Rate Study of Oligonucleotide Prodrugs[36]


Scheme 19. Trifluoromethylation of Coenzyme A[37]

group[14a] was applied for the synthesis of trifluoromethylated 2′-deoxy-2′-mercaptouridine **31** (Scheme 20).

In 2011, a patent was filed for multisubstituted fluoromethanes as bioactive isosteres of biological phosphates.[39] The inventor claims several SCF$_3$-containing structures that have been synthesized by use of reagent **1** and a substoichiometric amount of Zn(NTf$_2$)$_2$. Biologically relevant molecules such as amino acids and thiosugars were used as substrates.
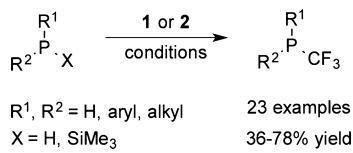
In 2013, Weng and co-workers[40] published the trifluoromethylation of sodium salts of arylsulfinates under copper catalysis. Not surprisingly, the substitution pattern of the aromatic ring influenced the yield of the transformation. Generally, π-acceptors and σ-donors in the para position increased the yield, whereas π-donors and σ-acceptors in the same position proved to be detrimental (Scheme 21).

5.1.2. Phosphorus-Centered Nucleophiles. After thiols, primary and secondary phosphines were chronologically the second type of heteroatom acceptor to be trifluoromethylated by use of reagents **1** and **2**. The electronic properties of the phosphorus atom of a trifluoromethylphosphine are drastically altered compared to both trialkyl or triaryl phosphines with respect to both σ-donating as well as π-accepting properties. However, the mono- or bistrifluoromethylated phosphines have also a significantly different steric demand as compared to more traditional tertiary phosphines. Thus perfluoroalkylphos-

The interest in protein−protein interactions in bioorganic chemistry inspired Khosla and co-workers[37] to use S-trifluoromethylated molecules as ^{19}F NMR spectroscopic probes. In a collaboration with Seebach and co-workers,[37] S-trifluoromethylated coenzyme A **29** was synthesized by use of reagent **1** and was used as a spectroscopic probe (Scheme 19).

Later, Micura and co-workers[38] published a further application of S-trifluoromethylated substrates as ^{19}F NMR probes. 2′-SCF$_3$ uridine **30** was used as a label in studies probing structure and function of RNA. The standard protocol for trifluoromethylation of sulfur nucleophiles reported by our

Scheme 20. Trifluoromethylation of Uridine by Use of Reagent 2[38]

31
80% yield

30
used for 19F NMR spectroscopic probing

Scheme 21. Trifluoromethylation of Arylsulfinate Sodium Salts[40]

R = donor or acceptor

13 examples
38-88% yield

phine ligands, because of their electronic and steric properties, are becoming interesting in transition metal catalysis and organometallic chemistry in general.[41]

Direct monotrifluoromethylation of primary and secondary phosphines was reported by our group in 2008.[42] The scope of the reaction is broad with both aryl and alkyl phosphines being trifluoromethylated as shown in Scheme 22. We speculated
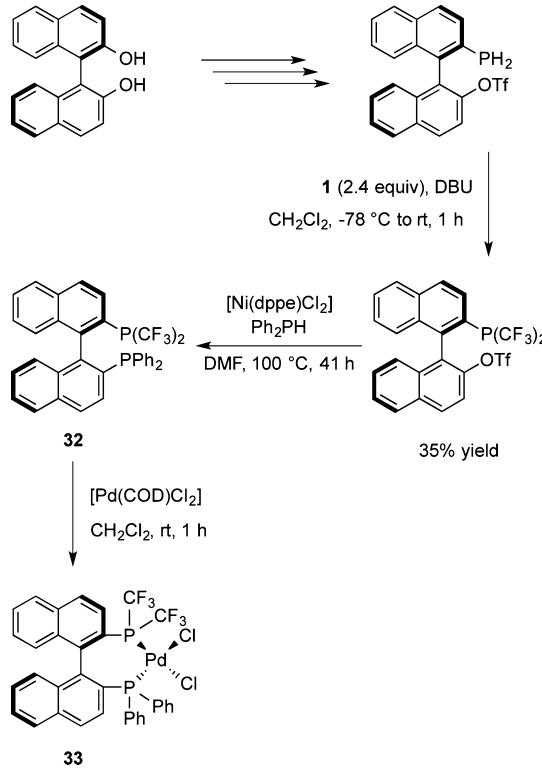
Scheme 22. Monotrifluoromethylation of Primary and Secondary Phosphines[42]

R^1, R^2 = H, aryl, alkyl
X = H, SiMe$_3$

23 examples
36-78% yield

about a radical reaction mechanism since CyP(CF$_3$)$_2$ could be observed as a side product in the reaction of Cy$_2$PH with **2**. This byproduct is most likely formed via homolytic cleavage of a C−P bond.

Further studies of our group in the field of trifluoromethylation of primary phosphines led to the report of the new bistrifluoromethylated 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (BINAP)-derived ligand **32** shown in Scheme 23. This ligand was used to form palladium dichloro complex **33**, which shows a shortened Pd−P(CF$_3$)$_2$ bond length [2.2230(4) Å] as compared to the Pd−P(Ph)$_2$ bond [2.2688(4) Å]. This can be explained by the high s-character of the phosphorus lone pair.[43]

As a next endeavor, our group started investigating the use of mono- or bistrifluoromethylated chiral phosphines as ligands for asymmetric catalysis. Thus, in 2011 we reported the synthesis of ferrocene-based (trifluoromethyl)phosphines starting from phenylphosphine (**34**) via the protocol described in Scheme 22. Two new ligands (**35a** and **35b**) and their palladium, iridium, and rhodium complexes were synthesized (Scheme 24).[44]

The ligands as well as the corresponding metal complexes were characterized by heteronuclear NMR spectroscopy and X-ray diffraction. In each metal complex, the metal−P(CF$_3$) bond distance is significantly shorter than the one involving the diaryl
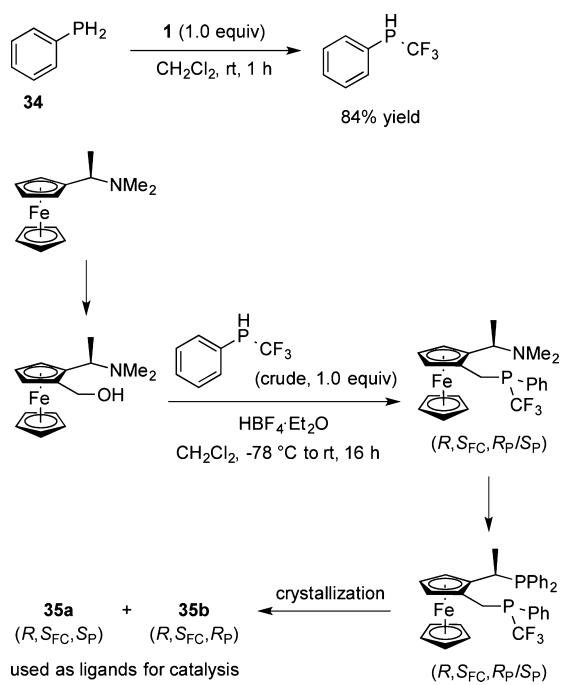
Scheme 23. Synthesis and Coordination of BINAP-Derived Bistrifluoromethylated Phosphine 32[43]

35% yield

32

33

phosphine phosphorus [e.g., for the iridium complex Ir−P(Ph$_2$) 2.3162(6) Å and Ir−P(CF$_3$)(Ph) 2.2731(6) Å]. This confirms our earlier findings that the stronger s-character of the phosphorus lone pair, which ultimately stems from the electron-withdrawing properties of the CF$_3$ moiety, results in a shorter bond. The catalytic performance of the new ligands was tested in Rh(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate. While the enantioselectivities achieved were only modest (up to 76% enantiomeric excess, ee), as compared to those obtained with existing systems, the reaction rates were exceptionally high.

Continuing the promising research on ligands with a P−CF$_3$ moiety, we were able to synthesize trifluoromethyl derivatives of Josiphos. Bistrifluoromethylated phenylphosphine **36** was added to Ugi's amine (**37**) to form the monotrifluoromethylated diastereomeric compounds **38a** (S_P) and **38b** (R_P), which were readily separated by column chromatography and then converted to the corresponding trifluoromethylated Josiphos analogues (**39a** and **39b**) (Scheme 25).[45]

The coordination behavior of ligands **39a** and **39b** with Pd and Rh was studied via X-ray crystallography and IR spectroscopy. The ligands were tested in Rh-catalyzed hydro-

**Scheme 24. Synthesis of Bistrifluoromethylated Ferrocene-based Ligands 35a and 35b[44]**

give synthetic chemists a new convenient method for late-stage formation of a trifluoromethoxy group.

Umemoto et al.[48] reported the first direct electrophilic trifluoromethylation of both aromatic and aliphatic alcohols, using a O-(trifluoromethyl)dibenzofuranium salt. However, this method suffers from several drawbacks, such as the in situ preparation of the reagent at low temperature, its instability, and the fact that the oxygen-bound CF_3 fragment in the reagent stems from a OCF_3 group that has to be constructed first. Thus, there is still an urgent need for methods addressing the trifluoromethylation of oxygen nucleophiles.

In 2008 we reported our first studies toward the O-trifluoromethylation of phenols.[12a] Using the simplest substrate, phenol, we only observed aromatic electrophilic substitution, that is, trifluoromethylation in ortho and para positions. However, when we used 2,4,6-trimethylphenol (**40**), in which these positions are blocked, we were able to isolate the desired O-trifluoromethylated product **41**, albeit in low yield (along with dearomatization products; see Scheme 26). Further
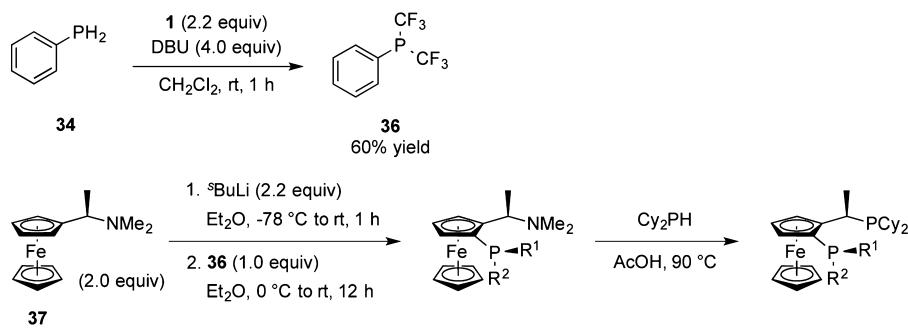
Scheme 26. O-Trifluoromethylation of 2,4,6-Trimethylphenol[12a]

genation of dimethyl itaconate (DMI) and α-acetimidoacrylate (MAA). The ligands performed very well in the case of DMI [turnover frequency (TOF) 3000 h^{-1}, 95% ee for **39a** (S_P); TOF 4000 h^{-1}, 97% ee for **39b** (R_P)] and also afforded high activities in the hydrogenation of MAA. Both ligands showed very high TOFs (6000 h^{-1}) for MAA and performed equally well or better in terms of enantioselectivity than the parent Josiphos (88% ee).[46] In this transformation, the influence of the absolute configuration of the phosphorus atom was more pronounced. Indeed, **39b** (R_P) outperformed its isomer **39a** (S_P) by 10% ee to achieve 98% ee.

5.1.3. Oxygen-Centered Nucleophiles. Methods to introduce a trifluoromethoxy group into a molecule by functional group interconversions mostly require the use of harsh reaction conditions and hazardous reagents, such as CCl_4/HF, COF_2, SF_4, or SbF_5.[47] Therefore, the synthesis of complex organic molecules containing an OCF_3 substituent heavily relies on available building blocks. Clearly, the electrophilic trifluoromethylation of a hydroxyl group would

investigation with other aromatic substrates showed that blocking the ortho and para positions is crucial in order to obtain O-trifluoromethylation. As soon as one of the positions was amenable to electrophilic aromatic substitution, such a transformation was observed exclusively.[12a]

After the first success with trifluoromethylation of **40** by hypervalent iodine reagent **1** (see Scheme 26), we extended these investigations toward the trifluoromethylation of aliphatic alcohols. When we applied the newly acquired knowledge of the activation of **1** by Zn(II) salts in trifluoromethylation of 1-pentanol as a model substrate (see section 4.1), we were able to obtain the corresponding trifluoromethyl ether in 83% yield. Thus, various other alkanols that can be used as both solvent and substrate afford excellent yields with respect to reagent **1**, used in this protocol as limiting species. When solid or more precious substrates are being reacted, a molar ratio of 5:1 between the alcohol and reagent **1** is an acceptable

**Scheme 25. Synthesis of Monotrifluoromethylated Josiphos Analogues 39a and 39b[45]**
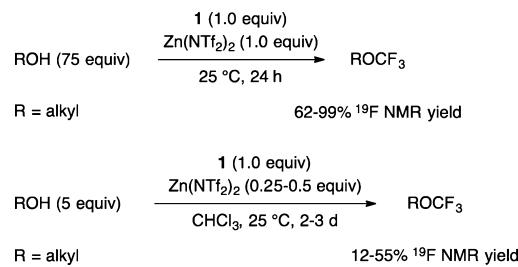
38a (S_P): R^1=Ph, R^2=CF$_3$, 41%   **39a** (S_P): R^1=Ph, R^2=CF$_3$, 76%
38b (R_P): R^1=CF$_3$, R^2=Ph, 51%   **39b** (R_P): R^1=CF$_3$, R^2=Ph, 83%
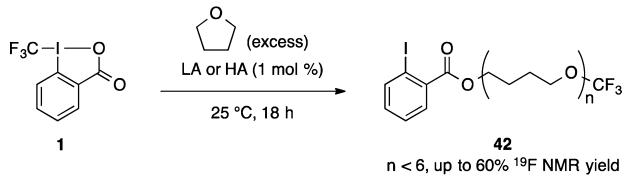
compromise, still giving the desired product in fair yields (Scheme 27).[21]

Scheme 27. Trifluoromethylation of Alcohols[21]

During the optimization of the aforementioned trifluoromethylation of alcohols (see Scheme 27), we observed that when the reaction was carried out in tetrahydrofuran (THF), none of the desired product was formed. However, ^{19}F NMR resonances at shifts typical for OCF$_3$ (ca. −60 ppm) were observed. Further investigation by 2D NMR spectroscopy revealed that the major products were **42a** (n = 1) and **42b** (n = 2), derived from a ring-opening process of THF, followed by oligomerization and trifluoromethylation of the terminal oxygen atom (Scheme 28). Reaction screening showed that

Scheme 28. Formation of Trifluoromethyl Ethers 42 from Tetrahydrofuran and 1[49]
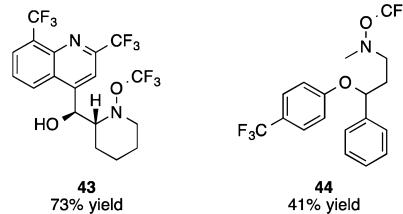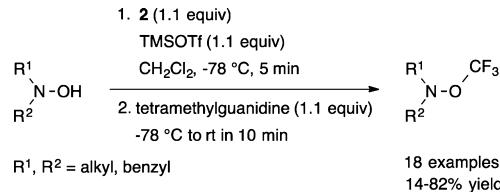
this reaction takes place in the presence of lanthanide triflimidates as Lewis acids, but HNTf$_2$ was also able to catalyze this trifluoromethylation, indicating that this transformation is (Lewis) acid-catalyzed.[49]

As shown above (see section 4.2.1, Scheme 8), sulfonic acids react preferentially with reagent **1** to afford the corresponding trifluoromethyl sulfonates in good to excellent NMR and isolated yields.[23a] These compounds were virtually unknown before, the triflate being an exception. Several of these new derivatives turn out to be stable toward nucleophiles and can be hydrolyzed only under basic aqueous conditions. Hence the intriguing question arises whether these sulfonates might be viewed as protected forms of sulfonic acids that are not alkylating and are much more soluble than their parent compounds even in nonpolar organic solvents.

Inspired by several reports describing the use of TEMPO as radical trapping reagent for mechanistic studies and a report by Li and Studer[50] involving a TEMPO sodium salt in tandem fluoroalkylation−aminooxylation of styrenes (see section 5.2.7), we decided to investigate the reactivity of reagents **1** and **2** toward N,N-dialkylhydroxylamines. Initial experiments with N,N-dibenzylhydroxylamine led to formation of the corresponding O-trifluoromethyl product in 61% yield. Optimized reaction conditions allowed hydroxylamines to undergo O-trifluoromethylation in moderate to good yields. Reagent **2** is activated by stirring with TMSOTf for 5 min, followed by the addition of deprotonated substrate. This

simultaneous double activation of substrate and reagent is crucial for a broad reaction scope (Scheme 29).[29]

Scheme 29. Trifluoromethylation of N,N-Dialkylhydroxylamines and O-Trifluoromethylated Hydroxylamine Analogues of Mefloquine (43) and Fluoxetine (44)[29]
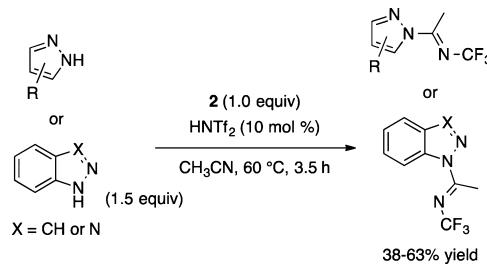

During this study we also prepared the new N-trifluoromethoxy compounds **43** and **44**, derived from the known drugs mefloquine and fluoxetine, respectively. The NOCF$_3$ moiety in organic molecules is a virtually unexplored functional group displaying an interesting conformational/configurational behavior. A n(N)−σ*(CF) hyperconjugative interaction is thought to stabilize the observed preferred conformation having a N−O−C−F antiperiplanar arrangement while raising the inversion barrier of the nitrogen atom.[29]

5.1.4. Nitrogen-Centered Nucleophiles. Current strategies toward N-trifluoromethyl organic compounds consist mainly of functional group interconversions[51] such as oxidative desulfurization−fluorination of dithiocarbamates.[52]

While investigating the trifluoromethylation of heteroarenes in our group,[53] we discovered a Ritter-type reaction of an azole when conducting corresponding reactions with reagent **2** in acetonitrile. Optimized reaction conditions allowed this first N-trifluoromethylation with our reagent to proceed in up to 63% isolated yield (Scheme 30).[54] The new derivatives are stable, often crystalline materials that contain a quite unique functional group.
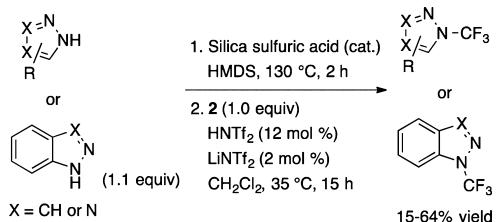
As a side product of the above-mentioned reaction, the compound derived from the trifluoromethylation of the nitrogen nucleophile was also observed, however, in less than 10% yield. The key to the selective direct N-trifluoromethylation was found to be in situ silylation of the substrate followed

Scheme 30. Ritter-type N-Trifluoromethylation of Various Azoles under HNTf$_2$ Catalysis[54]

by acid-catalyzed reaction with reagent **2**. These conditions were then successfully applied to a variety of substituted azoles as shown in Scheme 31.[55]

Scheme 31. Acid-Catalyzed Direct N-Trifluoromethylation of Azoles[55]

In 2013, Gilead Sciences published a patent describing potential agents for the treatment of HIV infections.[56] The CF₃ group was introduced via a slightly modified version of our original protocol. The authors investigated several thiazole-derived potential drug candidates, one of which bears an N-trifluoromethylated indazole moiety as shown in Figure 10.
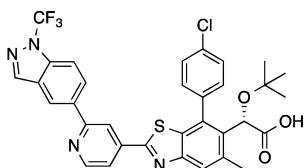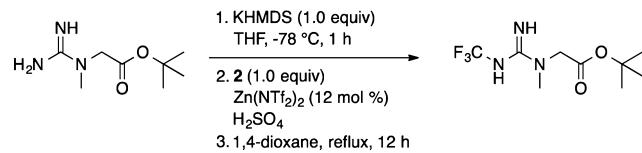
Figure 10. Potential anti-HIV drug bearing a NCF₃ moiety.[56]

The same patent that claimed various S-trifluoromethylated substances (see section 5.1.1) also reported an NCF₃-containing guanidine derivative (Scheme 32).[39]

Scheme 32. N-Trifluoromethylation of a Guanidine Derivative[39]
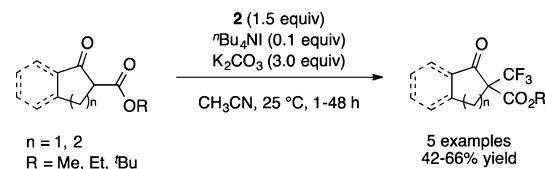
## 5.2. Trifluoromethylation of Carbon-Centered Nucleophiles
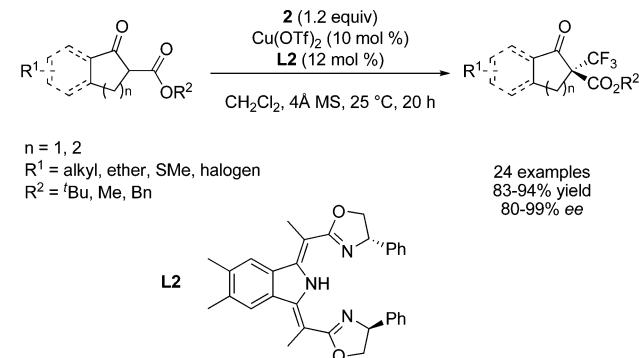
5.2.1. Carbonyl Compounds. One of the first trifluoromethylations using benziodoxole-based reagent **2** was the trifluoromethylation of β-keto esters under phase-transfer catalysis (Scheme 33).[1b,14a] However, this reaction, which requires a large excess of base for deprotonation at the α-position, proceeds only for 5- or 6-membered cyclic substrates.

More recently, Gade and co-workers[57] presented the enantioselective version of this transformation (Scheme 34). By using a catalytic system composed of a copper(II) precursor

Scheme 33. Trifluoromethylation of β-Keto Esters[1b,14a]
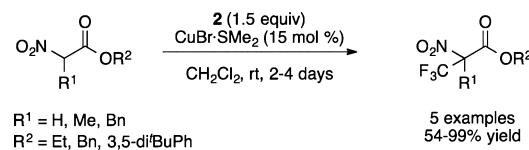
Scheme 34. Enantioselective Trifluoromethylation of β-Keto Esters[57]

and boxmi ligand **L2**, they could achieve up to 99% ee. This very efficient way to produce enantioenriched trifluoromethylated quaternary carbon centers suffers (as does the example presented above) from being applicable exclusively to cyclic substrates.

Similarly to β-keto esters, α-nitro esters also possess an easily enolizable position at the α-carbon due to the electron-withdrawing properties of the nitro group. Hence the trifluoromethylation of this class of compounds proceeds in a similar way as the above-presented trifluoromethylation of β-keto esters.[14a,58] This reaction, originally reported from our laboratory in 2007, works most efficiently under Cu(I) catalysis (Scheme 35) and consequently became the forerunner of a myriad of copper-catalyzed trifluoromethylations of carbon centers by use of reagents **1** and/or **2** (see section 4.3.2).
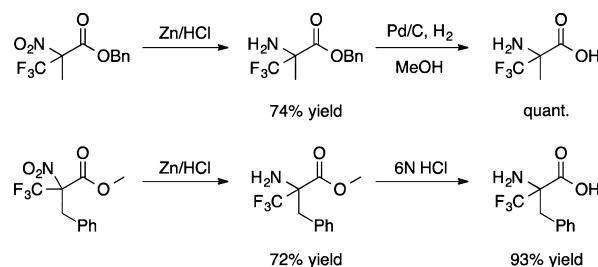
Scheme 35. Copper-Catalyzed Trifluoromethylation of α-Nitro Esters[58]

Noteworthy for nitro esters is that reduction of the nitro group with zinc powder and removal of the ester substituent allows access to α-trifluoromethylated α-amino acids as shown in Scheme 36.[58]
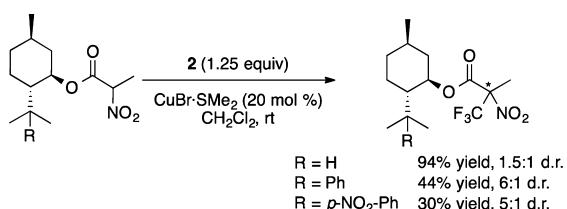
The access to α-trifluoromethylated amino acids clearly formulates the need for an enantioselective trifluoromethylation of α-nitro esters. Studies using chiral ligands together with copper(I) salts showed that enantioselectivity of up to only 24% ee could be achieved.[58] Therefore, the possibility of

Scheme 36. Synthesis of α-Trifluoromethylalanine and α-Trifluoromethylphenylalanine[58]

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accessing enantioenriched α-CF$_3$-α-amino acids was investigated through the application of chiral auxiliaries at the ester position.[22] In this way, formation of the C−CF$_3$ bond could proceed diastereoselectively via remote stereocenter control. Several naturally and non-naturally derived chiral esters were applied in the reaction, and diastereoselectivities of up to 6:1 were observed by use of a phenylmethyl-derived auxiliary (Scheme 37).
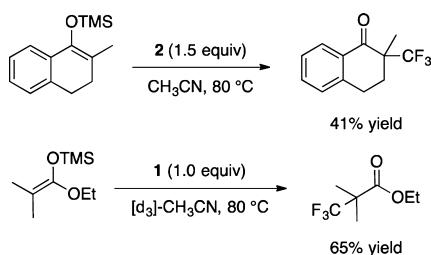
Scheme 37. Diastereoselective Trifluoromethylation of Chiral α-Nitro Esters[22]

R = H   94% yield, 1.5:1 d.r.
R = Ph   44% yield, 6:1 d.r.
R = p-NO$_2$-Ph   30% yield, 5:1 d.r.

The trifluoromethylation of both β-keto and α-nitro esters is mechanistically intriguing. At the present stage it is not known whether the enol or the enolate form of the substrate is the active species, either as a nucleophile or as acceptor of a CF$_3$ radical.
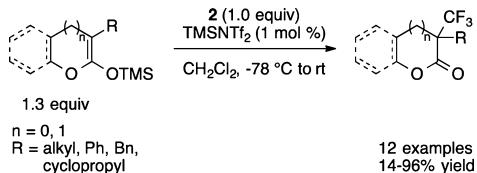
Direct trifluoromethylation of simple carbonyl compounds without an electron-withdrawing environment was less straightforward. The key to success for trifluoromethylation of ketones and esters is a two-step process including isolation of the corresponding silyl enol ethers or silyl ketene acetals. These strong nucleophiles undergo trifluoromethylation under rather mild conditions without requiring any further additives (Scheme 38).[59]

Scheme 38. Synthesis of Trifluoromethylated Ketones and Esters[59]

41% yield

65% yield

This reaction was further explored to incorporate lactone-derived silyl ketene acetals. Indeed, when cyclic silyl ketene acetals were used under trimethylsilyl triflimide (TMSNTf$_2$) catalysis, α-trifluoromethylated lactones could be obtained in up to 96% yield (Scheme 39).[22,60] Interestingly, the reaction is rather insensitive to steric bulk, with excellent yields for both isopropyl- and cyclohexyl-substituted lactones. Both 5- and 6-
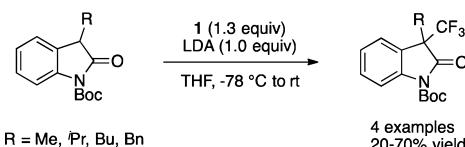
Scheme 39. Synthesis of Trifluoromethylated Lactones[22,60]

1.3 equiv
n = 0, 1
R = alkyl, Ph, Bn,
    cyclopropyl

12 examples
14-96% yield

membered α-trifluoromethylated lactones were successfully prepared by this method. While α-heteroatom-substituted silyl ketene acetals led to rapid and highly unselective trifluoromethylations, α-aryl-substituted substrates reacted only sluggishly; only a rather narrow range of substrates provide clean reactivity. Too electron-rich substrates react unselectively (probably as a result of single-electron-transfer processes), whereas aromatic silyl ketene acetals lack reactivity due to their diminished nucleophilicity. The latter can be explained by the extended aromatic conjugation into the corresponding ketene acetals.

Direct trifluoromethylation of oxindoles as an extension of α-trifluoromethylation of carbonyl compounds is a topic of major interest in medicinal chemistry. Similarly to other trifluoromethylations in this section, this reaction occurs via initial formation of the corresponding enolate by deprotonation with lithium diisopropylamide (LDA), which can then react with the electrophilic CF$_3$ source as shown in Scheme 40.[60] Alkyl

Scheme 40. Direct Trifluoromethylation of Oxindoles[60]

R = Me, ^{i}Pr, Bu, Bn

4 examples
20-70% yield
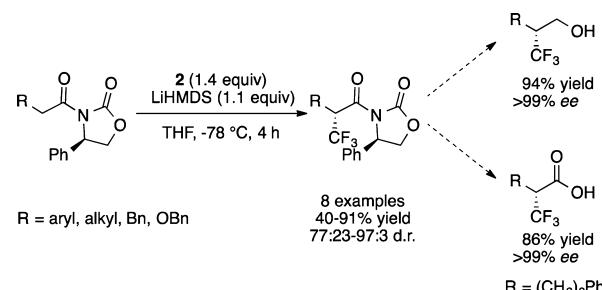
substituents are well-tolerated, even though the yields drop with increasing steric bulk. Additionally, enolates of 3-aryl-substituted oxindoles showed poor reactivity, similarly to aryl-substituted silyl ketene acetals. As already discussed above, this lack in reactivity is likely due to poor nucleophilicity because of extended aromatic conjugation.

Another way to access stereoselectively α-trifluoromethylated carbonyl compounds would be the use of chiral oxazolidinones as auxiliaries as already presented in 1981 by Evans et al.[61] Deprotonation of the N-acyl oxazolidinones with a strong base [lithium bis(trimethylsilyl)amide (LiHMDS) in this case] yields the corresponding enolates, which can then attack an electrophile. The use of reagent **2** as an electrophile is well-tolerated in this reaction to achieve a high level of stereocontrol (diastereomeric ratio, dr, of up to 97:3). The products can then be further derivatized to afford a number of functional derivatives such as β-trifluoromethylated alcohols or α-trifluoromethylated carboxylic acids with no degradation of enantiomeric excess at the newly formed stereocenter (Scheme 41).[62]
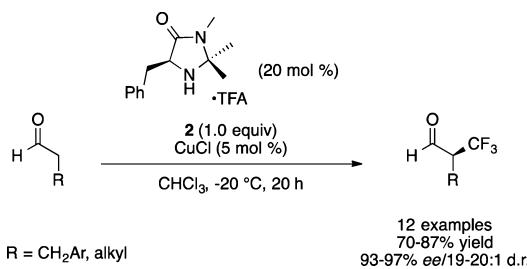
A very elegant method for the synthesis of enantioenriched α-carbonyl compounds was presented by Allen and MacMil-

Scheme 41. Synthesis of α-CF$_3$-Substituted Acyl Oxazolidinones and Their Derivatization[62]

R = aryl, alkyl, Bn, OBn

8 examples
40-91% yield
77:23-97:3 d.r.

94% yield
>99% ee

86% yield
>99% ee

R = (CH$_2$)$_3$Ph
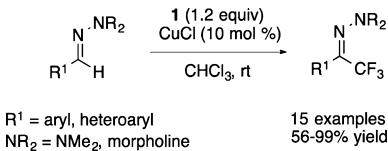
lan.[12b] Trifluoromethylation of aldehydes under a combination of organocatalysis and copper(I) catalysis afforded the corresponding α-trifluoromethyl aldehydes in up to 96% ee. Further derivatization gave access to trifluoromethylated products similar to those obtained by the auxiliary method presented above.

Scheme 42. Enantioselective α-Trifluoromethylation of Aldehydes under Organocatalysis[12b]

5.2.2. Hydrazones.
Another recent addition to the substrate scope of electrophilic trifluoromethylations came from Baudoin and co-workers[63] with the trifluoromethylation of N,N-dialkylhydrazones. This reaction is another interesting example of the excellent affinity between our hypervalent iodine reagents and Cu(I) catalysts, presumably via the formation of a CF$_3$ radical species resulting from SET (Scheme 43). The ipso-

Scheme 43. Copper-Catalyzed Trifluoromethylation of N,N-Dialkylhydrazones[63]

trifluoromethylated hydrazones are interesting intermediates since they allow access to a number of synthetically relevant products. For instance, functional-group transformations yield trifluoromethyl ketones by acid-mediated hydrolysis and hydrazines by reduction. The authors describe trifluoromethylation of a variety of substituted aromatic hydrazones, including heteroaromatic substrates such as pyridyl-, pyrazolyl-, and furanyldimethylhydrazones. The electronic properties of the aromatic substituent have little impact, as both electron-withdrawing and electron-donating groups are tolerated, regardless of their position. However, somewhat decreased yields are observed for particularly electron-rich aromatic systems due to competing aromatic trifluoromethylation.
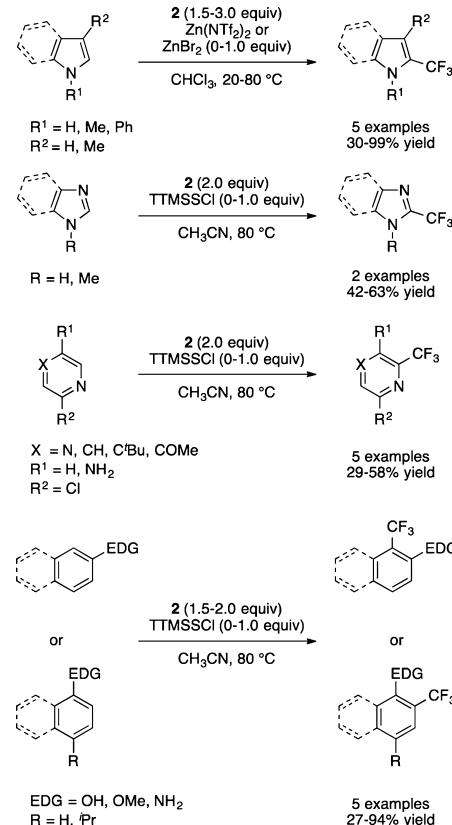
5.2.3. Aryl and Heteroaryl Compounds.
Aromatic trifluoromethylation by use of electrophilic reagents relies on two different strategies as illustrated in Scheme 44: (a) making use of the innate reactivity of arenes for direct functionalization or (b) introducing a leaving group for regioselective trifluoromethylation.

Scheme 44. Strategies for Electrophilic Trifluoromethylation of Aromatic Compounds

A first example of electrophilic aromatic trifluoromethylations is the direct reaction of electron-rich arenes and N-heteroarenes presented by our group.[53] As illustrated in Scheme 45, activation of the trifluoromethylating reagent may
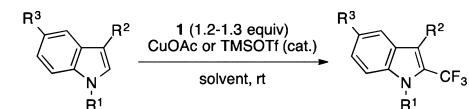
Scheme 45. Trifluoromethylation of Electron-Rich (Hetero)aromatic Compounds[53]


be necessary (depending on the nature of the substrates) and can be achieved by using Lewis acids such as Zn(NTf$_2$)$_2$, ZnBr$_2$, or tris(trimethylsilyl)silyl chloride (TTMSSCl) (see section 4.1). This work shows the successful trifluoromethylation of electron-rich aromatic systems, such as pyrroles, indoles, (benz)imidazoles, pyridines, and phenyl derivatives substituted with electron-donating groups. However, there is no general protocol that can be applied to a broad variety of substrates, and even within the same substrate class, the optimal reaction conditions may vary significantly. These trifluoromethylations are generally regioselective and are directed by the nitrogen atom of N-heterocycles or the presence of an ortho-directing group on phenyl derivatives.

Subsequently, Sodeoka and co-workers[64] published two additional approaches for C2 trifluoromethylation of indoles. These methods rely on the catalytic activation of reagent **1** by either TMSOTf or CuOAc as shown in Scheme 46. They are less substrate-dependent than the previously reported ones and are applicable to free and N-substituted indole derivatives. Electron-donating groups in position 3 or 5 increase the reactivity.
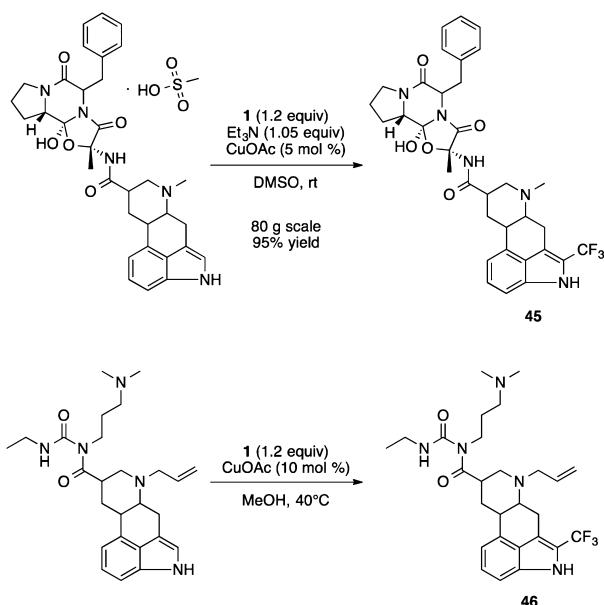
MAP Pharmaceuticals applied the CuOAc-catalyzed trifluoromethylation of indoles presented above in the scalable synthesis of one of their active pharmaceutical ingredients.[65] Ergoline derivative **45** has been synthesized on a 80 g scale and is currently being tested in clinical trials for the treatment of

Scheme 46. Direct C2 Trifluoromethylation of Indoles[64]

R[1] = H, Me, Bn, Ac, Boc
R[2] = Me, CO$_2$Me, (CH$_2$)$_2$CO$_2$Me, (CH$_2$)$_2$NHBoc,
  (CH$_2$)$_2$NHAc, CH$_2$CH(NHBoc)(CO$_2$Me)
R$_3$ = H, OMe, Br
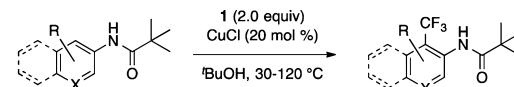
13 examples
5-90 % yield

migraine (Scheme 47). A similar protocol (however, on a smaller scale) has been applied to synthesize **46**, which was developed for the treatment of Parkinson's disease.[66]

Scheme 47. Synthesis of Trifluoromethylated Ergoline and Carboergoline Analogues[65,66]

Scheme 48. Pivalamido-Directed Ortho-Trifluoromethylation of Arenes[67]

R = H, alkyl, halogen, ether, CO$_2$Et
X = CH, N

13 examples
40-70% yield
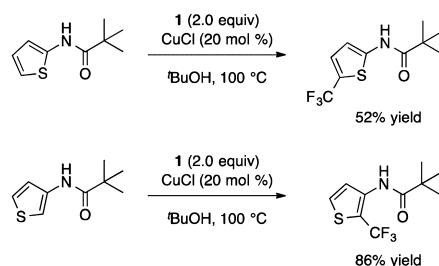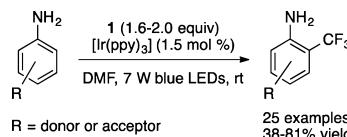
An extension to the ortho-trifluoromethylation of arenes was achieved by the use of N-pivalamide as directing group by Cai et al.[67] Phenyl, thiophene, and pyridine derivatives have been trifluoromethylated regioselectively in the ortho position to the pivalamido-directing group under Cu(I) catalysis (Scheme 48). Interestingly, for heteroarenes the directing properties of the heteroatom in the arene are more important than those of the pivalamido group, such that 2-thienyl pivalamide is trifluoromethylated ortho to the sulfur atom. 3-Substituted thiophenes are trifluoromethylated preferentially ortho to both sulfur and the directing group.

More recently, Xie et al.[68] achieved direct trifluoromethylation of unprotected anilines (Scheme 49). Their approach relies on the use of [Ir(ppy)$_3$] as a photoredox catalyst, which is believed to produce the active CF$_3$ radical. The trifluoromethylated products are obtained in moderate to good yields, with no major influence of the electronic properties of the substituents on reactivity. While para-substituted anilines are reported to furnish the corresponding trifluoromethylated products as single regioisomers, ortho- and meta-substitution yield a mixture of regioisomers. Regioselectivity is also observed for aryl-substituted anilines, which are trifluoromethylated only on the aniline ring, regardless of the position of the substituent. The authors additionally present the derivatization of trifluoromethyl-substituted anilines into a range of relevant

building blocks (quinolone, tetrazole, isatin, benzoxazole, benzothiazole, and azide), demonstrating the versatility of such aniline intermediates for synthetic purposes.

Another remarkable example of direct trifluoromethylation of aromatic substrates has been achieved by the radical trifluoromethylation under MTO initiation (see section 4.3.1).[27b] This method does not rely on directing or activating groups and can thus be applied to a very broad range of substrates (Scheme 50). This feature, combined with the radical

Scheme 49. Trifluoromethylation of Anilines under Photoredox Catalysis[68]

R = donor or acceptor

25 examples
38-81% yield

Scheme 50. Rhenium-Catalyzed Trifluoromethylation of Arenes[27b]

(1.5 equiv)
X = CH, N
R = donor, acceptor
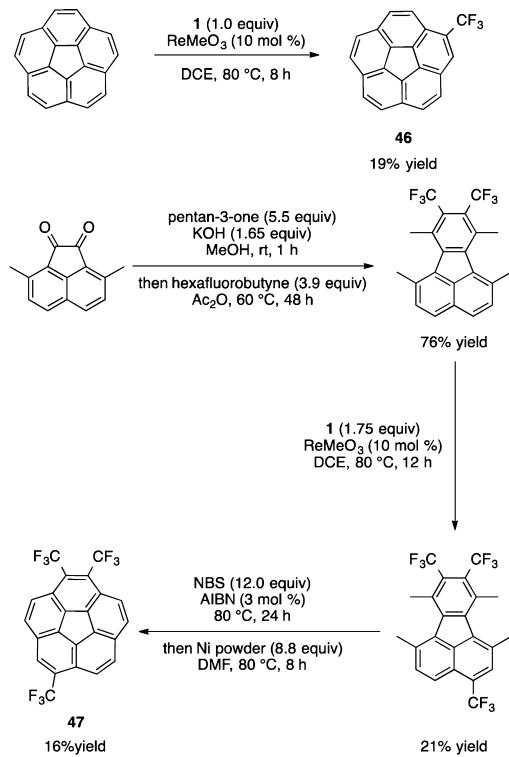
34 examples
13-77% ^{19}F NMR yield

nature of this process, results in very poor regioselectivity for most substrates since the different positions are often of similar reactivity. The product distribution accounts only very little for the electronic characteristics of the different positions. The largest electronic effect is observed for the very electron-withdrawing nitro group with a product distribution of 1:3.5:10 (ortho:meta:para). The highest yields are achieved for electron-rich substrates but electron-poor substrates can also be trifluoromethylated, however, in rather modest yields. Noteworthy is the first trifluoromethylation of ferrocene in 33% yield by use of an electrophilic trifluoromethylation reagent.

Interested in the potential of trifluoromethyl substituents to tune the electronic properties of materials, Lentz and co-workers[69] investigated trifluoromethylated corannulenes. In this endeavor they synthesized the trifluoromethylated and tristrifluoromethylated corannulenes **47** and **48** using MTO
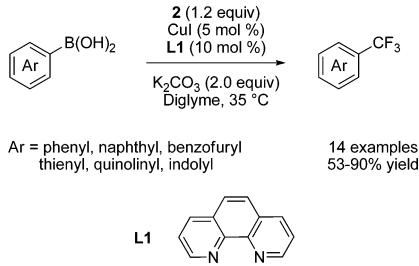
as initiator (Scheme 51). These compounds, owing to their exceptionally ordered solid-state structures, are candidates for new electrical materials.

Scheme 51. Synthesis of Trifluoromethylated Corannulenes[69]

Scheme 53. One-Pot Borylation and Trifluoromethylation of Arenes[71]

and electron-poor substrates. The authors proved the utility of their procedure by applying it to late-stage trifluoromethylation of several natural products.

A further addition to the toolbox of aromatic trifluoromethylations was made by Huang et al.[72] They replaced the aromatic boronic acids or esters by the more reactive trifluoroborates as substrates (Scheme 54). Selective trifluor-
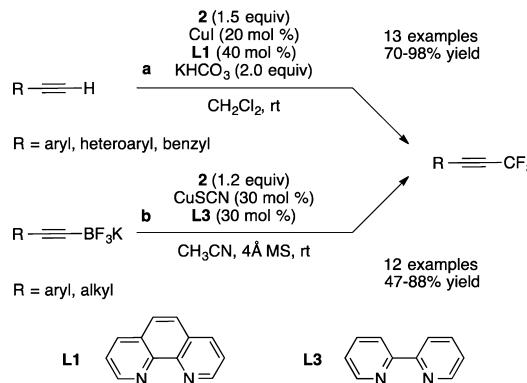
Scheme 54. Trifluoromethylation of Aromatic Tetrafluoroborates[72]

omethylation occurred in good yields on both electron-rich and electron-poor substrates. The milder conditions, that is, lower reaction temperatures and the absence of base, used in this protocol should allow for trifluoromethylation of more sensitive substrates.

5.2.4. Terminal Alkynes. In 2012, Weng et al.[73] presented the direct trifluoromethylation of acetylenes under Cu(I) catalysis in the presence of an excess of base (Scheme 55, route a). This reaction proceeds smoothly for electron-rich aryl-substituted acetylenes with up to 98% yield. It is worth mentioning that this methodology tolerates even bromides and amines as substituents on the aromatic fragments, which allows for further derivatization of the trifluoromethylated products.

As shown above, regioselectivity (if present) in the direct trifluoromethylation of arenes is influenced by regiodirecting groups. This did not allow functionalization of all available positions. To overcome this limitation, Liu and Shen[70] developed a method for trifluoromethylation of aryl boronic acids by use of reagent **2** (Scheme 52).

Scheme 52. Trifluoromethylation of Arene Boronic Acids[70]

This reaction, which is catalyzed by copper(I) iodide, proceeds smoothly for arenes and heteroarenes bearing electron-withdrawing and electron-donating groups. Subsequently, the same group extended this method to a one-pot procedure consisting of iridium-catalyzed borylation followed by copper-catalyzed trifluoromethylation.[71] This method (see Scheme 53) is applied to 1,3-substituted arenes with high regioselectivity. It is complementary to the ortho-directed trifluoromethylations mentioned above since it allows meta-substitution of the aromatic substrates. The reaction scope is broad since trifluoromethylation occurs on both electron-rich

Scheme 55. Synthesis of Trifluoromethylated Acetylenes[73,74]
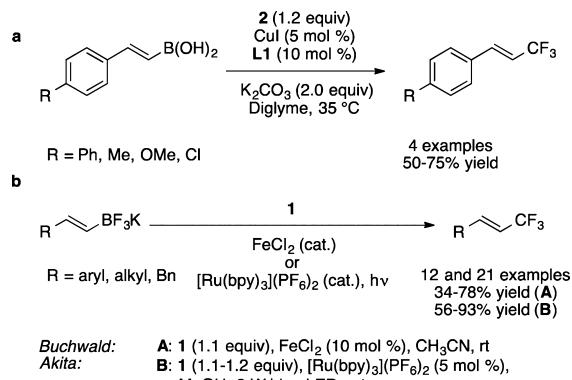
Additionally, the authors show that benzyl- and thiophene-substituted acetylenes are readily trifluoromethylated under the same reaction conditions.

As an extension of this work, the same group later presented the trifluoromethylation of prefunctionalized alkynes in the form of alkynyltrifluoroborates (Scheme 55, route b).[74] The need for prefunctionalization and higher catalytic loading is counterbalanced by the possibility to diminish the excess of reagent **2**. Additionally, more sensitive substrates could theoretically be trifluoromethylated under these reaction conditions, as no base is required. As a noteworthy extension, this method allows for trifluoromethylation of nonaromatic acetylenes as shown by the example of hept-1-ynyltrifluoroborate, which is converted to the corresponding product in 75% yield.

5.2.5. Vinylic Functionalization. The quest for the formation of vinyl-CF₃ bonds has been addressed by several groups in a similar fashion. Liu and Shen,[70] Buchwald and co-workers,[75] and Akita and co-workers[76] chose boron-substituted olefins as formal nucleophiles in this transformation. Vinyl-boronic acids as well as trifluoroborates can be trifluoromethylated by use of Cu(I), Fe(II), or a photoredox catalyst (Scheme 56). Stilbene-derived substrates as well as benzyl- or alkyl-
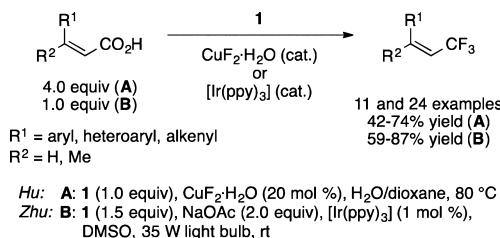
Scheme 56. Trifluoromethylation of Vinylboronic Acids and Tetrafluoroborates[70,75,76]

substituted olefins have been trifluoromethylated successfully by these methods. Stereoselectivity is good for the stilbene-type substrates, favoring the thermodynamic *E*-configured product, whereas non-phenyl-substituted olefins show lower stereoselectivity. Shen's Cu(I)-catalyzed trifluoromethylation of vinylboronic acids is less selective with respect to the configuration of the double bond than the two other methods.
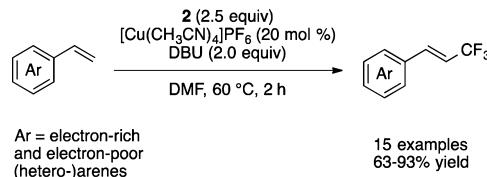
An additional approach has been developed by Hu and co-workers.[77] By use of vinylcarboxylic acids, they could obtain trifluoromethylated olefins via decarboxylation as described in Scheme 57. This method, which has been applied only to (hetero)aromatic olefins, shows excellent *E/Z* selectivity, favoring the formation of the *E*-configured product. This approach was improved later by Zhu and co-workers[78] by using [Ir(ppy)₃] as a photoredox catalyst. They were able to decrease the amount of catalyst needed to 1 mol %, while preserving excellent reactivity and *E/Z* stereoselectivity at room temperature. The scope was also further extended to other nonaromatic conjugated systems.

Scheme 57. Trifluoromethylation of Unsaturated Carboxylic Acids[77,78]

A method for direct trifluoromethylation of alkenes has been reported more recently by Wang et al.[79] (Scheme 58). The
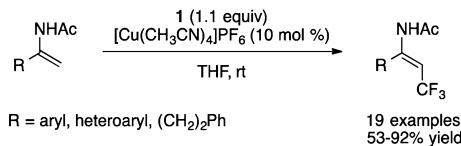
Scheme 58. Direct Trifluoromethylation of Alkenes[79]

same type of products corresponding to a vinylic trifluoromethylation may be obtained by elimination after an oxytrifluoromethylation process, as reported by Sodeoka and co-workers[91] and Szabó and co-workers[90] (see section 5.2.8). Under copper catalysis, the authors achieved good yields in this transformation, which can be applied to a wide range of aryl-substituted double bonds. Both electron-rich and electron-poor aromatic systems behave equally well in this reaction. When compared to the methods mentioned above, this procedure does not require the presence of either an activating or a directing group. However, one shortcoming is the fact that it has been applied exclusively to monosubstituted alkenes.
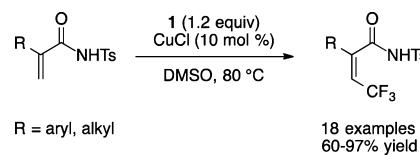
Another approach for the construction of α,β-unsaturated trifluoromethylated products is the use of activating groups for the direct trifluoromethylation of olefins. Activation of the double bond using electron-donating substituents (Scheme 59)[80] as well as directing-group-assisted C−H activation

Scheme 59. Trifluoromethylation of Electron-Rich Enamides[80]

(Scheme 60)[81] have both been described. Enamides have exceptionally electron-rich double bonds and react with reagent **1** under Cu(I) catalysis at room temperature (Scheme 59).
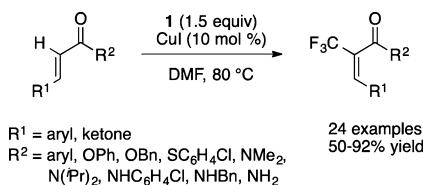
Scheme 60. Trifluoromethylation of Electron-Deficient Alkenes[81]

The second approach uses tosylamides as activating group, according to the authors for precoordination of the copper(I) catalyst. In this way, even electron-deficient olefins undergo efficient trifloromethylation, although at higher temperatures than in the case of electron-rich olefins (Scheme 60).

The method presented above only allows for the trifluoromethylation of α-substituted acrylamides. Bi and co-workers[82] developed an additional strategy to extend vinylic trifluoromethylation to the corresponding transformation of enones and other α,β-unsaturated carbonyl compounds such as esters, thioesters, and amides (Scheme 61). Good yields are
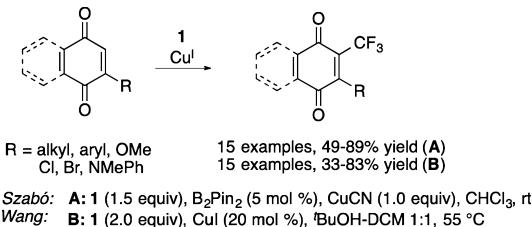
Scheme 61. Trifluoromethylation of Enones and Related α,β-Unsaturated Carbonyl Compounds[82]

R[1] = aryl, ketone
R[2] = aryl, OPh, OBn, SC₆H₄Cl, NMe₂, N(iPr)₂, NHC₆H₄Cl, NHBn, NH₂

24 examples
50-92% yield

achieved by this protocol, which takes advantage of copper(I) catalysis in N,N-dimethylformamide (DMF). As is the case for most Cu-catalyzed trifluoromethylations, this reaction is thought to proceed via a radical mechanism. Moreover, when compared to other conjugated vinylic systems, this method affords α-trifluoromethylation, most likely due to an increased stabilization of the newly formed radical. Quinones, pyridinone, and even uracil are suitable substrates for this transformation, which makes it interesting for trifluoromethylation of drug candidates and other bioactive compounds.

**5.2.6. Quinones.** Recently, Szabó and co-workers[83] and Wang et al.[84] published independently the trifluoromethylation of quinones in the presence of copper(I) (Scheme 62). While

Scheme 62. Synthesis of Trifluoromethylquinones[83,84]

R = alkyl, aryl, OMe
Cl, Br, NMePh

15 examples, 49-89% yield (A)
15 examples, 33-83% yield (B)

Szabó: **A:** 1 (1.5 equiv), B₂Pin₂ (5 mol %), CuCN (1.0 equiv), CHCl₃, rt
*Wang:* **B:** 1 (2.0 equiv), CuI (20 mol %), tBuOH-DCM 1:1, 55 °C
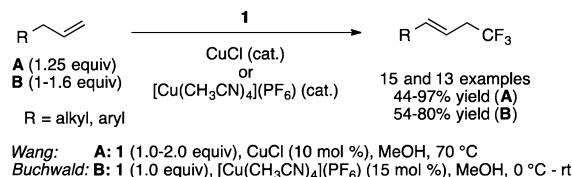
Szabó's procedure uses a stoichiometric amount of CuCN in the presence of catalytic bis(pinacolato)diboron, Wang's trifluoromethylation proceeds with a substoichiometric amount of copper(I) iodide. Both groups present a mechanistic investigation based on the formation of a radical CF₃ species, with copper(I) being a one-electron reducing agent.

The organoboron species in method A (Scheme 62) is thought to act as radical activator and is needed for acceleration and reproducibility of the reaction. However, its precise role remains unclear, especially in comparison to method B. The monotrifluoromethylations of quinone and benzoquinone (R = H) require an excess of substrate, as the presence of the first trifluoromethyl group activates the substrate to yield the ortho-bistrifluoromethylated product. Both methods are comparable with respect to chemical yields. It must be noted that almost exclusively electron-rich quinones have been tested for this reaction.

5.2.7. Allylic Functionalization. Allylic trifluoromethylation has first been described independently by Parsons and Buchwald[85] and Wang et al.[86] Reagent **1** reacts under copper(I) catalysis with terminal olefins to yield the trifluoromethylated allylic products (Scheme 63). The preferred stereoisomer is the
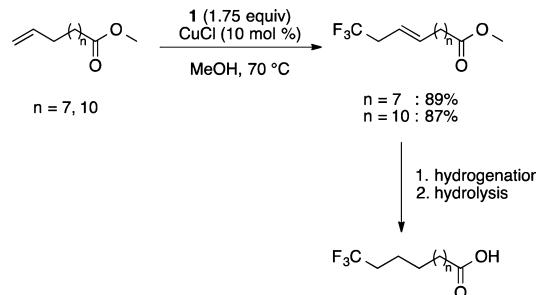
Scheme 63. Allylic Trifluoromethylation of Unactivated Olefins[85,86]

A (1.25 equiv)
B (1-1.6 equiv)

R = alkyl, aryl

15 and 13 examples
44-97% yield (**A**)
54-80% yield (**B**)

Wang: **A:** 1 (1.0-2.0 equiv), CuCl (10 mol %), MeOH, 70 °C
Buchwald: **B:** 1 (1.0 equiv), [Cu(CH₃CN)₄](PF₆) (15 mol %), MeOH, 0 °C - rt

thermodynamically favored E-olefin that is formed in high stereoselectivity (89:11−97:3). Alkyl-substituted allylic substrates give very good yields in this transformation, with various functional groups (e.g., esters, epoxides, amides, alcohols, or aldehydes) being well tolerated. Aryl-substituted substrates are more reluctant in this reaction and, in certain cases, the authors could identify the branched regioisomer as side product.

This procedure for allylic trifluoromethylation has been applied in the synthesis of fluoroanalogues of fatty acids (Scheme 64). Chiang et al.[87] investigated the regioselectivity
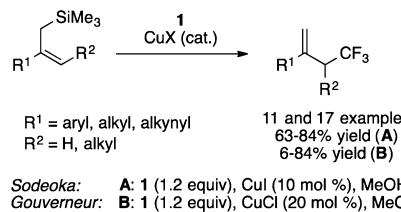
Scheme 64. Synthesis of Trifluoromethylated Fatty Acids[87]

n = 7, 10

n = 7 : 89%
n = 10 : 87%

1. hydrogenation
2. hydrolysis

and rate of hydroxylation of different fluorinated fatty acids by cytochrome P450 (wild-type and triple-mutant variants). The authors observed that hydrophobic interactions between the fluorine atoms and the hydrophobic pocket of the enzyme allow for much better stabilization of selected conformations. The consequence of this conformational rigidity is that hydroxylation by cytochrome P450 is much more regioselective (at ω-3) for the fluorinated substrates than for their nonfluorinated analogues.

Subsequently, two different groups reported the trifluoromethylation of allylsilanes (Scheme 65).[88] Internally substituted trifluoromethylated products have been obtained under very similar conditions as for the corresponding direct reaction
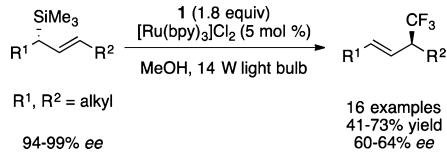
Scheme 65. Trifluoromethylation of Allylsilanes[88]

R[1] = aryl, alkyl, alkynyl
R[2] = H, alkyl

11 and 17 examples
63-84% yield (**A**)
6-84% yield (**B**)

Sodeoka: **A:** 1 (1.2 equiv), CuI (10 mol %), MeOH, rt
Gouverneur: **B:** 1 (1.2 equiv), CuCl (20 mol %), MeOH, 70 °C

of allylic substrates discussed above (Scheme 63). However, this method provides access to allylic trifluoromethylated products with different substitution patterns. Additionally, internally substituted olefins, which did not undergo any reaction in the direct trifluoromethylation, are reactive under these conditions.

Later, Gouverneur and co-workers[89] extended the field of trifluoromethylation of allylsilanes by applying photoredox catalysis using $[Ru(bpy)_3]Cl_2$ in this transformation (Scheme 66). Disubstituted olefins give preferentially the thermody-
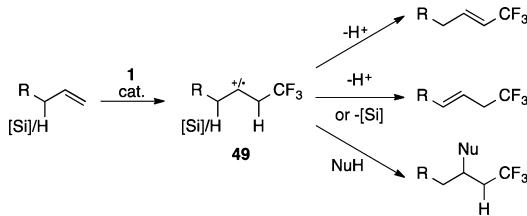
Scheme 66. Stereoselective Trifluoromethylation of Allylsilanes under Photoredox Catalysis[89]

namic *E*-configured product, with the *E/Z* ratio depending strongly on the size of the substituents. Interestingly, the authors observe a certain degree of stereoselectivity when enantioenriched allylsilanes are applied under those reaction conditions. It is noteworthy that the diastereoselectivity is determined by the configuration of the carbon center bearing the silyl group. It is assumed that this occurs via an anti addition of the trifluoromethyl group to the allylsilane. Remote stereocenters do not seem to have a major influence on the stereoselectivity of this reaction.

The solvent dependence of these transformations should not be neglected. Scheme 67 shows that, in several cases, the use of

**Scheme 67. Possible Fates of Trifluoromethylated Olefins**
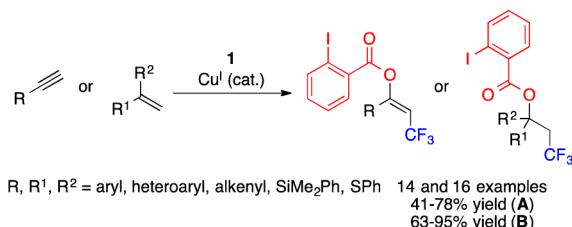
a nucleophilic solvent might lead to the addition product instead of the desired product via deprotonation of the trifluoromethylated cationic or radical intermediate. Deprotonation or desilylation at the γ-position results in formal allylic trifluoromethylation. The rate of deprotonation/desilylation versus trapping of intermediate **49** by a suitable nucleophile determines the reaction outcome. The leaving group of the trifluoromethylation reagent (i.e., 2-iodobenzoate) might also act as nucleophile. These kinds of addition reactions are discussed in section 5.2.8.

5.2.8. Additions Involving External Nucleophiles. Trifluoromethylative difunctionalization of olefins has been described independently by Szabó and co-workers[90] and Sodeoka and co-workers[91] with the 2-iodobenzoate leaving group of reagent **1** acting as external nucleophile (Scheme 68; 2-iodobenzoate is depicted in red). Both groups use a Cu(I) salt as catalyst for this transformation.

These products can be further derivatized to the corresponding β-trifluoromethyl alcohols via base-promoted hydrolysis (Scheme 69a) or to the trifluoromethylated olefins via Brønsted
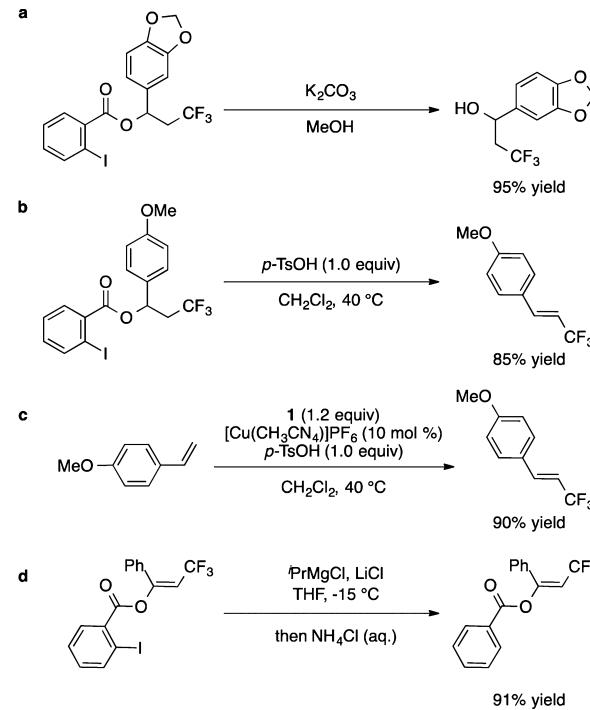
Scheme 68. Oxytrifluoromethylation of Alkenes and Alkynes[90,91]

R, R¹, R² = aryl, heteroaryl, alkenyl, SiMe₂Ph, SPh   14 and 16 examples
41-78% yield (**A**)
63-95% yield (**B**)

Szabó: **A₁**: **1** (1.5 equiv), CuI (10 mol %), CHCl₃, 20-120 °C, 16-18 h
A₂: **1** (1.5 equiv), CuI (10 mol %), CHCl₃, 120 μW, 1 h
Sodeoka: **B**: **1** (1.2 equiv), [Cu(CH₃CN)₄]PF₆ (10 mol %),
CH₂Cl₂, 23 °C, 5 min - 12 h
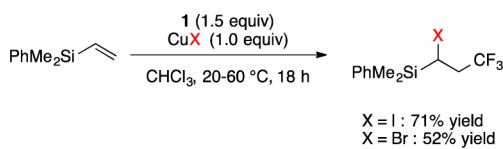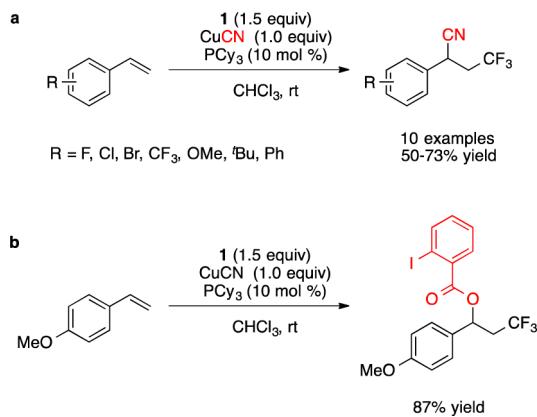
Scheme 69. Derivatization of Oxytrifluoromethylated Products[90,91]

acid-promoted elimination (Scheme 69b). Scheme 69c shows that direct access to the CF₃ olefins is possible via a one-pot process yielding the same products as from the direct vinylic trifluoromethylation of olefins (see section 5.2.5). Additionally, the iodine atom can be cleaved off by ⁱPrMgCl to give the corresponding benzoate-substituted product (Scheme 69d). The substrate scope is limited to almost exclusively aromatically substituted substrates, that is, phenylacetylene and stilbene derivatives. The electronic properties of the arenes influence the reactivity, with electron-donating substituents accelerating the reaction.
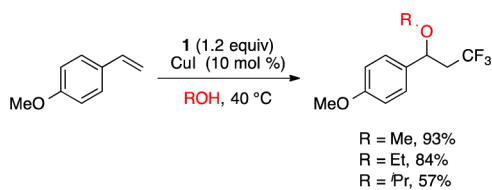
Szabó and co-workers additionally presented the use of further (external) nucleophiles for the addition reaction, allowing for an extension of the protocol to the synthesis of β-iodo-, β-bromo-,[90] (Scheme 70) and even β-cyano-trifluoromethylated[92] products by using a stoichiometric amount of copper(I) salts and leading to the incorporation of the corresponding counteranion (Scheme 71).

It is noteworthy that the cyanotrifluoromethylation reaction requires a catalytic amount of phosphine for smooth reactivity and proceeds only for substrates bearing electron-withdrawing
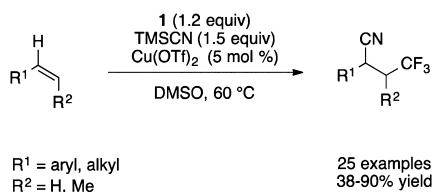
Scheme 70. Halotrifluoromethylation of Alkenes[90]

X = I : 71% yield
X = Br : 52% yield

Scheme 71. CuCN-Catalyzed Additions to Stilbene Derivatives[92]

a

R = F, Cl, Br, CF₃, OMe, ᵗBu, Ph

10 examples
50-73% yield

b

87% yield

substitutents in ortho and para positions relative to the olefin (Scheme 71a). For substrates containing electron-donating substituents, the aforementioned oxytrifluoromethylation outcome is favored (Scheme 71b).

Sodeoka and co-workers[91] reported that the use of alcohols as solvents enables synthesis of the corresponding β-trifluoromethyl ethers (Scheme 72).
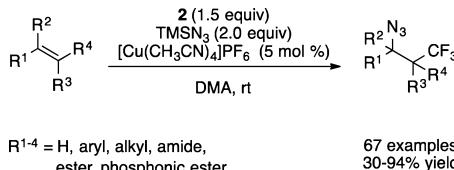
Scheme 72. Synthesis of β-Trifluoromethyl Ethers[91]

R = Me, 93%
R = Et, 84%
R = ⁱPr, 57%

Liang and co-workers[93] made a further contribution to the field of cyanotrifluoromethylation by using TMSCN as a cyanide source in the presence of a catalytic amount of copper(II) (Scheme 73). Good yields could be obtained for

Scheme 73. Cyanotrifluoromethylation of Olefins[93]

R¹ = aryl, alkyl
R² = H, Me

25 examples
38-90% yield
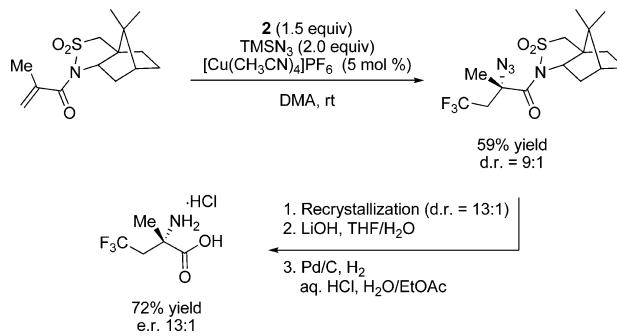
both aromatic and aliphatic substrates. The authors mention, as the only limitation to this methodology, that internally substituted olefins do not undergo any reaction. Interestingly, 1,2-disubstituted olefins are able to undergo the desired transformation with modest diastereoselectivity in the case of acyclic alkenes (dr 3:1) and good diastereoselectivity for the more rigid cyclohexene (dr 10:1).

Liu and co-workers[94] showed that the same approach was possible for the synthesis of β-trifluoromethyl azides by using TMSN₃ as presented in Scheme 74. The rather large reaction

Scheme 74. Azidotrifluoromethylation of Alkenes[94]

R¹⁻⁴ = H, aryl, alkyl, amide, ester, phosphonic ester

67 examples
30-94% yield
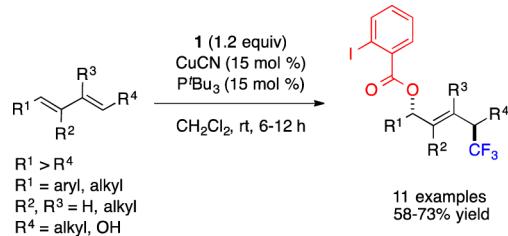
scope shows that the influence of electronic properties of the arene is negligible, and almost all stilbene derivatives react in good to excellent yields. Aliphatic alkenes are also well-tolerated, whereas 1,2-substituted alkenes show mediocre reactivity under these conditions.

Aliphatic alkenes can also be employed in this transformation. This report is so far the only example where difunctionalization of alkenes in the presence of a Cu(I) catalyst works best using reagent **2** instead of reagent **1**. Use of reagent **1** also yields productive trifluoromethylation, however, the nucleophilic attack of the trifluoromethylated intermediate by 2-iodobenzoate is a non-negligible side reaction. The azidotrifluoromethylation proceeds with diastereoselectivities of 5:1 to >20:1 for cyclic substrates. More modest diastereoselectivities (4:1 to 9:1) are observed when chiral sulfonamide-based auxiliaries are used for stereoinduction, which can then be reacted in two steps to yield enantioenriched trifluoromethylated α-amino acids (Scheme 75). The β-trifluoromethyl azides can be used for further transformations to afford, for example, corresponding triazoles, amines, or amides by standard procedures.
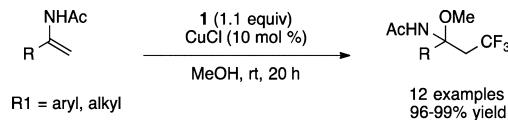
Scheme 75. Synthesis of Enantioenriched β-Trifluoromethyl α-Amino Acids[94]

59% yield
d.r. = 9:1

1. Recrystallization (d.r. = 13:1)
2. LiOH, THF/H₂O

3. Pd/C, H₂
aq. HCl, H₂O/EtOAc

72% yield
e.r. 13:1

Another recent addition to this area was made by Lu et al.,[95] introducing 1,4-oxytrifluoromethylation of $\alpha,\beta,\gamma,\delta$-unsaturated olefins by a Cu(I)/phosphine-catalyzed system (Scheme 76). The trifluoromethyl group and 2-iodobenzoate from reagent **1** are added to the diene via 1,4-difunctionalization, with the 2-iodobenzoate moiety adding to the more sterically hindered position in a diastereoselective fashion. The authors suggest furthermore the hydrolytic cleavage of 2-iodobenzoate to obtain 1,4-hydroxytrifluoromethylated products.
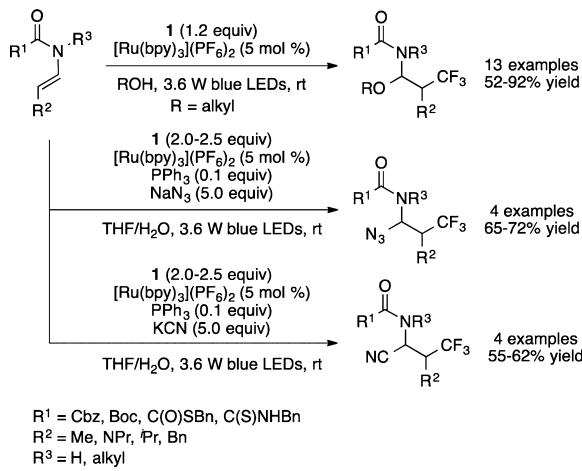
When enamides are applied in vinylic trifluoromethylation (see section 5.2.5) and methanol is used as a solvent, the transformation yields β-trifluoromethylated-α-methoxy amides (Scheme 77),[80] similar to the observation made by Sodeoka

Scheme 76. 1,4-Difunctionalization of Dienes[95]

1 (1.2 equiv)
CuCN (15 mol %)
P^{t}Bu$_3$ (15 mol %)

CH$_2$Cl$_2$, rt, 6–12 h

R^1 > R^4
R^1 = aryl, alkyl
R^2, R^3 = H, alkyl
R^4 = alkyl, OH

11 examples
58–73% yield

and co-workers (Scheme 72).[91] The reaction proceeds in high yields for several aromatic and aliphatic enamides.

Scheme 77. Methoxytrifluoromethylation of Enamides[80]

1 (1.1 equiv)
CuCl (10 mol %)

MeOH, rt, 20 h

R1 = aryl, alkyl

12 examples
96–99% yield
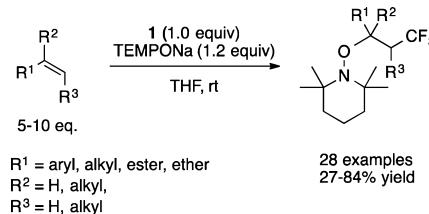
Furthermore, enecarbamates have been successfully subjected to trifluoromethylation by use of reagent **1** and a nucleophile as shown in Scheme 78.[96] Indeed, under

Scheme 78. Alkoxy-, Azido- and Cyanotrifluoromethylation of Enecarbamates[96]

1 (1.2 equiv)
[Ru(bpy)$_3$](PF$_6$)$_2$ (5 mol %)

ROH, 3.6 W blue LEDs, rt
R = alkyl

13 examples
52–92% yield

1 (2.0–2.5 equiv)
[Ru(bpy)$_3$](PF$_6$)$_2$ (5 mol %)
PPh$_3$ (0.1 equiv)
NaN$_3$ (5.0 equiv)

THF/H$_2$O, 3.6 W blue LEDs, rt

4 examples
65–72% yield

1 (2.0–2.5 equiv)
[Ru(bpy)$_3$](PF$_6$)$_2$ (5 mol %)
PPh$_3$ (0.1 equiv)
KCN (5.0 equiv)

THF/H$_2$O, 3.6 W blue LEDs, rt

4 examples
55–62% yield

R^1 = Cbz, Boc, C(O)SBn, C(S)NHBn
R^2 = Me, NPr, ^{i}Pr, Bn
R^3 = H, alkyl

photoredox conditions, addition of a trifluoromethyl moiety and an external nucleophile (alcoholate, cyanide, or azide) proceeds smoothly. Substrates bearing an internal nucleophile, such as alcohol-substituted enecarbamates, also react well under these conditions to furnish the cyclized products. Certainly, this method allows access to highly functionalized trifluoromethylated products, and since carbamates are easily cleaved to afford the free amines, this method should allow for further derivatizations for the synthesis of more complex molecules.
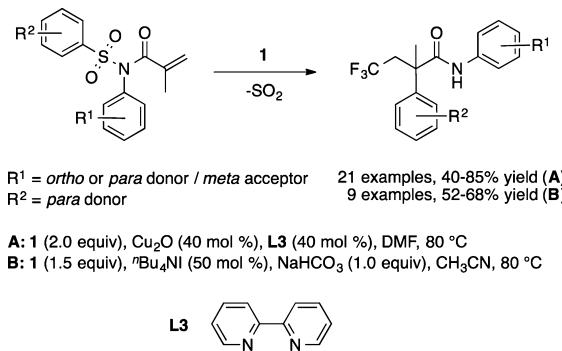
Li and Studer[50] introduced another interesting method for oxytrifluoromethylation of olefins. They hypothesized that the CF$_3$ radical does not have to be generated by a copper(I) catalyst but could also be issued by single electron transfer (SET) from the addition partner. This requires that a relatively stable radical is formed after the one-electron oxidation. The authors chose sodium 2,2,6,6-tetramethylpiperidine-*N*-oxylate (TEMPONa) as single-electron reductant, since TEMPO is known to be an exceptionally stable radical.[97] Not surprisingly, their observations for the scope of this reaction are consistent

with what has been elaborated earlier: electron-rich substrates react more readily than electron-poor ones (Scheme 79). The

Scheme 79. Radical Oxytrifluoromethylation of Olefins[50]

1 (1.0 equiv)
TEMPONa (1.2 equiv)

THF, rt

5–10 eq.

R^1 = aryl, alkyl, ester, ether
R^2 = H, alkyl,
R^3 = H, alkyl

28 examples
27–84% yield

method has also been successfully applied to olefins without aromatic substituents. Additionally, when disubstituted alkenes were subjected to the reaction conditions, diastereoselective addition was observed. This diastereoselectivity is very pronounced for cyclic systems where the diastereomeric ratio is >98:2. The β-trifluoromethyl alkoxyamines can be readily cleaved with elemental zinc to furnish the corresponding β-trifluoromethyl alcohols.
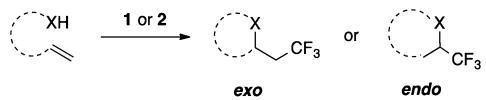
Further contributions by Nevado and co-workers[98] consisted of the desulfonylative trifluoromethylation of tosylamide-substituted olefins (Scheme 80). Addition of the CF$_3$ moiety

Scheme 80. Desulfonylative Hydrotrifluoromethylation of Tosylamides[98]

1
−SO$_2$

R^1 = *ortho* or *para* donor / *meta* acceptor
R^2 = *para* donor

21 examples, 40–85% yield (**A**)
9 examples, 52–68% yield (**B**)

A: **1** (2.0 equiv), Cu$_2$O (40 mol %), **L3** (40 mol %), DMF, 80 °C
B: **1** (1.5 equiv), ^{n}Bu$_4$NI (50 mol %), NaHCO$_3$ (1.0 equiv), CH$_3$CN, 80 °C

L3
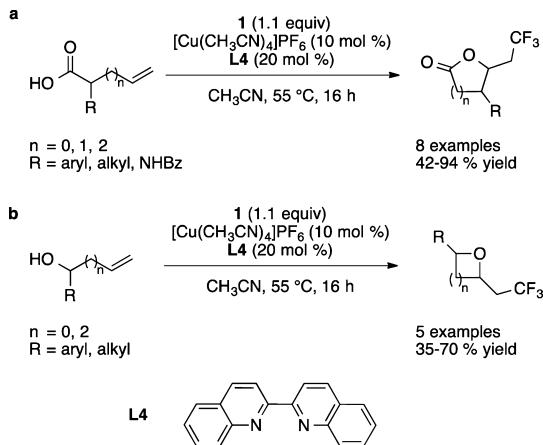
is followed by intramolecular aryl migration, desulfonylation, and hydrogen abstraction from the solvent to yield secondary β-trifluoromethylated amides. This transformation can be either Cu(I)- or ^{n}Bu$_4$NI-mediated, and interestingly, the authors suspect that both reactions proceed via inherently different pathways. They claim that the Cu(I) mechanism involves transient radical species, whereas ^{n}Bu$_4$NI generates ionic intermediates. The aromatic substituent directly bound to the nitrogen atom has only little importance for the reactivity. In both cases, better reactivity is observed if the migrating aryl group is electron-rich. Only N-arylated substrates are tolerated, while N-alkylated substrates undergo cyclization to form trifluoromethylated oxindoles (vide infra, Scheme 93).

5.2.9. Heterocyclizations. Trifluoromethylated heterocycles can be generated by a similar approach by use of nucleophiles linked to the olefin, as presented in Scheme 81. The size of the heterocycles is determined by the length of the linker and the mode of cyclization (exo vs endo cyclization).

The first example of such a process, the synthesis of 2,2,2-trifluoroethyl β-, γ-, and δ-lactones and even cyclic ethers under Cu(I)/biquinoline catalysis, is presented in Scheme 82a.[99] The
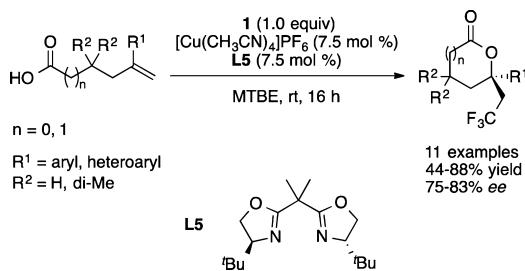
Scheme 81. Heterocyclization−Trifluoromethylation

use of internally substituted alkenes leads to mediocre diastereoselectivity (2.2:1−2.8:1).

Scheme 82. Oxytrifluoromethylation of Acids and Alcohols[99]

a

n = 0, 1, 2
R = aryl, alkyl, NHBz

8 examples
42-94 % yield

b

n = 0, 2
R = aryl, alkyl

5 examples
35-70 % yield

L4

Noteworthy is the reaction of allylic alcohols under the same reaction conditions to furnish 2,2,2-trifluoroethyl epoxides in good yields (Scheme 82b). When aromatic groups are used as substituents, excellent diastereoselectivities (up to >20:1) can be achieved. Enantiomerically pure allylic alcohols can be converted into the corresponding epoxides with complete retention of enantiopurity.
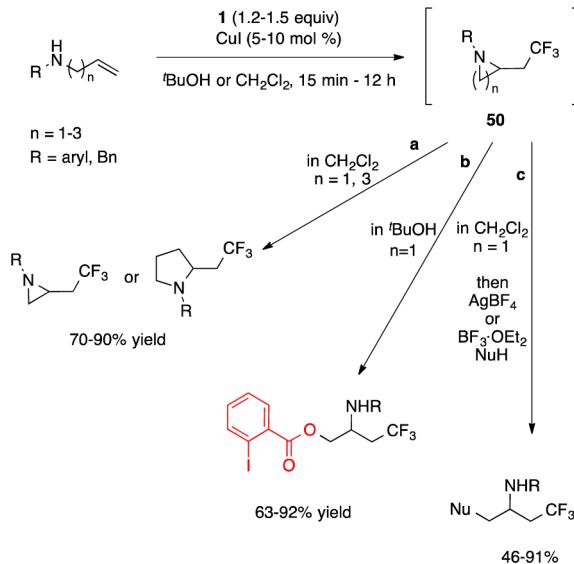
The same group reported later on the asymmetric version of this transformation by using a C_2-symmetric bis(oxazoline)-type ligand for enantioinduction (Scheme 83).[100] Formation of

Scheme 83. Enantioselective Synthesis of Trifluoromethylated Lactones[100]

n = 0, 1

R[1] = aryl, heteroaryl
R[2] = H, di-Me

11 examples
44-88% yield
75-83% ee

L5

the new stereogenic center is not concomitant with the C−CF$_3$ bond-forming process but arises from a stereoselective 6-exo−trig ring closure. The corresponding 2,2,2-trifluoroethyl lactones are obtained in good enantiomeric excess (up to 83% ee).
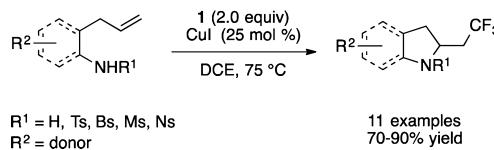
Similarly, Sodeoka and co-workers[101] used arylated allylamines as substrates for cyclizative trifluoromethylation. Depending on the reaction conditions, three different types of products can be observed, all suspected by the authors to originate from the same aziridine intermediate **50**. These three transformations are (a) N-migratory oxytrifluoromethylation, (b) aminotrifluoromethylation, and (c) N-migratory one-pot/

three-component coupling (Scheme 84). The first reaction taking place for all three transformations is copper(I)-catalyzed

Scheme 84. Trifluoromethylation of Allylamines[101]

n = 1-3
R = aryl, Bn

50

a in CH$_2$Cl$_2$ n = 1, 3

70-90% yield

b in ^{t}BuOH n=1 / c in CH$_2$Cl$_2$ n = 1 then AgBF$_4$ or BF$_3$·OEt$_2$ NuH

63-92% yield

46-91%

formation of **50** by addition of the amine and CF$_3$ units onto the olefin via a 3-exo−tet cyclization.
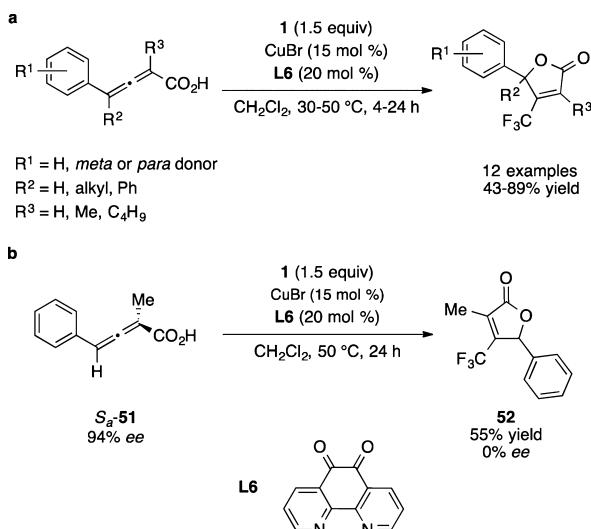
In the same work, Sodeoka and co-workers[101] showed that pentenamines could cyclize to give trifluoromethylated pyrrolidines. This kind of aminocyclization and trifluoromethylation sequence was then extended by Liu and co-workers[102] (Scheme 85). Using CuI as catalyst, the authors achieved the

Scheme 85. Aminotrifluoromethylation of Alkenes[102]

R[1] = H, Ts, Bs, Ms, Ns
R[2] = donor

11 examples
70-90% yield
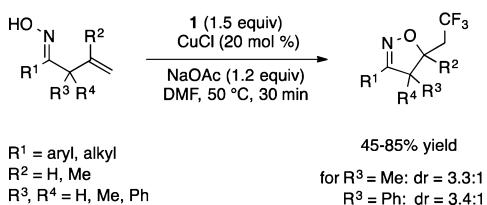
synthesis of both N-substituted and free trifluoroethylindolines. Primary amines appear to be more reactive and thus need a much lower catalyst loading. Good to excellent yields are obtained in both cases for electron-rich ortho- and para-substituted anilines. Nonaromatic amines also perform well under the same reaction conditions, with geminal disubstitution of the substrates favoring the cyclization step, as predicted by Beesley, Ingold, and Thorpe.[103]

Yu and Ma[104] then embarked on a similar journey by subjecting allenoic acids to copper(I)-catalyzed trifluoromethylation as shown in Scheme 86. They observed formation of the corresponding trifluoromethylated butenolides in high yields. Most substituents are well-tolerated in this reaction; only high steric bulk in R[3] gives lower yields. This is surprising since the Thorpe−Ingold effect would predict the reverse result.[103] Intriguingly, the axially chiral, enantioenriched substrate **51** gives rise to a racemic mixture of product **52** with no transfer of chiral information (Scheme 86b).
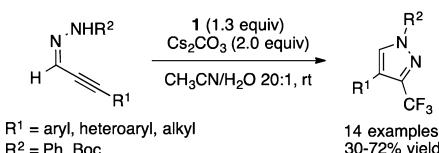
A further example of copper-catalyzed tandem trifluoromethylation−heterocyclization reaction is the synthesis of 2,2,2-trifluoroethyl isoxazolines.[105] β,γ-Unsaturated oximes react in the presence of 20 mol % CuCl and base with reagent **1** to

Scheme 86. Synthesis of Trifluoromethyl Butenolides[104]

a

R[1] = H, *meta* or *para* donor
R[2] = H, alkyl, Ph
R[3] = H, Me, C$_4$H$_9$

12 examples
43-89% yield

b

S_a-**51**
94% *ee*

52
55% yield
0% *ee*

L6

furnish 2,2,2-trifluoroethyl-substituted isoxazolines. The transformation, which is slightly dependent on the electronic properties of the oxime substituents, gives low diastereoselectivities for internally substituted alkenes (Scheme 87).

Scheme 87. Trifluoromethylation of Homoallylic Oximes[105]

R[1] = aryl, alkyl
R[2] = H, Me
R[3], R[4] = H, Me, Ph

45-85% yield

for R[3] = Me: dr = 3.3:1
R[3] = Ph: dr = 3.4:1
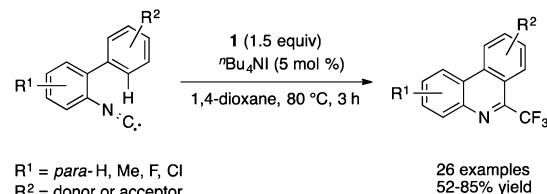
A more recent example of tandem trifluoromethylation–cyclization is the synthesis of 3-trifluoromethylpyrazoles by Ji et al.[106] (Scheme 88). Under basic conditions, alkynyl hydrazones

Scheme 88. Synthesis of 3-Trifluoromethylpyrazoles[106]

R[1] = aryl, heteroaryl, alkyl
R[2] = Ph, Boc

14 examples
30-72% yield

undergo trifluoromethylation and subsequent cyclization to yield the corresponding azoles in moderate to good yields. Rather surprisingly, this reaction proceeds under transition-metal-free conditions, and only Cs$_2$CO$_3$ is needed to promote this transformation. Aromatic as well as aliphatic substitution of the alkyne is well-tolerated, with only little impact of the electronic demand of the substituents. However, substitution at the terminal hydrazine nitrogen plays a more important role, and Boc protection is less tolerated than phenyl substitution. The Boc-protected pyrazole, which is obtained in low yield (30%), is nevertheless a valuable intermediate for further functionalization.
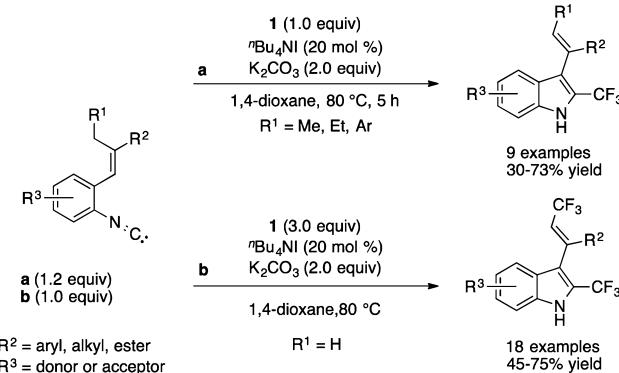
5.2.10. Carbocyclizations. Tandem cyclization–trifluoromethylation reactions as presented above were further elaborated to include nucleophilic carbon centers as cyclization partners. One interesting account for such a procedure is the

radical cyclization of isonitriles. Studer and co-workers[107] showed that tetrabutylammonium iodide (TBAI) was an efficient radical initiator for this transformation. A mere 5 mol % initiator was sufficient to promote the formation of trifluoromethyl phenanthridines as illustrated in Scheme 89.

Scheme 89. Synthesis of Trifluoromethylated Phenanthridines[107]

R[1] = *para*- H, Me, F, Cl
R[2] = donor or acceptor

26 examples
52-85% yield

The reaction was insensitive to electronic effects of the substituents. The only influence the authors observed was that ortho-substitution on the aromatic ring not bearing the isonitrile functionality moderately decreased the yields, indicating a slight steric bias. Another indication of the very low influence of electronic properties of the aromatic system is that nonsymmetrically substituted substrates react with low regiocontrol.
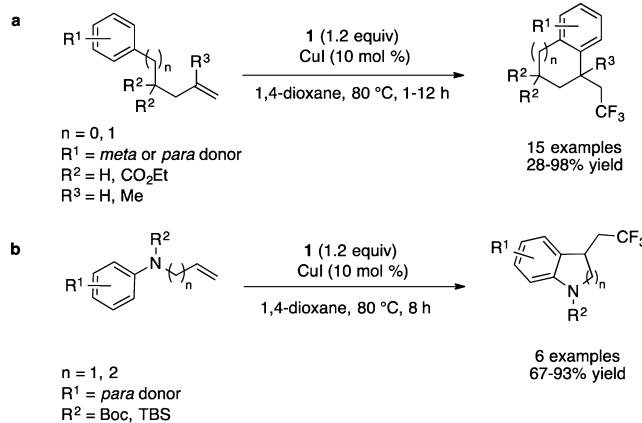
An extension of this concept was contributed later by the same group. Isocyanostilbenes react under similar reaction conditions to furnish trifluoromethylated indoles (Scheme 90a).[108] Migration of the double bond yields the *E*-configured

Scheme 90. Synthesis of Trifluoromethylated Indoles[108]

a
1 (1.0 equiv)
^{n}Bu$_4$NI (20 mol %)
K$_2$CO$_3$ (2.0 equiv)
1,4-dioxane, 80 °C, 5 h
R[1] = Me, Et, Ar

9 examples
30-73% yield

b
1 (3.0 equiv)
^{n}Bu$_4$NI (20 mol %)
K$_2$CO$_3$ (2.0 equiv)
1,4-dioxane, 80 °C
R[1] = H

18 examples
45-75% yield

a (1.2 equiv)
b (1.0 equiv)

R[2] = aryl, alkyl, ester
R[3] = donor or acceptor

olefin with selectivities depending on the steric bulk of the substituents. Interestingly, monotrifluoromethylation is favored only when 1-substituted stilbenes are used. Otherwise, bistrifluoromethylation is predominant, with both trifluoromethylation of the indole and the alkene taking place as shown in Scheme 90b. Interestingly, this alkene trifluoromethylation is highly *Z*-selective (only phenyl substitution of the olefin yields *E* selectivity). In both cases, electronic properties of the substituents in vinylic position have only little effect on the reactivity, while substitution of the aromatic ring modulates the reactivity mildly, with electron-donating substituents increasing the reactivity.

CF$_3$-containing partially saturated carbocycles and N-heterocycles are accessible via a procedure developed by Sodeoka and co-workers[109] (Scheme 91). Once again, copper(I) proved to be an excellent catalyst for this transformation. Electron-rich arenes are best tolerated as cyclization partners, but also electronically neutral aromatic ring systems are compatible
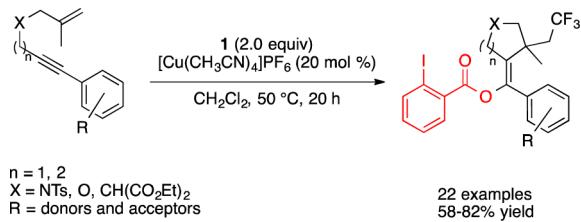
Scheme 91. Formation of 2,2,2-Trifluoroethylated Carbocycles and Heterocycles[109]

a

n = 0, 1
R[1] = *meta* or *para* donor
R[2] = H, CO_2Et
R[3] = H, Me

1 (1.2 equiv)
CuI (10 mol %)
1,4-dioxane, 80 °C, 1-12 h

15 examples
28-98% yield

b

n = 1, 2
R[1] = *para* donor
R[2] = Boc, TBS

1 (1.2 equiv)
CuI (10 mol %)
1,4-dioxane, 80 °C, 8 h

6 examples
67-93% yield

substrates. Geminal disubstitution of the linker has a positive effect on the reaction yields, supposedly by preorganization of the substrates in the conformation suitable for cyclization (Scheme 91a). Both 5- and 6-membered ring systems can be synthesized in good yields, whereby unsymmetrically substituted substrates react with mediocre regioselectivity (2.5:1). Since the most electron-rich position of the aromatic system reacts preferentially, the favored product contains the newly formed C−C bond ortho to the most electron-donating group. The N-heterocycles (Scheme 91b) formed in this way are regioisomers of the products described above by Lin et al.[102] (Scheme 85). The formation of 7-membered rings is kinetically disfavored, and only the 1,6-oxytrifluoromethylated product with incorporation of 2-iodobenzoate is observed for this reaction.

By analogy with the addition of 2-iodobenzoate and a trifluoromethyl moiety presented by Szabó and co-workers[90] and Sodeoka and co-workers[91] (Scheme 68), Liang and co-workers[110] presented a method for a similar addition sequence with concomitant enyne cyclization. This reaction, which yields 5- and 6-membered carbocycles or nitrogen- or oxygen-containing heterocycles, proceeds by use of $[Cu(CH_3CN)_4]PF_6$ for activation (Scheme 92). An internal methyl substituent is

Scheme 92. Enyne Cyclization and Trifluoromethylation[110]

n = 1, 2
X = NTs, O, CH$(CO_2Et)_2$
R = donors and acceptors

1 (2.0 equiv)
$[Cu(CH_3CN)_4]PF_6$ (20 mol %)
CH_2Cl_2, 50 °C, 20 h

22 examples
58-82% yield
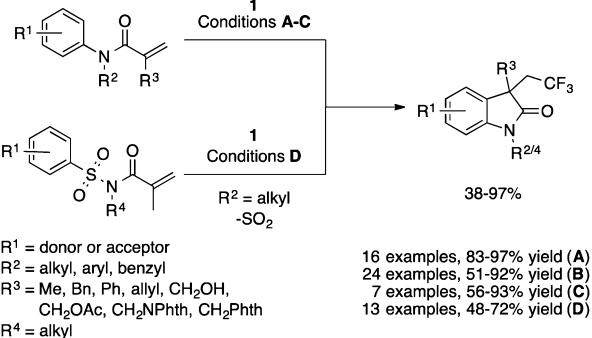
required at the olefin, and the acetylene needs to bear an aromatic ring for good reactivity. However, this is independent of substitution on the aromatic system, and electron-withdrawing as well as -donating substituents are well-tolerated in ortho, meta, and para positions.

Due to the great interest of the medicinal chemistry community in oxindoles, much effort has been invested in the development of synthetic procedures for synthesis of their trifluoromethylated derivatives by cyclization of acryloanilides. Consequently, Sodeoka and co-workers,[111] Zhu and co-workers,[112] and Nevado and co-workers[98b] published similar

strategies for the synthesis of such trifluoromethylated compounds (Scheme 93). Sodeoka's straightforward method

Scheme 93. Strategies for Synthesis of Trifluoromethylated Oxindoles via Cyclization[98,111,112]

1
Conditions A-C

1
Conditions D

R[2] = alkyl
-SO_2

R[1] = donor or acceptor
R[2] = alkyl, aryl, benzyl
R[3] = Me, Bn, Ph, allyl, CH_2OH,
   CH_2OAc, CH_2NPhth, CH_2Phth
R[4] = alkyl

16 examples, 83-97% yield (**A**)
24 examples, 51-92% yield (**B**)
7 examples, 56-93% yield (**C**)
13 examples, 48-72% yield (**D**)

Sodeoka: **A**: 1 (1.05 equiv), CuI (10 mol %), CH_2Cl_2, 40 °C
Zhu: **B**: 1 (2.0 equiv), [Ru(phen)$_3$]Cl$_2$ (1 mol %), CH_2Cl_2, 5 W blue LEDs, rt
Nevado: **C**: 1 (2.0 equiv), ^{n}Bu$_4$NI (30 mol %), CH_3CN, 80 °C
D: 1 (2.0 equiv), $[Cu(CH_3CN)_4]PF_6$ (20 mol %), **L3** (40%), CH_3CN, 80 °C
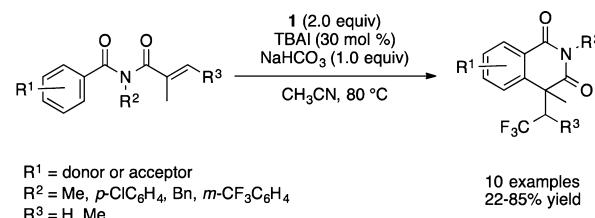
uses catalytic CuI (Scheme 93A), while Zhu's protocol relies on generation of CF_3 radicals by photoredox catalysis with [Ru(phen)$_3$]Cl$_2$ as catalyst (Scheme 93B). Finally, Nevado's approach proceeds without the use of a metal for activation. As already presented above for direct additions (Scheme 80), activation of reagent **1** can be achieved by simple use of TBAI (Scheme 93C). A very similar product scope is described for these different methods, with the same limitation that only N-substituted oxindoles can be obtained. A further requirement common to these three methods is that electron-rich arenes are required for good reactivity.

Another approach for the formation of trifluoromethylated oxindoles by cyclization was also presented by Nevado and co-workers.[98a] Tosyl amides react under copper(I) catalysis to yield the desired oxindole product after desulfonylation (Scheme 93D). This reaction occurs via migration of the aryl group. Only alkyl groups as R[2] substituents are tolerated. For N-arylated substrates, hydrotrifluoromethylation without cyclization is the predominant reaction pathway as shown above (Scheme 80).

Nevado's TBAI-activated approach can also be applied to the synthesis of isoquinolinediones, with the same limitation that free amines do not undergo cyclization (Scheme 94).[98b]

5.2.11. Rearrangements. In 2013, three groups independently published metal-catalyzed trifluoromethylations of allylic alcohols to form β-trifluoromethyl ketones via 1,2-migration of aryl or alkyl groups. Zhang and Tu and co-workers,[31a] Wu and co-workers,[31b] and Sodeoka and co-workers[113] reported metal-

Scheme 94. Synthesis of Trifluoromethylated Isoquinolinediones[98b]
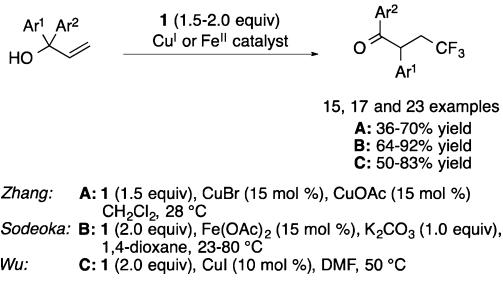
R[1] = donor or acceptor
R[2] = Me, *p*-ClC$_6$H$_4$, Bn, *m*-CF$_3$C$_6$H$_4$
R[3] = H, Me

1 (2.0 equiv)
TBAI (30 mol %)
NaHCO$_3$ (1.0 equiv)
CH_3CN, 80 °C

10 examples
22-85% yield
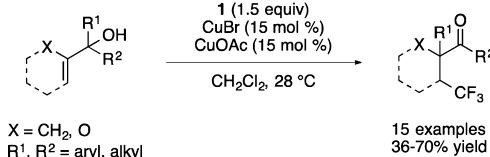
catalyzed trifluoromethylation of α,α-diaryl allylic alcohols followed by 1,2-migration of an aryl group (Scheme 95).

Scheme 95. Copper- or Iron-Catalyzed Trifluoromethylation of Allylic Alcohols to Form β-Trifluoromethyl Ketones[31,113]

15, 17 and 23 examples
A: 36-70% yield
B: 64-92% yield
C: 50-83% yield

Zhang: **A:** 1 (1.5 equiv), CuBr (15 mol %), CuOAc (15 mol %) CH$_2$Cl$_2$, 28 °C
*Sodeoka:* **B:** 1 (2.0 equiv), Fe(OAc)$_2$ (15 mol %), K$_2$CO$_3$ (1.0 equiv), 1,4-dioxane, 23-80 °C
Wu: **C:** 1 (2.0 equiv), CuI (10 mol %), DMF, 50 °C

As shown in Scheme 96, Zhang and Tu and co-workers[31a] could expand the scope of the reaction to substrates bearing alkyl substituents in the β-position to afford α-quaternary centers.

Scheme 96. Expanded Reaction Scope[31a]

X = CH$_2$, O
R^1, R^2 = aryl, alkyl

15 examples
36-70% yield
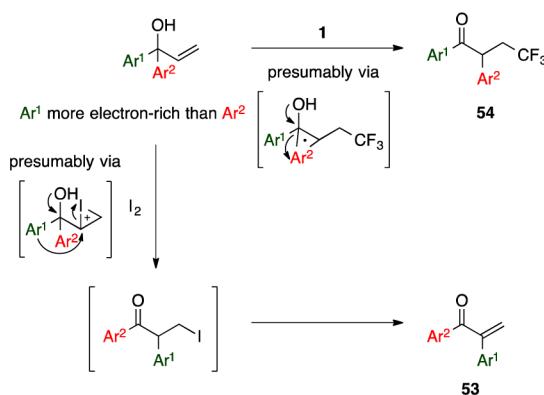
While investigating the trifluoromethylation and 1,2-aryl migration of unsymmetrically α,α-substituted allylic alcohols, all three groups found that for meta- and para-substituted substrates the more electron-deficient aryl group (Ar^1) migrated preferentially. This selectivity is anticipated for a (radical) neophyl rearrangement,[114] whereas for a semipinacol rearrangement the migration of the more electron-rich aryl group is expected, owing to better stabilization of the positive charge in the transition state.[115]

Regardless of their electronic properties, ortho-substituted aryl rings migrated less effectively, due to steric hindrance as the authors assume. For aryl- and alkyl-substituted allylic alcohols, the more electron-rich aryl group migrated exclusively.[31,113]
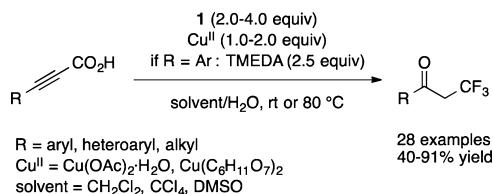
In addition, Liu et al.[31b] investigated the possibility of an iodonium intermediate. When the protocol described by Ciganek and Calabrese[116] was used, Liu et al. observed the product of a semipinacol rearrangement (**53**), whereas trifluoromethylation mainly afforded the neophyl-type rearranged product **54**, thus confirming their assumption of a radical mechanism rather than a cationic pathway (Scheme 97).[31b]

When Hu and co-workers[117] explored the trifluoromethylation of phenylpropiolic acid to form trifluoromethylphenylacetylene via decarboxylation—similar to their procedure developed for acrylic acids (see section 5.2.5, Scheme 57)—they discovered that no trifluoromethylation of the acetylene occurred. However, they observed that formation of α-trifluoromethylated acetophenone took place in 70% yield when water was used as a cosolvent (Scheme 98).[117] After further optimization of the reaction conditions, they reported 90% yield for this copper(II)-catalyzed transformation. Other aromatic or heteroaromatic acetylenes (predominantly with electron-donating substituents) were also subjected to the same

**Scheme 97. Migration of Aryl Rings via Iodonium Intermediate (Bottom) or Neophyl Rearrangement (Top)[31b]**
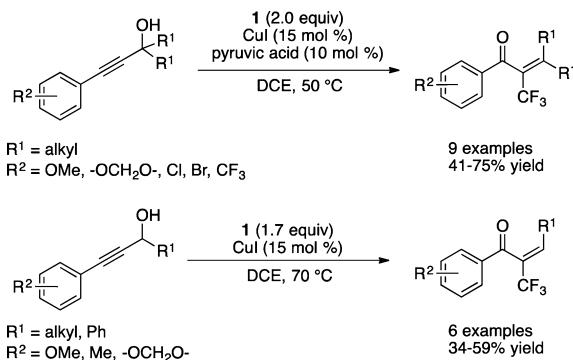
Scheme 98. Synthesis of α-Trifluoromethylated Ketones from Propiolic Acids[117]

R = aryl, heteroaryl, alkyl
Cu^{II} = Cu(OAc)$_2$·H$_2$O, Cu(C$_6$H$_{11}$O$_7$)$_2$
solvent = CH$_2$Cl$_2$, CCl$_4$, DMSO

28 examples
40-91% yield

reaction conditions, giving the corresponding α-trifluoromethyl ketones in good yields. Nonaromatic acetylenes reacted poorly when the same protocol was applied. Nevertheless, a slight modification of the reaction conditions allowed for improved reactivity, and good yields were achieved also for alkyl-substituted substrates, though these generally still show poorer reactivity when compared to their aromatic counterparts in this exceptional transformation.

Liu and co-workers[118] developed a method to generate α-trifluoromethyl enones via a Meyer–Schuster-type rearrangement. This rearrangement–trifluoromethylation sequence proceeds with moderate yields for secondary and tertiary propargylic alcohols (Scheme 99). E-configured products are
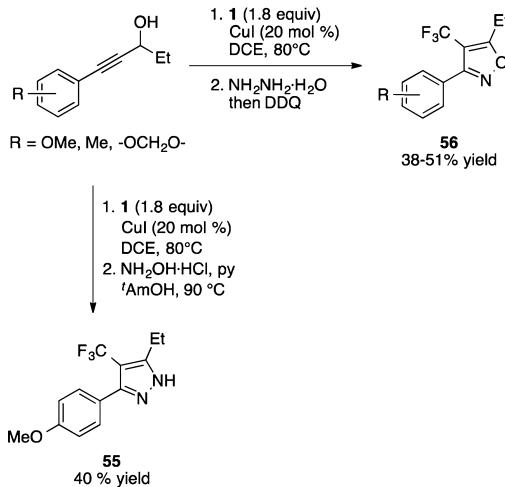
Scheme 99. Trifluoromethylative Meyer–Schuster Rearrangement[118]

R^1 = alkyl
R^2 = OMe, -OCH$_2$O-, Cl, Br, CF$_3$

9 examples
41-75% yield

R^1 = alkyl, Ph
R^2 = OMe, Me, -OCH$_2$O-

6 examples
34-59% yield

favored when secondary propargylic alcohols are used, yet with selectivities between 3.5:1 and 7.5:1 depending on the substrate. Since only symmetrically substituted tertiary propargylic alcohols have been used as substrates, it remains unclear whether some E/Z-stereoselectivity can be achieved.

The authors further demonstrated the utility of their reaction by developing a one-pot two-step process for synthesis of trifluoromethylated heterocycles (Scheme 100). Thereby, they

**Scheme 100. One-Pot Synthesis of Trifluoromethylated Heterocycles from Propargylic Alcohols[118]**
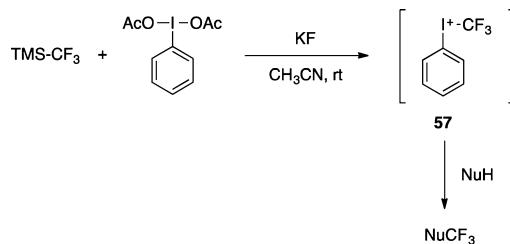
were able to obtain CF_3-substituted pyrazoles **55** and isoxazoles **56**, frameworks that are relevant in medicinal chemistry. Addition of either hydroxylamine or hydrazine and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the reaction mixture after completion of the trifluoromethylative Meyer–Schuster rearrangement led to the corresponding target compounds in moderate yields.

6. IN SITU FORMATION OF [ArICF$_3$]$^+$

The synthesis of electrophilic trifluoromethylating reagents **1** and **2** is an *Umpolung* of a nucleophilic CF_3 fragment into a formal CF_3^+ (see section 2). The *Umpolung* step, which links the CF_3 to the iodine(III) center, is usually performed on benziodoxole- and benziodoxolone-based structures since noncyclic trifluoromethyliodane compounds lack intrinsic stability required for isolation. However, phenyliodine trifluoromethyl acetate, $[PhI(CF_3)(OAc)]$, was anticipated to be a powerful electrophilic trifluoromethylation reagent in spite of its inherent instability. Accordingly, several groups embarked on the in situ synthesis of such a trifluoromethylating reagent, similar in structure to the aryl perfluoroalkyl iodonium salts of Yagupolskii et al.[11] The presumed active trifluoromethylating species would then be the $[PhICF_3]^+$ cation **57**. Compared to the protonated form of trifluoromethylation reagent **2**, which presents only I–O bond elongation, the active intermediate is supposed to be a real iodonium species, with complete loss of the acetate group from the coordination sphere of iodine. This effect can be assigned to the absence of a tethering effect (Scheme 101).
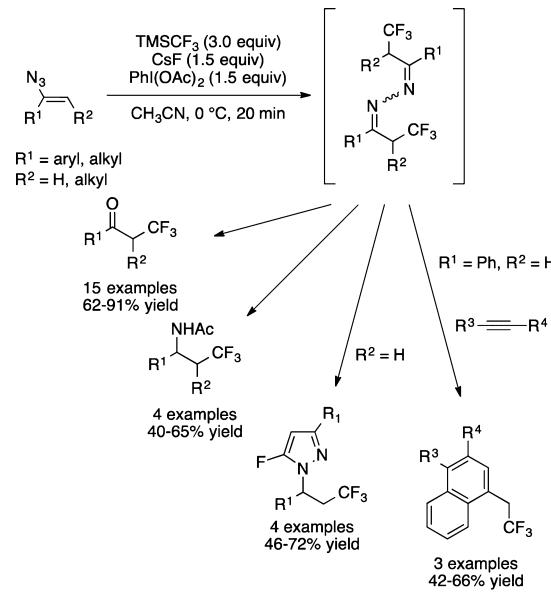
Several reports have thus emerged over the past few years describing the use of a nucleophilic CF_3 source ($TMSCF_3$ or $NaSO_2CF_3$) and a hypervalent iodine-based oxidant [e.g., $PhI(OAc)_2$ or $PhI(OCOCF_3)_2$] for the generation of this presumed iodonium-based trifluoromethylation reagent. The addition of an activator such as a fluoride source or a base is often required for smooth reactivity. This in situ *Umpolung* of a CF_3 unit allowed efficient trifluoromethylation of nucleophilic centers such as ketene dithioacetals,[119] indoles,[119,120] al-

Scheme 101. In Situ Generation of [PhICF$_3$]$^+$ [119]

kenes,[121] or electron-rich arenes.[122] Interestingly, this method has been applied for C-2 and C-3 trifluoromethylation of indoles, unlike trifluoromethylations with reagents **1** or **2**, which have so far been described only as addressing position 2 of indoles. Additionally, trifluoromethylation with concomitant cyclization for the synthesis of oxindoles,[123] phenanthrides,[124] and related structures[125] has been achieved, similar to what was presented in section 5.2.8. Several of these reactions need the presence of benzoquinone, TEMPO, or a transition-metal catalyst for efficient transfer of the CF_3 moiety. A particularly interesting and novel trifluoromethylation procedure has been developed by Chiba and co-workers.[126] They discovered that vinyl azides react in α-position to yield α-trifluoromethyl azines. These nonisolable intermediates can then be further transformed into a number of trifluoromethylated products as shown in Scheme 102.

Scheme 102. Synthesis of Trifluoromethylated Azines and Derivatization Products[126]

7. CONCLUSIONS

This review was intended to provide a first comprehensive coverage of the chemistry of reagents **1** and **2**, newcomers in the important field of trifluoromethylation chemistry. When these compounds were first prepared and reported, we did not anticipate that they would find such a broad response by the synthetic community in terms of number and disparity of applications presented and discussed above. One must not forget that, after all, synthetic organofluorine chemistry is represented by a relatively small community and that,

correspondingly, the impact of any single contribution may be relatively modest. However, precisely organofluorine chemistry, because of its increasing significance for the pharmaceutical and crop protection industries, relies on the development of new reagents and reactions. Reagents **1** and **2** have evidently fulfilled the role of ice-breaking tools also for research groups who were not known before for their contributions to the area of organofluorine chemistry. While some of the chemistry described in this review already deserves the connotation "incremental", we trust that more innovative contributions will come in the near future, as long as trifluoromethylated compounds keep their significance and utility. In this sense, the real meaning of the enabling role of reagents of type **1** and **2** will be shown by how soon this review article will be outdated (the sooner the better).

The concept that a well-suited hypervalent iodine scaffold serves as platform for the efficient transfer of this peculiar CF_3 group to a large variety of accepting organic molecules generates legitimate expectations toward its extension to more complex (functionalized) perfluoroalkyl groups. More-over, as is typical for advances in synthetic chemistry associated with new functional compounds, the application scope hurries ahead of mechanistic understanding. These two aspects serve as guidance and motivation for our future work in this fascinating area.

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Notes

The authors declare no competing financial interest.

Biographies

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Natalja Früh was born in Zürich in 1988. She completed her Master of Science in Interdisciplinary Sciences at the Swiss Federal Institute of Technology Zürich (ETH) in 2012, carrying out undergraduate research in the group of Professor Antonio Togni. She then moved to Berkeley, California, to realize her Masters thesis in the group of Professor Dean F. Toste on asymmetric phase-transfer fluorinations. After an industrial internship in process development at Novartis Pharma AG in Basel (Switzerland), she joined the group of Professor Antonio Togni at ETH Zürich in 2012 for her Ph.D. studies. Her current research includes the development and application of hypervalent iodine reagents for trifluoromethylation.

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NOTE ADDED IN PROOF

A number of journal articles and patents dealing with trifluoromethylation reactions using hypervalent iodine reagents (mainly 1 and 2) appeared after the first submission of this review. These are listed below but not discussed or commented upon explicitly:

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