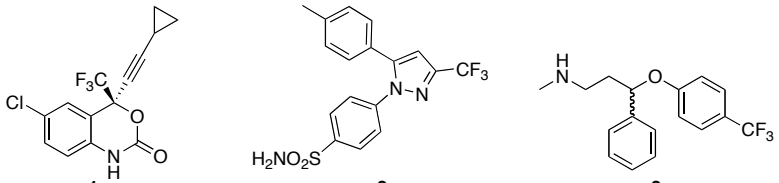
DIRECT INTRODUCTION OF THE TRIFLUOROMETHYL GROUP

Reported by Vincent M. Carroll December 4, 2008

Introduction

The field of organofluorine chemistry has, in recent years, progressively developed a significant role in a wide range of applications (Figure 1).[1] Among fluorinated compounds, trifluoromethyl-substituted molecules have generated considerable attention. The interesting medicinal properties that the trifluoromethyl group imparts have spurred synthetic efforts to selectively and directly introduce that group.[2] Conventional strategies have relied on two approaches: one involves C-F bond formation via a functional group transformation by a fluorinating reagent (e.g. DAST and SF_4), and the other includes C-C bond formation from a commercially available fluorine-substituted compound.[3] More recent efforts have aimed to directly install the trifluoromethyl moiety at a late synthetic stage using inexpensive materials.[4] To accomplish this, nucleophilic, electrophilic, free radical, and transition metal-catalyzed processes have been developed, with an emphasis on asymmetric induction. This lecture will focus on nucleophilic, electrophilic, free radical, and transition metal-catalyzed trifluoromethylation strategies.

Figure 1: Notable Drugs Containing a Trifluoromethyl Group



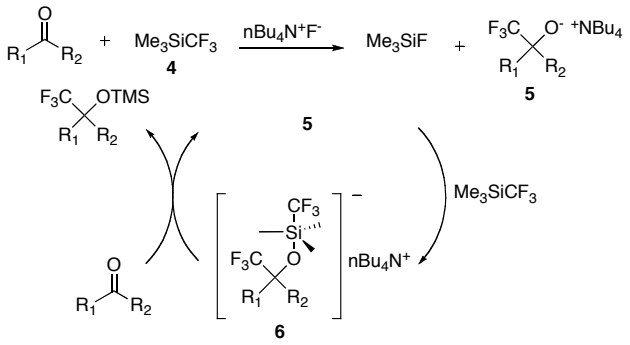
Nucleophilic Trifluoromethylation

The initial challenges to realizing nucleophilic trifluoromethylation required controlling the inherent reactivity of the "naked" trifluoromethyl anion which readily decomposes into a fluoride anion and difluorocarbene.[5] To circumvent this decomposition, strategies for stabilization have been achieved through bonding to transition metals (e.g. Cu) or main group elements (e.g. Si).[5]

Since its initial disclosure in 1984, the Ruppert-Prakash reagent,[6] CF_3SiMe_3 (**4**), has become the reagent of choice for nucleophilic trifluoromethylation. For nucleophilic addition to occur, this reagent must be activated, which can be achieved with a fluoride source (Scheme 1). This process is believed to be a fluoride-initiated/alkoxide-catalyzed reaction proceeding through a proposed pentavalent silicon

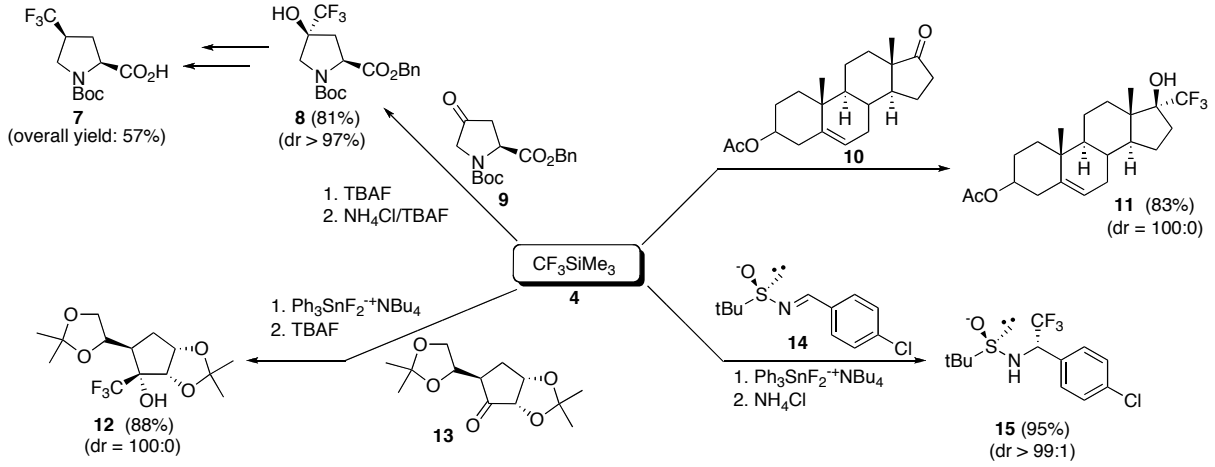
species (**6**).[7] The application of this method has been well documented with a wide range of electrophiles being utilized, including imines, esters, imides, lactones, aldehydes, and ketones.[8]

Scheme 1: Mechanism of Nucleophilic Trifluoromethylation



Addition of **4** to chiral compounds in which the faces of a carbonyl group are diastereotopic leads to the diastereoselective introduction of the trifluoromethyl group. This process has been applied to amino acids (**7**), steroids (**11**), and sugars (**12**).[9] More recently, trifluoromethylated chiral amines (**15)** were synthesized by addition to chiral sulfinylimines. Excellent diastereoselectivities and yields were obtained. Hydrolysis of the sulfinimine to the corresponding chiral amine salt proceeded readily without racemization (Scheme 2).[10]

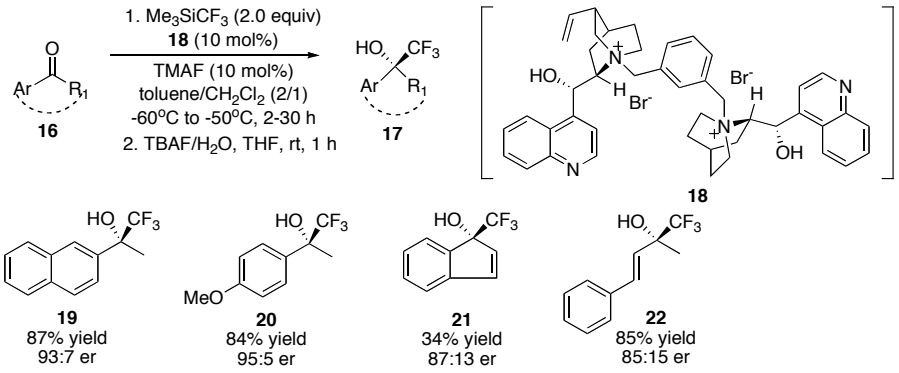
Scheme 2: Applications in Nucleophilic Trifluoromethylation



Enantioselective trifluoromethylation is considerably less developed. Strategies for enantioselective additions have generally involved the use of cinchona alkaloids as chiral Lewis bases for aldehydes and ketones as first reported by Iseki *et al.* in 1994.[11] First attempts yielded only moderate enantioselectivities and yields, but more recently, Shibata *et al.* developed a bis(cinchoninium)

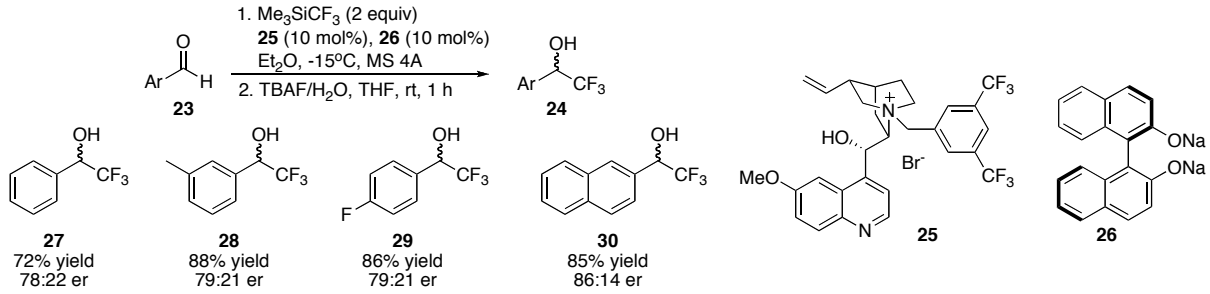
derivative (**18**) to achieve enantioselectivities in upwards of 95:5 er with aryl ketones (Scheme 3). Poor selectivity was observed when aryl aldehydes and aliphatic ketones were used.[12]

Scheme 3: Catalytic, Enantioselective Nucleophilic Trifluoromethylation of Ketones



To improve the selectivity for addition to aryl aldehydes, Feng *et al.* employed a combination of a chiral ammonium salt (**25**) with disodium (*R*)-binaptholate (**26**). This catalytic system achieved moderate to excellent yields (68-95%) and enantioselectivities (in upwards of 86:14) (Scheme 4). A proposed mechanism involves a hexavalent silicon species with activation of the carbonyl group of the aromatic aldehydes by the chiral ammonium catalysts.[13]

Scheme 4: Catalytic, Enantioselective Nucleophilic Trifluoromethylation of Aldehydes

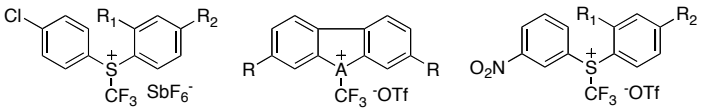


Electrophilic Trifluoromethylation

Although nucleophilic methods are well established, electrophilic trifluoromethylation is rather underdeveloped. Since the initial discovery of the first electrophilic trifluoromethylating species (**31**, **32**) by Yagupol'skii *et al.* in 1984,[14] two major classes of reagents have been developed. The first class, reported by Umemoto *et al.*, is the trifluoromethylchalcogenium salts (**33-36)**.[15] These reagents react

with an assortment of nucleophiles, including silyl enol ethers, enamines, thiolates, and electron rich aromatics yielding the trifluoromethylated products in useful yields.

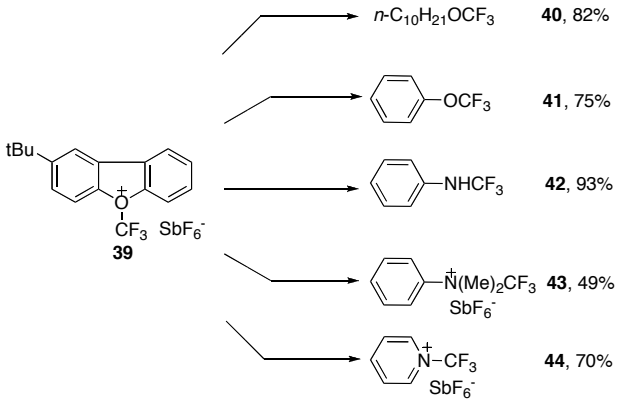
Figure 2: Electrophilic Trifluoromethylating Reagents



31 $R_1=R_2=Me$
32 $R_1=OMe$, $R_2=H$
33 A=S, R=H
34 A=S, R=NO_2
35 A=Se, R=H
36 A=Te, R=H
37 $R_1=R_2=H$
38 $R_1=F$, $R_2=H$

A major drawback of these reagents was their inability to successfully yield *O*- and *N*-CF_3 compounds. This problem was circumvented by the same group after the development of *O*-(trifluoromethyl)-dibenzofuranium salts[16] (**39**) as well as by Shreeve[17] *et al.* with their non-heterocyclic fluoro- and nitro-substituted trifluoromethyldiarylsulfonium triflates (**37**, **38**). Both sets of compounds successfully trifluoromethylated alcohols (**40**), phenols (**41**), amines, anilines (**42**), and pyridine (**44**) in moderate to excellent yields under mild conditions (Scheme 6).

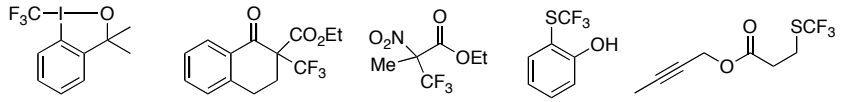
Scheme 6: Electrophilic Trifluoromethylation of *O*- and *N*- Compounds



39
40, 82%
41, 75%
42, 93%
43, 49%
44, 70%

Hypervalent iodine compounds based on the 1,2-benziodoxole core structure are a promising new set of electrophilic trifluoromethylating agents. Umemoto *et al.* previously established that this core structure is a viable source of perfluoroalkylating agents, but the trifluoromethyl derivative proved too unstable under their reaction conditions. Successfully synthesized in 2006[18] by Togni *et al.*, **45** showed high functional group tolerance: amines, amides, carboxylic acids, alcohols, and alkynes were left untouched, while cyclic ß-keto esters (**46**), α-nitro esters (**47**), phosphines, and aromatic (**48**) and aliphatic thiols (**49**) were trifluoromethylated in moderate to high yields (Figure 3).[19]

Chart 1: Representative Products of Electrophilic Trifluoromethylation using Hypervalent Iodine



45 | **46** 67% yield | **47** 99% yield | **48** 91% yield | **49** 53% yield

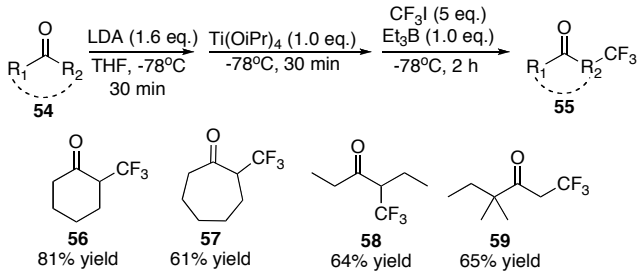
Largely underdeveloped, the first example of asymmetric electrophilic trifluoromethylation was reported by Umemoto *et al.* utilizing chiral borepins in the alkylation of potassium enolates in moderate yields and diastereoselectivities.[20] Stereochemical rationale coordinates the bulky Lewis acid on the less hindered α-face, with alkylation occurring on the ß-face.

Free Radical Trifluoromethylation

Carbonyl compounds bearing an α-CF_3 represent synthetically useful moieties allowing for further transformation of the carbonyl group to a diversified array of trifluoromethylated products. Because the electronegativity of the fluorines, CF_3-X reagents do not readily undergo alkylation reactions; however, radical pathways represent an attractive solution for the synthesis of α-CF_3 carbonyl compounds from these commercially available starting materials. Precedent for this type of transformation is extremely rare, especially for ketones because of the facile ß-elimination of the α-CF_3 product.[21]

In 2005, Itoh *et al.* reported the successful generation of an α-CF_3 ketone through radical trifluoromethylation. Respectable yields were obtained only in the presence of excess amounts of LDA and $Ti(OiPr)_4$ (Scheme 7). Nonetheless, moderate yields of α-CF_3 ketones were obtained, without any observable ß-elimination of fluoride. The linearity of the Ti-O bond is due to the back donation of a electron pair from oxygen into an empty *d*-orbital of titanium.[22]

Scheme 7: Radical Trifluoromethylation with Titanium Ate Enolates



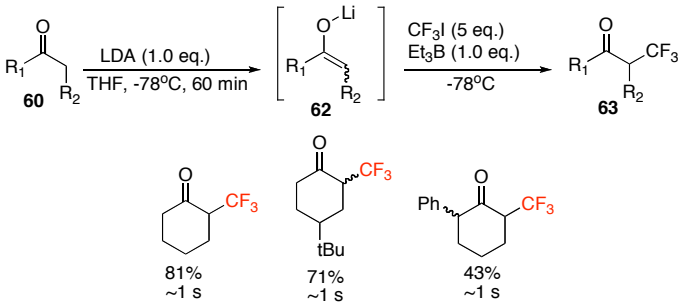
54 | **55**

56 81% yield | **57** 61% yield | **58** 64% yield | **59** 65% yield

Investigation of the radical trifluoromethylations of the titanium-ate enolates also led to the discovery of lithium enolates as potential precursors. A variety of ketones were investigated using LDA

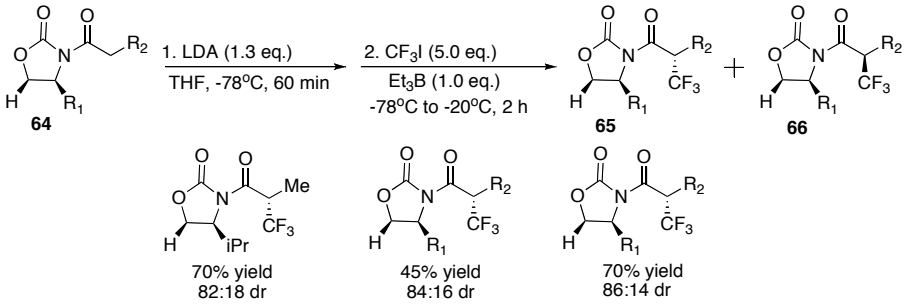
to generate the lithium enolate. The reactions proceeded extremely rapidly and afforded moderate yields of the corresponding α-CF_3 products (Scheme 8). The substrate scope, however, failed when esters and amides were present, along with poor yields for acyclic ketones.[23]

Scheme 8: Radical Trifluoromethylation with Lithium Enolates



Although the addition to a trifluoromethyl radical has proven difficult to control, Iseki *et al.* reported moderate diastereoselectivities for reactions of lithium enolates, with the use of chiral oxazolidinones (Scheme 9). Removal of the chiral auxiliary with $LiBH_4$ afforded synthetically useful α-trifluoromethyl alcohols without racemization.[21]

Scheme 9: Diastereoselective Trifluoromethylation of Chiral Imide Enolates

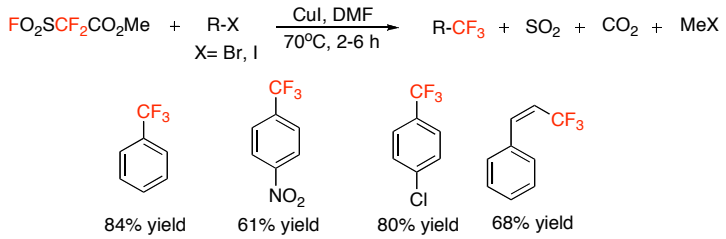


Transition Metal-Catalyzed Trifluoromethylation

The incorporation of the trifluoromethyl moiety by transition metal-mediated reactions (most notably by copper) is well established. Kobayashi *et al.* reported the trifluoromethylation of aryl, vinyl, alkyl, and heterocyclic halides by a trifluoromethyl copper species, generated from CF_3I or CF_3Br in the presence of copper powder.[24] Decarboxylative trifluoromethylation of sodium trifluoroacetate and methyl fluorosulfonyldifluoroacetate (Scheme 10), as reported by Matsui and Chen respectively, generated the trifluoromethyl anion, which is subsequently trapped by copper to form the

trifluoromethylcopper.[25] Fuchikami reported a similar approach to the in situ generation and capture of trifluoromethyl copper species from CF_3SiEt_3. Aryl, vinyl iodides, allyl iodides and benzyl bromide were trifluoromethylated in low to excellent yields.[26]

Scheme 10: Trifluoromethylation using Methyl Fluorosulfonyldifluoroacetate



These methods often require vigorous conditions for the reaction to proceed, which may not be compatible with sensitive functional groups. Kumadaki *et al.* in 2004 reported the α-trifluoromethylation of α,ß-unsaturated ketones in the presence of Et_2Zn and $RhCl(PPh_3)_3$. Cyclic and acyclic systems were utilized, with moderate yields obtained.[27]

Conclusion and Outlook

The interesting properties that the trifluoromethyl moiety imparts on organic compounds have stimulated a tremendous growth in synthetic methods for its incorporation in recent years. This has largely been accomplished through nucleophilic, electrophilic, free radical, and transition metal-catalyzed strategies. While nucleophilic trifluoromethylation has gained recent success, the other three methods are still in their infancy. This method has been applied to a wide variety of nucleophiles as well as diastereo- and enantioselective methods being reported. Further investigation of substrate scope, kinetic studies and computational modeling of enantioselective trifluoromethyl addition may result in further development of the field. Electrophilic trifluoromethylation has been developed by the chalcogenium and iodonium salts, but further mechanistic studies are needed to understand how these reagents are reacting and thus, limit its substrate scope. Free radical trifluoromethylation has been recognized only in recent years, but due to its lack of functional group compatibility (only cyclic and acyclic ketones have been employed), this method lacks synthetic feasibility. Transition metal-catalyzed trifluoromethylation by the use of copper and rhodium hold great promise for α-trifluoromethylated carbonyl compounds. Nonetheless, the utility for direct trifluoromethylation in late-stage functionalization is still an extremely attractive goal. Since the initial discoveries by Yagupol'skii and

Ruppert, numerous reports have been reported that have ultimately advanced the field. However, robust, high yielding and stereoselective methods are still lacking.

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