Trifluoromethylation

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Transition-Metal-Free Trifluoromethylaminoxylation of Alkenes**

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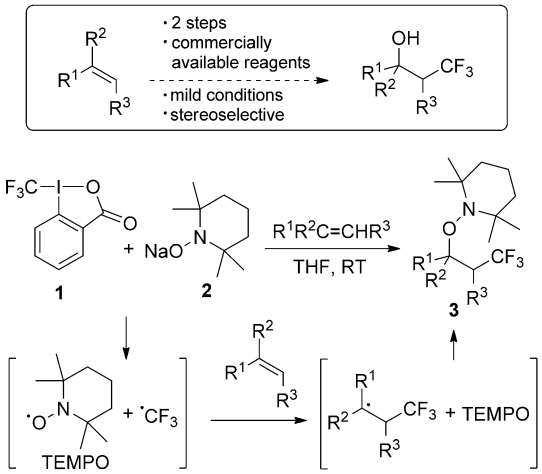
The trifluoromethyl group is a privileged chemical entity found in many drugs and drug candidates in medicinal chemistry.[1] Introduction of a CF_3 group leads to changes in the chemical and physical properties of a potential drug candidate. For example, the solubility and lipophilicity are altered, leading to compounds that show better membrane permeability and increased bioavailability. Fluorinated compounds often show increased metabolic stability because they have higher resistance towards oxidative degradation. It is therefore important to develop novel methods for C–CF_3 bond formation. Transition-metal-mediated or -catalyzed[2–10] and radical[11,12] aromatic trifluoromethylation have been studied intensively recently. However, the trifluoromethylation of alkenes, in particular unactivated alkenes, is valuable but highly challenging.[13] Nucleophilic CF_3 reagents[14] do not react with unactivated alkenes and electrophilic CF_3 reagents react only with electron-rich double bonds (metal enolates, silyl enol ethers, and enamines).[15,16] Radical chemistry should be well suited for the trifluoromethylation of alkenes because the CF_3 radical reacts rapidly with various olefinic acceptors.[17–22] We herein describe easy-to-conduct, transition-metal-free radical trifluoromethylations of alkenes using the commercially available hypervalent-iodine–CF_3 reagent **1** (Togni reagent).[15]

The Buchwald[23] and Wang[24] groups showed that reagent **1**[15] can be used as a clean source of the CF_3 radical for the trifluoromethylation of alkenes. These trifluoromethylations rely on Cu catalysis and experimental evidence for the involvement of free CF_3 radicals was provided. Based on these results, we planned to use the readily available sodium aminoalkoxide **2** as a single-electron-transfer (SET) reagent for reduction of hypervalent-iodine–CF_3 reagent **1** to generate the CF_3 radical along with the corresponding persistent TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) radical[25,26] and *o*-$IC_6H_4CO_2Na$. Addition of the CF_3 radical to an alkene and subsequent selective trapping steered by the "persistent radical effect"[27] (oxidation of the C radical) with TEMPO should eventually provide the corresponding trifluoromethylated product **3** (Scheme 1).

The process comprises the formation of a C–C and a C–O bond and the organic reagent **2** is transformed from a reducing



Scheme 1. Radical trifluoromethylation of alkenes with the Togni reagent **1**.

reagent (TEMPONa) into an oxidizing reagent (TEMPO). In synthesis, such redox behavior is usually reserved for transition metals.[28] Surprisingly, TEMPONa has not found any application as a SET reagent in synthesis and the N–O bond in alkoxyamines of type **3** is readily cleaved with Zn in acetic acid[25,26] to give products of formal trifluoromethylhydroxylation. Such trifluoromethyl-substituted alcohols are not directly accessible by epoxide opening with nucleophilic CF_3 reagents.[29]

Careful reaction optimization revealed that the trifluoromethylation is best conducted in THF at high concentration. TEMPONa was readily generated in situ by stirring commercially available TEMPO with sodium in the presence of naphthalene (see the Supporting Information). The TEMPONa solution (1.2 equiv, THF) was slowly added by syringe pump to a solution of the alkene (5 to 10 equiv) and **1** (1 equiv) in THF at room temperature (RT). Results of the trifluoromethylation of various alkenes are summarized in Table 1 and Scheme 2.

Styrene and styrene derivatives were readily trifluoromethylated and the corresponding products **3a**–**h** were isolated in good yields (Table 1, entries 1–8).[30] For styrene we showed that reaction worked equally well on a large scale and **3a** was isolated in 83% yield (0.86 g). A side product in these radical trifluoromethylations was $TEMPOCF_3$ resulting from the direct trapping of the CF_3 radical with TEMPO. However, the in situ generation of TEMPO ensures a low concentration of the nitroxide during the reaction which suppresses the formation of $TEMPOCF_3$. Under the applied conditions telomerization was not observed. The *ortho*-iodobenzoic acid sodium salt formed as a by-product from **1** was easily removed by basic extraction, and $TEMPOCF_3$ was removed by simple

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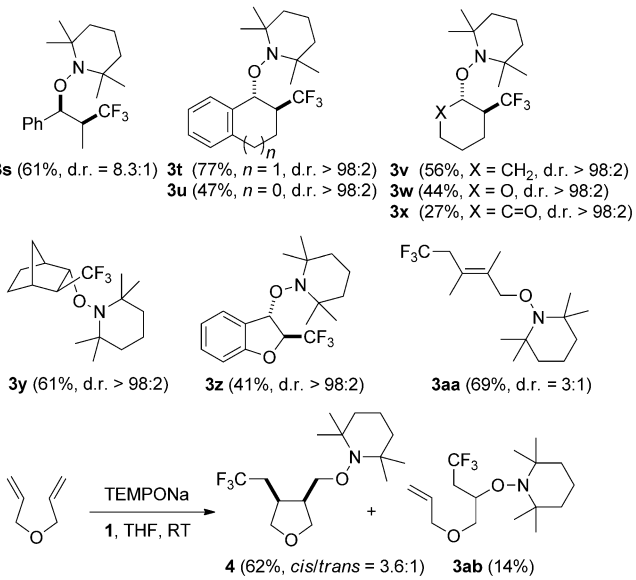
Table 1: Radical trifluoromethylaminoxylation of terminal alkenes (for structures see Scheme 1, $R^3 = H$).

Entry	R^1	R^2	Compound	Yield [%][a]
1	C_6H_5	H	**3a**	84
2	4-$CH_3C_6H_4$	H	**3b**	72
3	4-$CH_3OC_6H_4$	H	**3c**	65
4	4-ClC_6H_4	H	**3d**	62
5	4-BrC_6H_4	H	**3e**	82
6	β-naphthyl	H	**3f**	75
7	C_6F_5	H	**3g**	56
8	4-pyridyl	H	**3h**	67
9	$(CH_2)_2Ph$	H	**3i**	73
10	$(CH_2)_3CH_3$	H	**3j**	53
11	$(CH_2)_3Br$	H	**3k**	76
12	$(CH_2)_4OH$	H	**3l**	58
13	$(CH_2)_2(CHOCH_2)$	H	**3m**	65[b]
14	CO_2CH_3	H	**3n**	27
15	OBu	H	**3o**	75
16	CO_2CH_3	CH_3	**3p**	53
17	C_6H_5	CH_3	**3q**	45
18	CH_2CH_3	CH_2CH_3	**3r**	71

[a] Yields of isolated products. [b] Obtained as a 1:1 mixture of diastereoisomers.



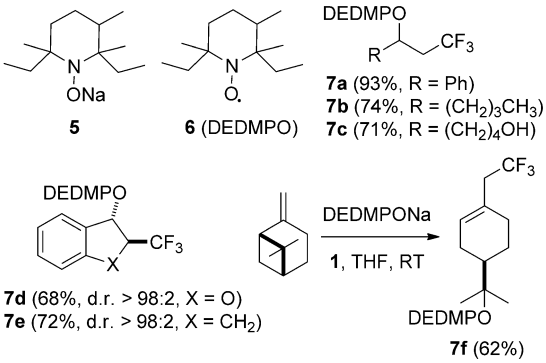
Scheme 2. Diastereoselective trifluoromethylation.

evaporation. A substrate containing an aryl bromide group, which is susceptible to reaction with transition metals, was tolerated (**3e**; Table 1, entry 5). Electronic effects exerted by the aryl substituent as judged by comparing yields were not that pronounced in the styrene series and also 4-vinylpyridine afforded the trifluoromethylaminoxylation product **3h** in good yield (Table 1, entry 8). Trifluoromethylation of the pyridine ring did not occur. Pleasingly, reactions with non-activated aliphatic terminal alkenes delivered the targeted products **3i**–**m** in good yields and neither the terminal bromide (**3k**) nor the epoxide (**3m**) interfered with the trifluoromethylation (Table 1, entries 9–13). Not surprisingly, considering the electrophilic nature of the CF_3 radical, trifluoromethylaminoxylation of the electron-poor methylacrylate afforded **3n** in low yield (Table 1, entry 14). In contrast, the reaction with the electron-rich butyl vinyl ether was more efficient, and **3o** was isolated in 75% yield (Table 1, entry 15). Changing the electronic properties of the acrylate by introducing an additional methyl group at the alkene, such as in methyl methacrylate, led to an improved yield and **3p** was obtained in 53% yield (Table 1, entry 16). This example shows that formation of quaternary C centers is possible (see also **3q** and **3r**; Table 1, entries 17 and 18).

We switched to internal alkenes as substrates to study the diastereoselectivity[31] of the trifluoromethylaminoxylation (Scheme 2). The selectivity of the reactions was determined by ^1H NMR analysis of the crude products. β-Methylstyrene reacted with high regioselectivity (20:1) to give regioisomer **3s** as the major product in 61% yield. Product **3s** was formed with a diastereoselectivity of 8.3:1 and the assignment of the relative configuration was based on the allylic A[1,3] strain model.[32] As expected, *trans*- and *cis*-β-methylstyrene delivered the same product ratio. The diastereoselectivity was even better for cyclic systems. Dihydronaphthalene, indene, and benzofuran reacted with excellent selectivity (> 98:2) to give the corresponding products **3t**, **3u**, and **3z** (41–77% yield). The trifluoromethylaminoxylation of cyclohexene was also highly selective (see **3v**). The transformation of dihydropyran provided **3w** as the major regioisomer (44% yield) with complete *trans* selectivity along with the other regioisomer in 7% yield (not shown in Scheme 2). Norbornene reacted with complete *exo* selectivity for the initial CF_3-radical addition and perfect *trans* selectivity in the TEMPO-trapping step (**3y**). Moderate diastereoselectivity was obtained in the transformation of 2,3-dimethylbutadiene (**3aa**).

We also tested whether the trifluoromethylaminoxylation can be used to "open and close" a cascade reaction comprising an additional typical radical step such as a 5-*exo* cyclization. Indeed, the trifluoromethylaminoxylation of bisallyl ether gave tetrahydrofuran **4** in 62% yield as a 3.6:1 mixture of *cis*/*trans* isomers along the noncyclized product **3ab** in 14% yield (Scheme 2). Despite this useful result, this experiment clearly showed that the fast trapping of the intermediate radical with TEMPO in the cascade process lowers the yield of **4**. To remedy this problem, we tested the bulky sodium aminoalkoxide **5** as a SET reagent for the generation of CF_3 radicals from **1** (Scheme 3). Salt **5** can be generated from TEMPO congener **6**, which in turn was readily prepared on a large scale in analogy to the synthesis of TEMPO.[33] C-centered radicals react with very bulky nitroxides significantly slower than with TEMPO.[34] Importantly, also the undesired direct CF_3-trapping reaction will be suppressed and higher yields for radical trifluoromethylaminoxylation should be obtained.

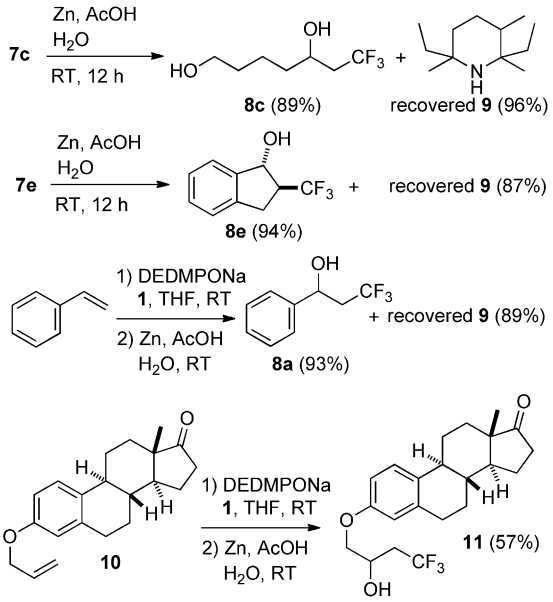
We were pleased to observe that the reaction of **5** with alkenes gave adduct yields that were generally 10 to 25% higher than those of the analogous TEMPONa-mediated processes (compare Table 1, Scheme 2 and Scheme 3). Hence, trifluoromethylation of styrene with **5** afforded **7a** in 93% yield. Aliphatic unactivated alkenes underwent addition/trapping reaction in good yields (see **7b** and **7c**). Benzofuran and indene reacted with excellent diastereoselectivities (**7d**



Scheme 3. Trifluoromethylation of various alkenes with **5** and **1**.

and **7e**) and β-pinene underwent the addition/fragmentation/trapping reaction to give **7f** (with TEMPONa,[35] **7f**–TEMPO was formed in 37% yield, not shown).

Although we expect that the trifluoromethylated compounds bearing the bulky TEMPO moiety will be tested in medicinal chemistry, we consider the corresponding N–O-cleaved β-trifluoromethyl-substituted secondary alcohols as major targets. The N–O bond in alkoxyamines **3** and **7** was readily cleaved with Zn in acetic acid under mild conditions (RT). The corresponding alcohols **8** were isolated in high yields (89–94%, Scheme 4 and the Supporting Information). It was also practicable to run the trifluoromethylation/cleavage reactions without purifying the intermediate alkoxyamines. Examples for these two-step processes are also given in Scheme 4. Piperidine **9** which formed during cleavage can be recovered in high yield (up to 96%). Recovery of the

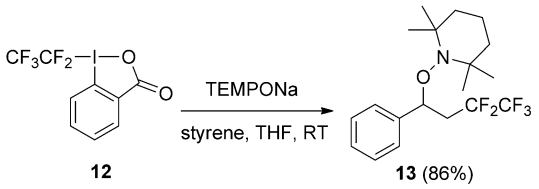


Scheme 4. Synthesis of β-trifluoromethyl-substituted alcohols.

amine is particularly useful if the starting nitroxide, such as **6**, is not commercially available. Oxidation[33] of piperidine **9** regenerates nitroxide **6**, increasing the economy of the method. We successfully applied the two-step protocol to trifluoromethylhydroxylate the steroidal allylether **10** to give alcohol **11** in 57% overall yield.

Finally, we showed that our novel method is not restricted to trifluoromethylation. The hypervalent-iodine reagent **12** bearing a C_2F_5 substituent was prepared using commercially available $TMSCF_2CF_3$ in analogy to the synthesis of **1**.[15] We were pleased to find that **12** reacted cleanly with TEMPONa and styrene to give the corresponding addition/trapping product **13** in 86% yield (Scheme 5).

In conclusion, we have introduced a novel approach for the radical trifluoromethylation of alkenes. We found that TEMPONa, which is readily generated from commercially available TEMPO and sodium, is a useful SET reagent for generation of CF_3 radicals from the Togni reagent **1**. In these



Scheme 5. Pentafluoroethylation of styrene.

transformations TEMPONa first acts as a mild organic reducing reagent (SET) for the generation of C radicals along with formation of the TEMPO radical, which then acts as an oxidant for trapping the C radicals. The in situ generation of TEMPO ensures a low concentration of the nitroxide during the reaction, which is the key for the successful intermolecular addition of the CF_3 radical and TEMPO-trapping reaction. The trifluoromethylations are easy to conduct, occur under mild conditions, and show a broad substrate scope. Excellent diastereoselectivity was obtained for the trifluoromethylaminoxylation of cyclic alkenes. Product alkoxyamines can be reduced under mild conditions to give the corresponding β-trifluoromethylated secondary alcohols. Yields could be further improved upon switching to a bulky nitroxide as the trapping reagent. Importantly, the piperidine moiety released during N–O bond cleavage could be recovered in high yield. The method is also applicable for pentafluoroethylation of an alkene.

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