Organic LETTERS

Letter

pubs.acs.org/OrgLett

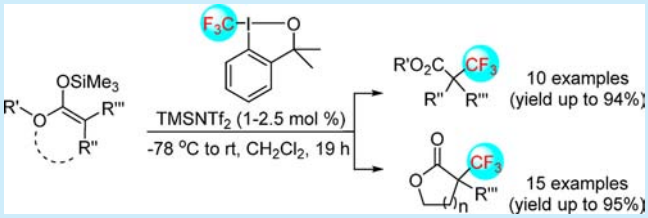
Lewis Acid Catalyzed Synthesis of α-Trifluoromethyl Esters and Lactones by Electrophilic Trifluoromethylation

Dmitry Katayev, Václav Matoušek, Raffael Koller, and Antonio Togni*

Department of Chemistry and Applied Biosciences, Swiss Federal Institute of Technology, ETH Zurich, Vladimir-Prelog-Weg 2, CH-8093 Zurich, Switzerland

Supporting Information

ABSTRACT: An electrophilic trifluoromethylation of ketene silyl acetals (KSAs) by hypervalent iodine reagents **1** and **2** has been developed. The reaction proceeds under very mild conditions in the presence of a catalytic amount of trimethylsilyl bis(trifluoromethanesulfonyl)imide (up to 2.5 mol %) as a Lewis acid providing a direct access to a variety of secondary, tertiary, and quaternary α-trifluoromethyl esters and lactones in high yield (up to 98%).



The introduction of a trifluoromethyl group at the enolizable position of carbonyl compounds significantly alters their physicochemical properties.[1] For example quaternary α-trifluoromethylated amino acids differ from their natural counterparts in a variety of parameters, including lower pK_a values of the carboxyl and amino moieties,[2] higher lipophilicity,[2b,3] resistance toward enzymatic proteolysis,[4] distinct conformational behavior,[5] and a weaker propensity to accept hydrogen bonds.[6] In addition, α-trifluoromethylated carbonyl compounds can serve as versatile precursors for the synthesis of α-trifluoromethylated carboxylic acids, α-trifluoromethylated alcohols and amines, etc.[7]

Currently, there is a relatively limited number of methods to construct a trifluoromethylated quaternary carbon adjacent to a carbonyl center.[8] To this end, there are generally two approaches. The classical approach relies on a radical trifluoromethylation of nucleophilic metal enolates or enolate surrogates such as enamines or silyl enol ethers with trifluoromethyl iodide. Conceptually newer methods employ electrophilic trifluoromethylating reagents, in particular trifluoromethyl diarylchalcogenium salts[8f,9] and hypervalent iodine(III)-CF_3 reagents **1** and **2**, which were introduced by our group in 2006 (Figure 1).[10]

Figure 1. Hypervalent iodine-based reagents **1** and **2**.

The introduction of the trifluoromethyl unit through enolate derivatives using gaseous trifluoromethyl iodide was, for instance, promoted by organoboronic esters[11] or initiated by visible-light photocatalysts[12] or by transition-metal catalysts.[13] However, methods for the formation of a quaternary carbon center by hypervalent iodine-CF_3 reagents **1** and **2** are still very scarce. To date, the only reported transformations of this type are the synthesis of α-CF_3-β-keto esters under phase-transfer catalysis[10c,14] and its enantioselective version,[15] the related copper-catalyzed synthesis of α-CF_3-α-nitro esters,[14a,c,16] and the recently developed synthesis of α-CF_3 compounds from silyl enol ethers[13a,14a,b,16a] and silyl ketene imines[17] under copper and vanadium catalysis, respectively. The advantages of using reagents **1** and/or **2** in organic synthesis over other CF_3 sources is that they are easily accessible, are stable crystalline solids, and can be handled in air.[10a] Therefore, the development of new methods for the generation of trifluoromethylated all-carbon quaternary centers using hypervalent iodine-CF_3 reagents **1** and **2** is essential.

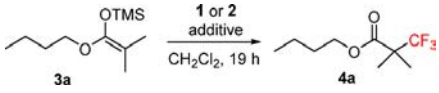
For the aforementioned reasons, we targeted the synthesis of α-trifluoromethylated derivatives of carboxylic acids. Preliminary experiments demonstrated that the in situ generated lithium enolate of butyl isobutyrate provided only trace amounts of the desired product when reacted with reagent **1** or **2**. Subsequently, we turned our attention to ketene silyl acetals (KSAs), which have been broadly investigated as nucleophiles for the formation of α-carbonyl quaternary carbon centers.[18] Their trifluoromethylation with CF_3I has previously been reported; however, a large excess of CF_3I had to be used and only a narrow substrate scope and moderate yields were reported.[11g,12a] We hypothesized that KSAs might be suitable to react with hypervalent iodine reagent **1** or **2** in the absence of any metal catalysts and strong bases. Herein, we report an operationally simple and highly efficient method for the α-trifluoromethylation of substituted ester- and lactone-derived ketene silyl acetals by reagents **1** and **2** in the presence of catalytic amounts of trimethylsilyl triflimide ($TMSNTf_2$) (1−2.5 mol %) or under catalyst-free conditions.

In order to examine the feasibility of such a transformation, we chose KSA **3a** as a model substrate for the reaction with reagent **1**

Received: October 25, 2015
Published: November 20, 2015

DOI: 10.1021/acs.orglett.5b03088
Org. Lett. 2015, 17, 5898−5901

Table 1. Development of the Catalytic Trifluoromethylation of 3a[a]



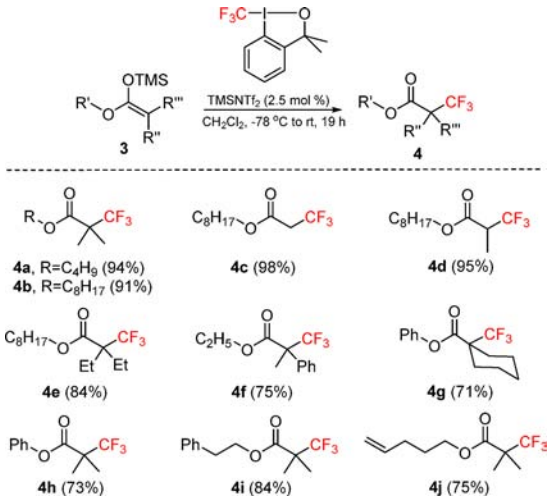
entry	reagent	additive (mol %)	T [°C]	**4a** [%][b]
1	**1 or 2**	–	rt	<5
2	**1**	$Zn(NTf_2)_2$ (10)	rt	22
3	**2**	$Zn(NTf_2)_2$ (10)	rt	39
4	**2**	$Zn(NTf_2)_2$ (10)	0	58
5	**2**	$Zn(NTf_2)_2$ (10)	−20	60
6	**2**	$Zn(NTf_2)_2$ (10)	−78 to rt	66
7	**2**	$Zn(NTf_2)_2$ (2.5)	−78 to rt	75
8	**2**	$HNTf_2$ (2.5)	−78 to rt	69
9	**2**	$LiNTf_2$ (2.5)	−78 to rt	47
10	**2**	$AgNTf_2$ (2.5)	−78 to rt	65
11	**2**	$CuNTf_2$ (2.5)	−78 to rt	52
12	**2**	$TMSNTf_2$ (2.5)	−78 to rt	85
13[c]	**2**	$TMSNTf_2$ (2.5)	−78 to rt	96(94)[d]
14[c]	**2**	$TMSNTf_2$ (2.5)	−78 to rt	54

[a]Reaction conditions: **3a** (0.3 mmol, 0.3 M in CH_2Cl_2), **1** or **2** (0.2 mmol), additive (0.5−10 mol %), −78 °C to rt, Ar atmosphere, 19 h. [b]Yields were determined by ^{19}F NMR using benzotrifluoride as an internal standard. [c]0.05 M in CH_2Cl_2. [d]Yield of isolated product.

and **2** (Table 1). The direct trifluoromethylation of **3a** using either **1** or **2** in CH_2Cl_2 at room temperature gave only trace amounts of the product (Table 1, entry 1). In this case an excess of KSA (1.5 equiv) was used. The addition of catalytic amounts of $Zn(NTf_2)_2$ (10 mol %), a known activator of reagent **1**,[17,19] to the reaction mixture led to modest yields of **4a**. Reagent **2** demonstrated slightly better reactivity, and **4a** was formed in 39% yield compared to the corresponding reaction with **1**, where only 22% was observed (Table 1, entries 2−3). Therefore, subsequent reactions were conducted using reagent **2**. Reducing the catalyst loading to 2.5 mol % and the reaction temperature to −78 °C improved the yield of **4a** to 75% (Table 1, entries 4−7). To further enhance the reactivity of reagent **2**, we tested various triflimides as additives including $HNTf_2$, $AgNTf_2$, $LiNTf_2$, and $Cu(NTf_2)_2$ (Table 1, entries 8−12). Among them, trimethylsilyl triflimide proved to be a particularly efficient additive and increased the yield of **4a** to 85% (Table 1, entry 12). Dilution of the reaction mixture improved the reactivity, and after 19 h the desired product was obtained in 94% isolated yield (Table 1, entry 13). Reducing the catalyst loading to 0.5 mol % led to lower conversion of the starting material (Table 1, entry 14). Further screening of solvents and variation of the molar ratio of **3a** and **2** did not significantly improve the yield (see the Supporting Information).

With this trifluoromethylation protocol in hand, we next examined the reaction scope with various substituted KSAs, which were easily prepared by the lithiation of the corresponding esters followed by trapping with TMSCl. The results are summarized in Scheme 1. KSAs bearing different alkoxy groups such as octyloxy- (**3b**), ethyloxy- (**3f**), phenyloxy- (**3h**), and 2-phenylethoxy- (**4i**) demonstrated excellent reactivity toward reagent **2** under the optimized reaction conditions giving the corresponding quaternary α-CF_3-substituted esters in high yields. Equally, KSAs bearing one or no alkyl substituents at the carbon atom in α-position gave the corresponding products in excellent yields (**4b** and **4c**). Replacement of the methyl groups at the α-carbon atom of KSA **3a** by larger substituents led

Scheme 1. Trifluoromethylation of KSAs: Ester Scope[a]

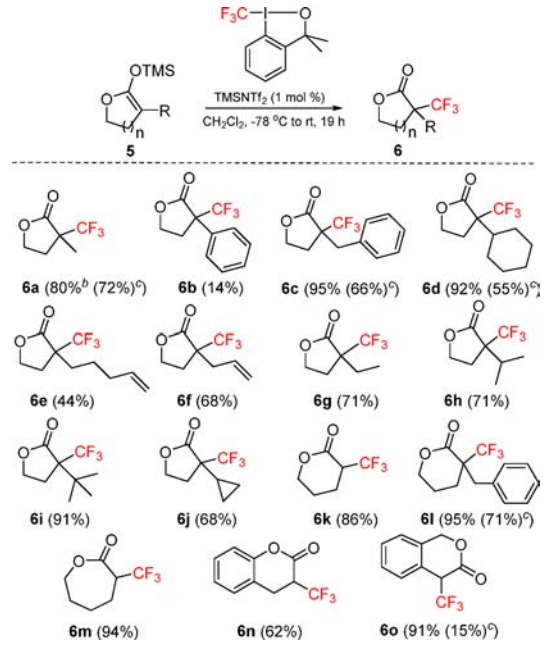


[a]Reaction conditions: **3** (1.5 mmol, 0.05 M in CH_2Cl_2), **2** (1.0 mmol), $TMSNTf_2$ (1.0 mol %), −78 °C to rt, Ar atmosphere, 19 h. Yields of isolated products are given.

to slightly decreased yields, presumably due to the increased steric bulk at the reactive carbon center. Furthermore, the presence of a terminal alkene substituent in KSA **3j** was also well tolerated under the reaction conditions and the corresponding α-trifluoromethylated ester was formed in 75% yield. The fact that the terminal olefin remained intact during the reaction is a key benefit of our approach over previously developed trifluoromethylation methods of carbonyl compounds.

We next explored the reaction scope of other carbonyl compounds and focused on KSAs derived from lactones (Scheme 2). In contrast to ester-derived KSAs, their synthesis

Scheme 2. Trifluoromethylation of KSAs: Lactone Scope[a]



[a]Reaction conditions: **5** (1.3 mmol, 1.5 M in CH_2Cl_2), **2** (1.0 mmol), $TMSNTf_2$ (1.0 mol %), −78 °C to rt, Ar atmosphere, 19 h. Yields of isolated products are given. [b]94% ^{19}F NMR yield. [c]In the absence of $TMSNTf_2$.

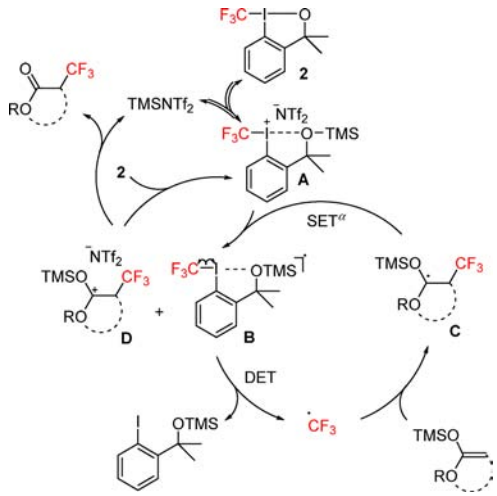
DOI: 10.1021/acs.orglett.5b03088
Org. Lett. 2015, 17, 5898−5901

was more straightforward, as the isolated crude products were sufficiently pure to be used directly for the subsequent trifluoromethylation step (see the Supporting Information). Preliminary experiments using KSA **5a** as a model substrate showed that its trifluoromethylation with reagent **2** takes place even without a catalyst providing the corresponding α-trifluoromethylated lactone **6a** in 72% yield. However, only a few other lactone-derived KSAs gave satisfactory trifluoromethylation without $TMSNTf_2$ catalysis (**5a**, **5c**, **5d**, **5l**, **5o**). We assume that a high level of trifluoromethylation efficiency achieved for KSA **5a** under catalyst-free reaction conditions is the result of a combination of the low steric requirements of the substrate and its high electron density. Addition of a catalytic amount of $TMSNTf_2$ (1 mol %) to the reaction mixture significantly improved the reactivity as shown in Scheme 2. Furthermore, reducing the amount of lactone-derived KSAs from 1.5 to 1.3 equiv did not significantly affect the yield of products. KSAs derived from γ-butyrolactone with a variety of α-alkyl substituents such as benzyl (**5c**), cyclohexyl (**5d**), ethyl (**5g**), isopropyl (**5h**), *tert*-butyl (**5i**), and cyclopropyl (**5j**) showed excellent reactivity delivering the corresponding α-trifluoromethylated lactones in good to high yields. The reaction tolerates steric bulk in the α-position, and **5d** and **5i** reacted with **2** to give **6d** and **6i** in high yields. In the case of α-phenyl substituted KSA **5b**, the low yield of the corresponding product might be explained by the depleted electron density of the double bond due to conjugation. KSAs with α-alkyl substituents bearing a terminal olefin, **5e** and **5f**, were also tolerated under the developed reaction conditions. Finally, various α-trifluoromethylated six- (**6k–l**, **6n–o**) and seven-membered (**6m**) lactones can be accessed in excellent yields by this approach demonstrating its broad applicability.

Further investigations were performed to obtain insight into the mechanism of the trifluoromethylation of KSAs. The presence of an excess of radical acceptors, such as 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or styrene in the reaction mixture of **3b**, completely suppressed product formation (see the Supporting Information). These findings suggest that radical species are likely reactive intermediates in the transformation.

Based on the above results, we propose the following mechanism for this trifluoromethylation reaction (Scheme 3). In the case of the Lewis acid catalyzed transformation we assume that $TMSNTf_2$ activates reagent **2** to form intermediate **A**. In the presence of the KSA substrate, intermediate **A** participates further in a single electron transfer (SET) to give a neutral radical species **B**. This highly reactive intermediate, upon thermally induced internal dissociative electron transfer (DET), leads to the formation of CF_3 radicals. The feasibility of such mechanistic pathways has been recently demonstrated in our group by *ab initio* molecular dynamics simulations, in particular metadynamics.[20] The liberation of a CF_3 radical species accounts for an activation barrier of as little as 2.8 kcal mol^{-1}, starting from the protonated form of reagent **2**. In the next step of the catalytic cycle, the electrophilic trifluoromethyl radical rapidly reacts with the substrate to give intermediate **C**, which subsequently takes part in a second SET with intermediate **A**, restoring the active radical species **B** and forming the silyloxycarbenium species **D**. The latter will rapidly undergo desilylation in the presence of the triflimide anion (NTf_2^-) to form the corresponding trifluoromethylated product and regenerate the active catalyst $TMSNTf_2$. Alternatively, intermediate **D** can directly silylate another molecule of reagent **2**. In the case of noncatalyzed

Scheme 3. Plausible Catalytic Cycle for the Trifluoromethylation of KSAs by Reagent 1

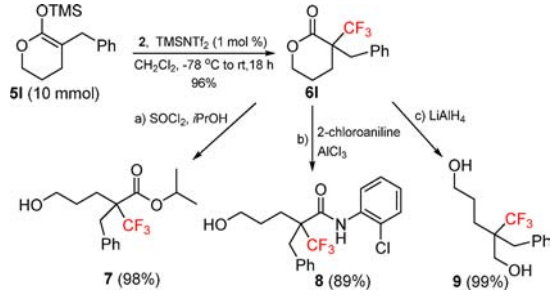


DET: dissociative electron transfer. SET: single electron transfer. [a]SET by the substrate (KSA) in the beginning of the catalytic cycle.

transformations, often observed with electron-rich and sterically nondemanding lactone-derived KSAs, we assume that the reaction takes place via initial generation of a charge-transfer complex (CTC) between the substrate and reagent **2**. The following transfer of a silyl group leads to the formation of a species similar to **A**, which further liberates CF_3 radicals.

To illustrate the practical utility of this protocol, we have performed the synthesis of quaternary α-CF_3 lactone **6l** from 10 mmol of the corresponding ketene silyl acetal **5l** in 96% yield. Lactones are versatile precursors in organic synthesis,[21] and hence product **6l** was subjected to different transformations (Scheme 4). Refluxing **6l** in a solution of isopropanol and thionyl

Scheme 4. Follow-up Functionalizations of 6l[a]



[a]Reaction conditions: (a) *i*PrOH, $SOCl_2$, reflux, 24 h; (b) 2-chloroaniline, DCE, $AlCl_3$, 0 °C to rt, 4.5 h; (c) THF, $LiAlH_4$, 0 °C, 2 h.

chloride yielded quaternary α-CF_3 ester **7** in almost quantitative 98% yield. The reaction with an amine, such as 2-chloroaniline, in the presence of aluminum chloride gave α-CF_3 amide **8** in 89% yield. Reduction of lactone **6l** using $LiAlH_4$ produced β-CF_3 alcohol **9** again in nearly quantitative yield. These simple functionalizations of lactone **6l** give access to more complex molecules containing quaternary substituted centers next to an ester, amide, or alcohol functional group, scaffolds with potential applications in medicinal chemistry[22] and agrochemistry.[23]

In conclusion, we have developed a simple and efficient protocol for the trifluoromethylation of ketene silyl acetals by

DOI: 10.1021/acs.orglett.5b03088
Org. Lett. 2015, 17, 5898–5901

hypervalent iodine reagents, which proceeds under Lewis acid catalysis leading to the formation of various quaternary α-trifluoromethylated esters and lactones in good to excellent yields. We have also demonstrated that the reaction can be conducted without a catalyst for lactone-derived KSAs. The reaction could be realized on gram scale without a decrease in yield. The synthetic utility of the method was demonstrated by the transformation of an α-trifluoromethylated lactone into synthetically useful organofluorine building blocks such as β-CF_3 alcohols and α-CF_3 esters and amides which are difficult to synthesize by other methods. This reaction concept opens up a wealth of opportunities for the development of new efficient transformations using hypervalent iodine reagents **1** and **2**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03088.

Experimental procedures and detailed characterization data of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: atogni@ethz.ch.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by ETH Zürich. D.K. thanks the Swiss National Science Foundation (SNSF) for a fellowship.

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DOI: 10.1021/acs.orglett.5b03088
Org. Lett. 2015, 17, 5898−5901