Trifluoromethylation Hot Paper

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Vanadium-Catalyzed Solvent-Free Synthesis of Quaternary α-Trifluoromethyl Nitriles by Electrophilic Trifluoromethylation**

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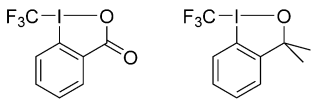
Abstract: *The direct electrophilic trifluoromethylation of silyl ketene imines (SKIs) with hypervalent iodine reagents leads to the formation of quaternary α-trifluoromethyl nitriles in good yields. This new reaction has been carried out with a variety of substituted SKIs under solvent-free conditions using a vanadium(IV) catalyst (5 mol%). The corresponding products may be transformed into useful organofluorine building blocks.*

The development of readily accessible and shelf-stable hypervalent iodine reagents **1** and **2** (Figure 1) for direct electrophilic trifluoromethylation has been a key addition to the existing methods of organofluorine chemistry. Indeed these compounds have become very popular since the initial publication in 2006 by our group,[1] as evidenced by numerous reports concerned with the trifluoromethylation of a large variety of carbon- and heteroatom-based nucleophiles.[2]

The synthetically enabling power of reagents **1** and **2** is illustrated by the more than 50 articles since 2012 reporting the formation of a new C–CF_3 bond.[2,3] However, reactions leading to the formation of a new quaternary carbon center upon the trifluoromethylation of a suited substrate by **1** or **2** are still scarce. So far the only reported transformations of this type are the synthesis of α-CF_3-β-keto esters,[1,4] described by our group and the corresponding enantioselective version later by Gade and co-workers,[5] the related formation α-CF_3-α-nitro esters,[4a,b,6] and the preparation of α-CF_3 carbonyls from silyl ketene acetals.[4b,c,6b,7] The scarcity of such transformations prompted us to investigate reactions of substrates that would afford products containing a new quaternary trifluoromethylated carbon center. For various reasons, nitriles and their activated form, silyl ketene imines, caught our attention. Nitriles are important intermediates in organic synthesis,[8] and the cyano group is found in natural products,[9] as well as in an increasing number of pharmaceuticals;[10] in the latter, the cyano group is typically attached to an aromatic ring or to a fully substituted carbon atom, such as, for example, in the calcium channel antagonist verapamil. The reason for this is that substitution patterns potentially leading to the formation of cyanohydrins upon metabolic oxidation also imply the potential release of toxic cyanide. Based on these considerations, it appeared worthwhile to investigate the α-trifluoromethylation of secondary nitriles.



1 2

Figure 1. Hypervalent-iodine-based electrophilic trifluoromethylation reagents **1** and **2**.[1]

Preliminary experiments showed that simple deprotonation of 2-methyl-3-phenylpropanenitrile by a strong base and subsequent reaction with reagent **1** did not lead to product formation, and only decomposition of **1** was observed under various conditions. Consequently, we turned our attention to silyl ketene imines, compounds reminiscent of the analogous silyl ketene acetals, known to react with reagent **1**. Even though SKIs have been known for a long time,[11] their use as nucleophiles has not been investigated as thoroughly as that of sily ketene acetals.[12] It has been pointed out that SKIs have significant advantages for the construction of quaternary carbon centers compared to silyl ketene acetals because the substituents reside in two mutually orthogonal planes.[13] Thus, we hypothesized that silyl ketene imines might be a suitable class of nucleophiles to react with **1** and/or **2** to form quaternary α-trifluoromethylated nitriles.

SKI **3a** was chosen as a model substrate for the envisaged trifluoromethylation using reagent **1** or **2** (Table 1).[14] Indeed, the transformation proceeded in 32% yield relative to **1** when reagent **1** was exposed to 1.75 equivalents of SKI **3a** (entry 1). Additives known to activate our reagents[2] such as $HNTf_2$, $Zn(NTf_2)_2$, CuCl, and $FeCl_3$ did not catalyze the transformation and gave only low product yields (entries 2–5). However, when VO(salen) complex **4a** was used as a catalyst (10 mol%), the yield increased to 89% (entry 6). Furthermore, we found that other metal catalysts with salen-type ligands and Fe or Mn centers similarly catalyzed the reaction (see the Supporting Information). Reagent **2** performed less well under the same reaction conditions, product **6a** being obtained in only 7% yield (entry 7). Reducing the amount of SKI to 1.25 equivalents led to lower conversion and after 24 h 20% of reagent **1** was found unreacted (entry 8), while changing the solvent to CH_2Cl_2 gave the product in 71% yield and full conversion after 24 h (entry 9). Further screening of catalysts revealed that complex **4b** with a more electron-rich and bulky salen ligand increased the yield to 81% (entry 10) and lowering the reaction temperature to 0°C further improved the yield (entry 11). To our surprise, when applying

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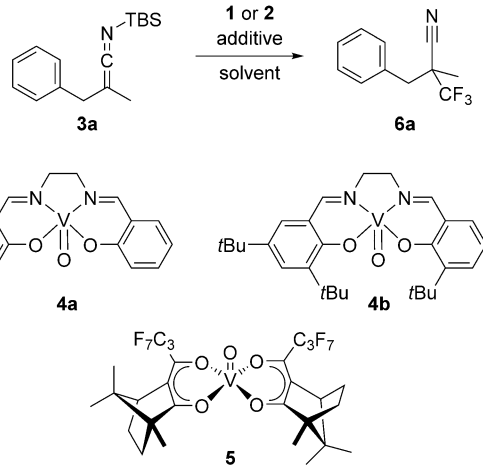
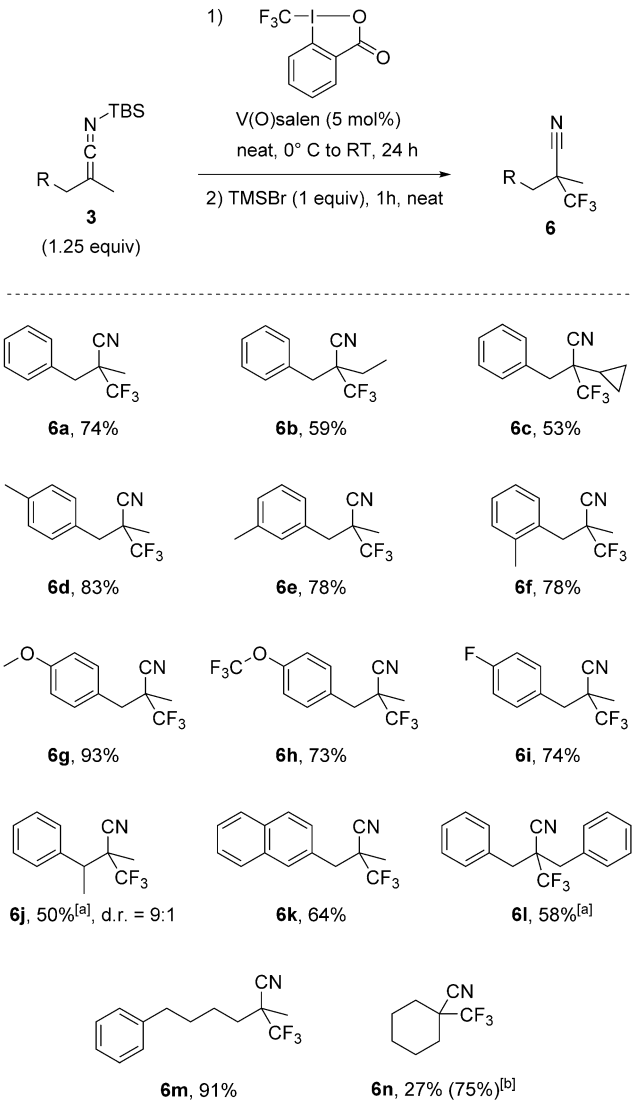
Table 1: Reaction optimization for product **6a**.[14]



Entry[a]	Reagent	Additive (mol%)	Equiv of SKI	*T*	Solvent	Yield [%][b]
1	**1**	–	1.75	RT	CH_3CN	32
2	**1**	$HNTf_2$ (20)	1.75	RT	CH_3CN	9
3	**1**	$Zn(NTf_2)_2$ (20)	1.75	RT	CH_3CN	14
4	**1**	CuCl (20)	1.75	RT	CH_3CN	5
5	**1**	$FeCl_3$ (20)	1.75	RT	CH_3CN	19
6	**1**	**4a** (10)	1.75	RT	CH_3CN	89
7	**2**	**4a** (10)	1.75	RT	CH_3CN	7[c]
8	**1**	**4a** (10)	1.25	RT	CH_3CN	53[d]
9	**1**	**4a** (10)	1.25	RT	CH_2Cl_2	71
10	**1**	**4b** (10)	1.25	RT	CH_2Cl_2	81
11	**1**	**4b** (10)	1.25	0°C to RT	CH_2Cl_2	87
12	**1**	**4b** (5)	1.25	0°C to RT	–	89
13	**1**	**5** (5)	1.25	0°C to RT	–	86

[a] Reaction conditions: A solution of reagent **1** (0.13 mmol, 1 equiv, 0.25 M in solvent) was added to the additive under argon. A solution of SKI **3a** (0.4 M in solvent) was added and the reaction mixture was stirred at the given temperature. After 24 h $C_6H_5CF_3$ (10 μL, 0.65 equiv) was added and after vigorous stirring an aliquot was taken for ^{19}F NMR spectroscopy. [b] The yield was determined relative to $C_6H_5CF_3$ as an internal standard by integration of the appropriate signals. [c] Reaction did not reach full conversion, 40% of reagent **2** was left after 24 h. [d] Reaction did not reach full conversion, 20% of reagent **1** was left after 24 h.



Scheme 1. Reaction scope for the trifluoromethylation of SKIs. [a] 1.75 equiv of SKI was used. [b] ^{19}F NMR yield is given in brackets.

solvent-free conditions we could even reduce the catalyst loading to 5 mol% and the transformation still proceeded in excellent 89% yield (entry 12). Applying the chiral oxovanadium complex **5**, a complex known to catalyze hetero-Diels–Alder reactions with a high degree of enantioselectivity,[15] led under these conditions to 86% yield. Unfortunately, however, no chiral induction was observed (entry 13). We are not aware of any other direct electrophilic trifluoromethylation using reagents **1** or **2** proceeding under solvent-free conditions. Also the use of a vanadium(IV) complex as a catalyst in transformations of these reagents is unprecedented.

After optimization of the reaction conditions, SKI **3a** was subjected to the reaction conditions on a preparative scale. After 24 h the neat reaction mixture was directly subjected to flash column chromatography and α-trifluoromethylated nitrile **6a** was obtained, albeit TBS-protected iodobenzoic acid coeluted with the chosen solvent system. Therefore, before purification, 1 equiv of TMSBr was added to the reaction mixture to cleave the silyl ester.[16] After flash column chromatography, nitrile **6a** was obtained in pure form in good yield (Scheme 1). We then explored the reaction scope with a variety of substituted SKIs, which were prepared by lithiation of the corresponding nitriles followed by trapping with TBSCl.[17] The optimized reaction conditions were applied and in all cases the corresponding α-trifluoromethylated nitrile was obtained in good to excellent yields (Scheme 1). Replacement of the methyl group of **6a** by a larger substituent led to slightly decreased yields, presumably due to the increased steric bulk for ethyl (**6b**, 59%), cyclopropyl (**6c**, 53%), and benzyl (**6l**, 58%). Good yields were obtained with *para*-, *meta*-, and *ortho*-methyl-substituted benzyl moieties (**6d–6f**, 78–83%). Furthermore, naphthyl substitution instead of phenyl (**6k**) was also well tolerated. *Para*-methoxy-substituted SKI **3g** delivered the corresponding nitrile **6g** in excellent 93% yield. Electron-

withdrawing substituents were equally well tolerated (**6h**, **6i**), while a sterically more demanding substrate with a methyl group in β-position gave the desired product in good diastereomeric ratio (9:1 d.r.) but modest yield. Finally, the reaction scope could be extended to substrates containing two alkyl substituents. Thus, nitrile **6m** was obtained in excellent yield (91%). SKI **3n** also underwent efficient trifluoromethylation but isolation of the product **6n** turned out to be difficulty due to its volatility.

A crystal of α-trifluoromethylated nitrile **6l** suitable for X-ray structure determination was obtained by slow sublimation under vacuum in a sealed glass tube at 70°C (Figure 2). A CCDC database search revealed no crystallographic data of either all-carbon-substituted α-trifluoromethylated nitriles or non-fluorinated analogues with the exception of compounds of the type $PhC(CN)(CF_3)R$, where R is either a sulfonate or an amino group.[18] Closer inspection of these structures showed that the geometry of the quaternary carbon atom C1 is insignificantly affected by its substitution. The C–CF_3 bond of 1.5287(17) Å in **6l** is slightly shorter than in the two known examples (1.536(9) Å[18a] and 1.541(6) Å[18b]) and the CF_3-C-CN angle (106.78(10)°) is within the same range (107.5(6)° and 105.4(4)°). As expected, the CF_3 group adopts a staggered conformation with F1 in an antiperiplanar orientation with respect to the CN group, as shown by the torsion angle F1-C2-C1-C3 of 172.65(10)°. This conformation may be indicative of a hyperconjugative interaction σ*(C2-F1)–π.

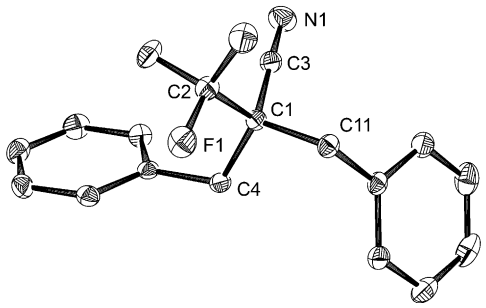
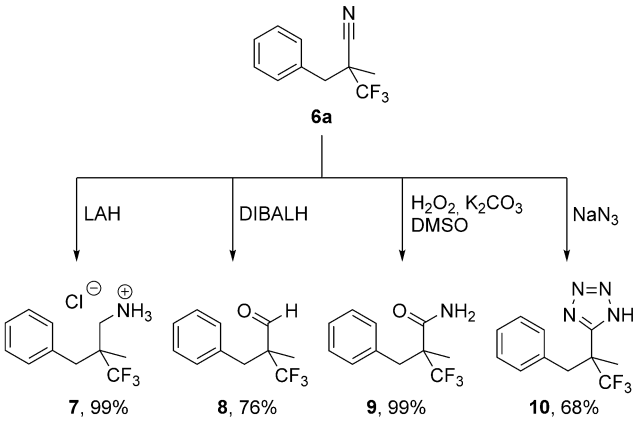


Figure 2. ORTEP representation of compound **6l.** Hydrogen atoms are omitted for clarity and thermal ellipsoids are drawn at the 30% probability level. Selected bond lengths [Å] and bond angles [°]: C1–C2 1.5287(17), C1–C3 1.4778(15), C2–F1 1.3345(14), C3–N1 1.1425(16), C1–C4 1.5521(16), C1–C11 1.5605(16); F1-C2-C1 113.20(10), C2-C1-C3 106.78(10), C4-C1-C11 110.16(9), C3-C1-C2-F1 172.65(10).

To illustrate the practicality of our reaction, we synthesized α-trifluoromethylated nitrile **6a** from 2 grams of the corresponding SKI **3a** in 82% yield. As mentioned above, nitriles are valuable intermediates in organic synthesis and hence the α-trifluoromethylated nitrile **6a** was subjected to different standard transformations (Scheme 2). Reduction of the nitrile moiety using LAH yields β-CF_3 amine hydrochloride **7** in quantitative yield after acidic workup, while quaternary α-CF_3 aldehyde **8** was obtained in 76% yield by reduction using DIBAL-H. Quaternary α-CF_3 aldehydes were previously not accessible using a recently reported protocol.[19] Conversion of nitrile **6a** to amide **9** under



Scheme 2. Derivatization of α-trifluoromethylated nitrile **6a**. Reaction conditions: a) 1. $LiAlH_4$, Et_2O, RT, 16 h, 2. HCl, Et_2O; b) 1. DIBAL-H, hexanes, −78°C to RT, 6 h, 2. ethyl formate, 1 h; c) H_2O_2, K_2CO_3, DMSO, 0°C to RT, 2 h; d) NaN_3, $Et_3N{\cdot}HCl$, toluene, 110°C, 36 h. DIBAL-H = diisobutylaluminum hydride.

oxidative conditions proceeds in quantitative yield. Moreover, reaction with sodium azide allowed the formation of α-quaternary, α-CF_3-substituted tetrazole **10**, a scaffold with potential applications in medicinal chemistry and agrochemistry.

In conclusion, we have developed an unprecedented trifluoromethylation of silyl ketene imines allowing the formation of variously substituted quaternary α-trifluoromethylated nitriles in good to excellent yields. The reaction could be performed on a gram scale without a decrease in yield and the corresponding α-CF_3 nitrile was converted into valuable organofluorine building blocks. The reaction proceeds under solvent-free reaction conditions using a vanadium catalyst, these being two aspects that have never been applied with our reagents before. The former aspect adds practicality to the use of reagents **1** and **2**, whereas the finding that not only copper salts and simple complexes are able to effect catalytic transformations of these reagents opens new venues towards the development of new and more efficient syntheses in trifluoromethylation chemistry.

At the present stage we do not have any experimental evidence concerning a possible mechanism for this new reaction. However, the fact that the best catalysts are well-defined vanadyl(IV) systems, that is, complexes that are both Lewis acidic and redox active, hints at a possible redox-catalytic process. Additionally, one should also take the silylating properties of the SKI substrates into account and hence their ability to transfer the silyl group to reagent **1**. If this indeed happens, the resulting cationic (iodonium) species should be able to engage the catalyst in a SET process enabling the formation of CF_3 radicals, which are rapidly trapped by the deprotonated nitrile. The radical anionic form of the product generated as an intermediate would then reduce the vanadyl(V) form of the catalyst back to its original oxidation state, thereby closing the catalytic cycle. Clearly, this is nothing more than a reasonable conjecture guiding our experimental scrutiny into the mechanism.

Experimental Section

A flame-dried 4 mL screw-cap vial was charged with **4b** (17.4 mg, 0.03 mmol, 0.05 equiv) and **1** (198 mg, 0.63 mmol, 1.00 equiv). At 0 °C, silyl ketene imine **3** (0.78 mmol, 1.25 equiv) was added and the green suspension was stirred from 0 °C to ambient temperature for 24 h (500 rpm). During this time the color usually changed from green to brown to dark-red to olive-green. After 24 h bromotrimethylsilane (83 μL, 0.63 mmol, 1.00 equiv) was added and the mixture was stirred for another hour at ambient temperature. The reaction mixture was directly purified by flash column chromatography (SiO_2; pentane, then pentane/Et_2O) to yield the pure product.

CCDC 1004038 (**61**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[14] Table 1 shows selected experiments; for a more extensive overview consult the tables in the Supporting Information.
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