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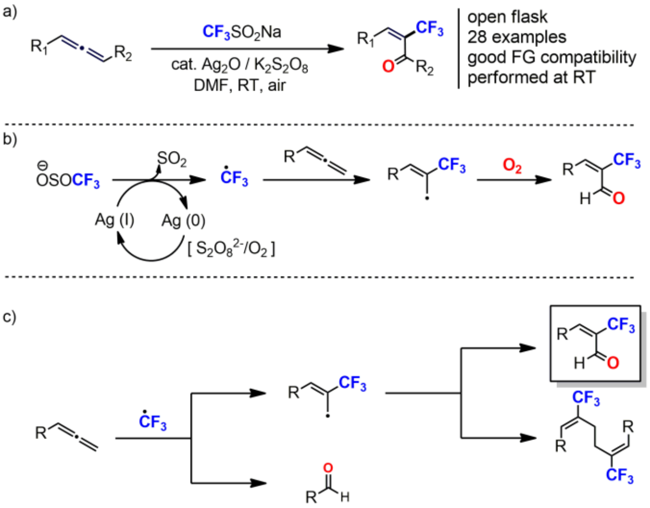
Trifluoromethylation of Allenes: An Expedient Access to α-Trifluoromethylated Enones at Room Temperature

Massimo Brochetta,[a] Tania Borsari,[a] Andrea Gandini,[a] Sandip Porey,[b] Arghya Deb,[c] Emanuele Casali,[a] Arka Chakraborty,[b] Giuseppe Zanoni,*[a] and Debabrata Maiti *[a,b]

ABSTRACT: A silver(I) catalyzed regioselective trifluoromethylation of allenes using Langlois's salt ($NaOSOCF_3$) is demonstrated. This transformation enables direct expedient access to α-trifluoromethylated acroleins which are valuable synthons for a number of pharmaceuticals and agrochemicals containing vinyl-CF_3 moieties. Versatility of this trifluoromethylation method has been established with good yield and excellent regioselectivity. Preliminary experiments and computational studies were carried out to elucidate the mechanistic insight of this protocol.

The ubiquity of trifluoromethyl group (-CF_3)[1,2] in myriads of pharmaceuticals, agrochemicals and functional materials has inspired chemists to develop numerous trifluoromethylation strategies over the years.[3,4] Among different protocols, trifluoromethyl radical based methods were found to be highly captivating due to their high reactivity, milder reaction conditions and easily accessible resources.[5-7] In spite of having advantageous features, a number of important trifluoromethylated scaffold synthesis still remain unaddressed. In this context, α-trifluoromethyl substituted enones is one such important moiety which has drawn significant attention in recent years due to its presence in many pharmaceutical and bioactive molecules. [8,9]

Recently, we have developed a method to access α-CF_3 substituted ketones from simple unactivated olefins and alkynes using an inexpensive radical trifluoromethylating source Langlois's reagent ($NaOSOCF_3$) at room temperature (Scheme 1a).[10] We envisaged the possibility of accessing α-trifluoromethyl substituted enones starting from allene. The highly electrophilic *sp* hybridized carbon center in allene core structure is expected to be reactive towards the trifluoromethyl radical. High *regio*- and *stereo* selectivity of product were expected due to the unique structural feature of allenes. Utilizing these potential, development of regioselective trifluoromethylation of allenes to access α-trifluoromethyl substituted enones by direct radical based C–H functionalization approach could become one of the highly appealing and useful synthetic strategy.



Scheme 1. a) Oxidative trifluoromethylation of allenes. b) Plausible mechanistic pathway. c) Challenges and possible side products during trifluoromethylation of allene.

At the outset of this study, phenyl allene was selected as a model substrate along with Langlois's reagent ($NaOSOCF_3$) to examine the feasibility of radical reactions to afford α-trifluoromethylated acrolein. To our delight, we obtained 26% yield of α-CF_3 substituted acrolein which was highly encouraging to pursue further optimization. After extensive studies with different silver salts, silver oxide (Ag_2O) was found to be the best catalyst to generate the trifluoromethylated product in 67% yield with *N*,*N*-dimethylformamide (DMF) as solvent under air. Optimum use of 20 mol% potassium persulfate ($K_2S_2O_8$) was resulted from detailed optimization with different oxidants. However, further attempts to improve the yield of trifluoromethylated product by increasing the amount of silver catalyst as well as oxidant was unsuccessful due to the increased oxidation of allene to the corresponding aldehydes (Scheme 1c).

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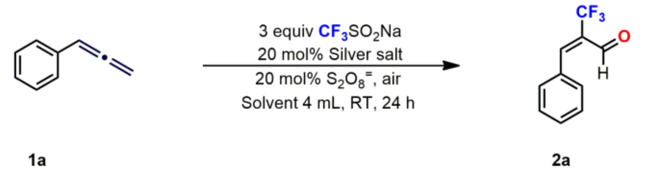
Table 1. Trifluoromethylation of allene.[a]



1a

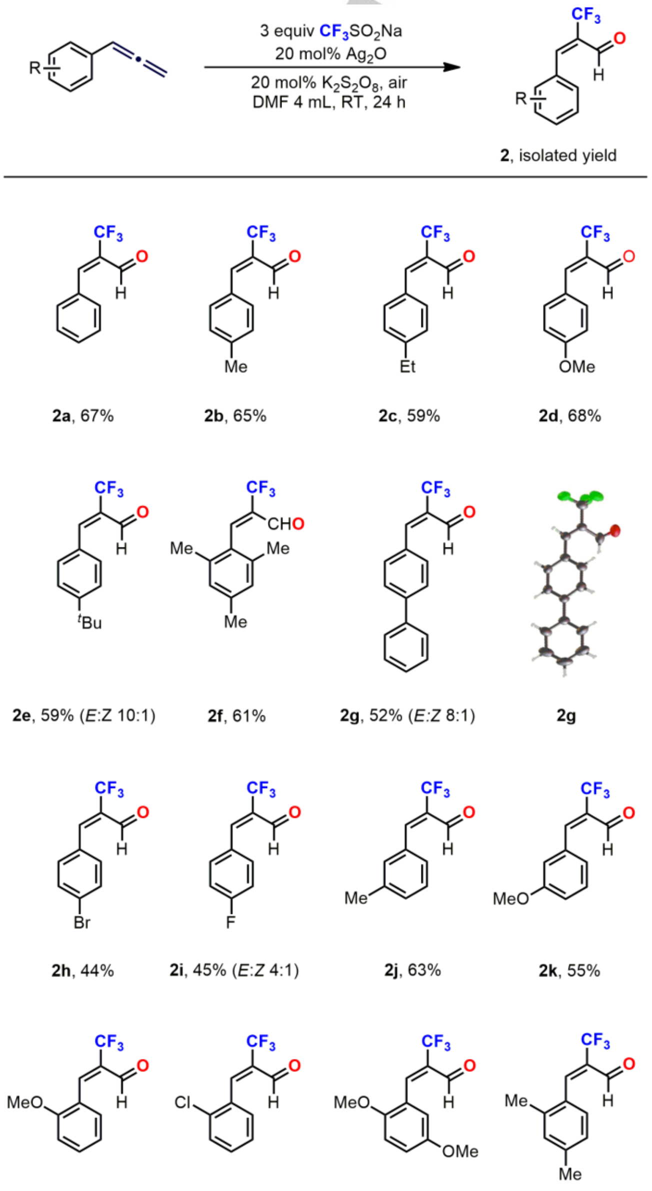
2a

Entry.	Silver salt[b]	Oxidant[b]	Solvent	Yield[c]
1	$AgNO_3$	$K_2S_2O_8$	DMF	26
2	$AgNO_3$	$K_2S_2O_8$	DMA	6
3	Ag_2SO_4	$K_2S_2O_8$	DMF	40
4	$\mathbf{Ag_2O}$	$\mathbf{K_2S_2O_8}$	**DMF**	**70 (67[d])**
5	Ag_2O	$Na_2S_2O_8$	DMF	51
6	Ag_2O	$(NH_4)_2S_2O_8$	DMF	53
7	Ag_2O	TBHP	DMF	32
8	Ag_2O	DTBP	DMF	28
9	Ag_2O	-	DMF	6

[a]All reactions performed at rt, [b]20 mol% w.r.t allene.[c]GC yield except as noted, [d]Isolated, DMF: *N*,*N*-dimethyl formamide, DMAc: *N*,*N*-dimethyl acetamide

With optimized reaction condition, we started to explore the generality of this radical trifluoromethylation protocol by varying substituents in the aryl ring of phenyl allenes. Electron rich *para*-tolyl and methoxy allenes gave thermodynamically favorable (*E*)-selective trifluoromethylated acrolein in 65% and 68% yields, respectively. Bulky *tert*-butyl (**2e**) substituted allene produced corresponding trifluoromethylated product in synthetically useful yield. The product from 1,1'-biphenyl-4-allene has been characterized by X-ray crystallography (**2g**,CCDC1846274). Electron withdrawing halogen substituted allenes (**2h** and **2i**) gave the desired product albeit in lower yield. A *meta*-methoxy group resulted in exclusive *E* isomer (**2k**). However, electron richness as well as steric influences in the aromatic ring resulted 10:1 *E/Z* selectivity for 2,4-dimethyl allene (**2o**). Polyaromatic allenes like 2-naphthyl (**2p**) derivative gave the corresponding α-trifluoromethylated acroleins in 61% yields. Synthetic efficiency of the current protocol has been perceived by accessing aliphatic α -trifluoromethylated cyclohexyl acrolein in 56% yield from unactivated cyclohexyl allene (**2z**).[11]

Table 2. Scope of oxidative trifluoromethylation with allenes



2a, 67% **2b**, 65% **2c**, 59% **2d**, 68%

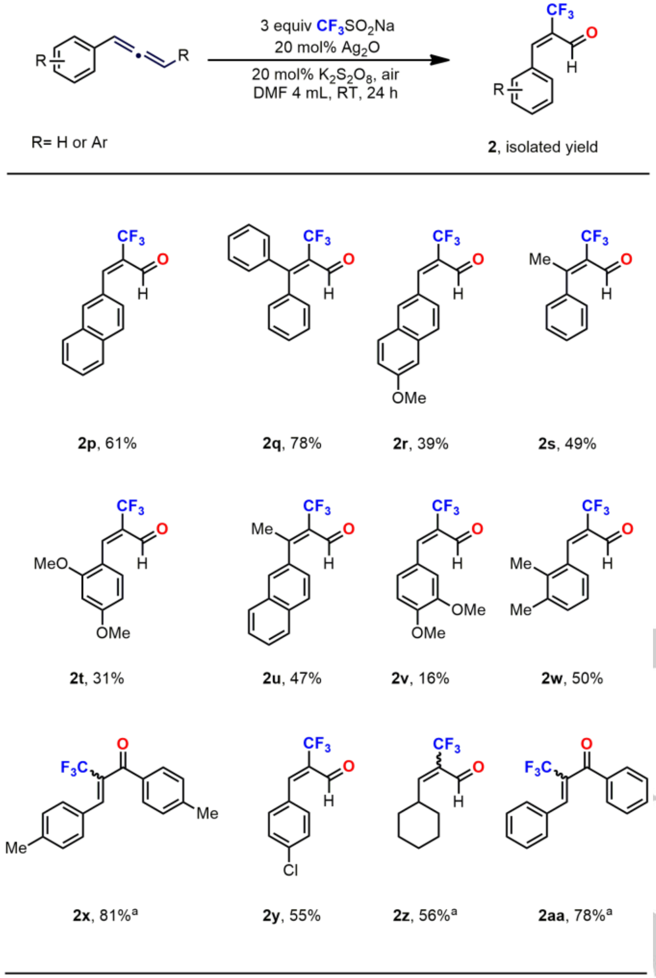
2e, 59% (*E*:*Z* 10:1) **2f**, 61% **2g**, 52% (*E*:*Z* 8:1) **2g**

2h, 44% **2i**, 45% (*E*:*Z* 4:1) **2j**, 63% **2k**, 55%

2l, 45% (*E*:*Z* 4:1) **2m**, 48% **2n**, 63% (*E*:*Z* 4:1) **2o**, 78% (*E*:*Z* 10:1)

Investigation into the trifluoromethylation mechanism suggested that the CF_3 radical is likely to be involved in the reaction. Under the optimized conditions, *para-tert*-butyl allene did not produce α-CF_3 substituted enone in presence of TEMPO (Scheme 2c). Expectedly, TEMPO-CF_3 was detected by GC-MS analysis. Homocoupling product (**3a**) was isolated in 90% yield in a closed cap reaction highlighting the influence of air as the oxidizing agent (Scheme 2a). Furthermore, attempt for trifluoromethylation reaction under O_2 atmosphere resulted in the oxidation of the aryl allene into the carbonyl derivative (Scheme 2b).[9] Four different allenes were tested under oxygen atmosphere, and all of them produced corresponding aromatic aldehyde. Formation of aldehyde from allene has previously been reported in the literature. Mechanism of trifluoromethylation reaction with different pathways has been proposed (Scheme 3). We supposed that the trifluoromethyl radical is produced during the reaction, which involve silver and $NaOSOCF_3$.

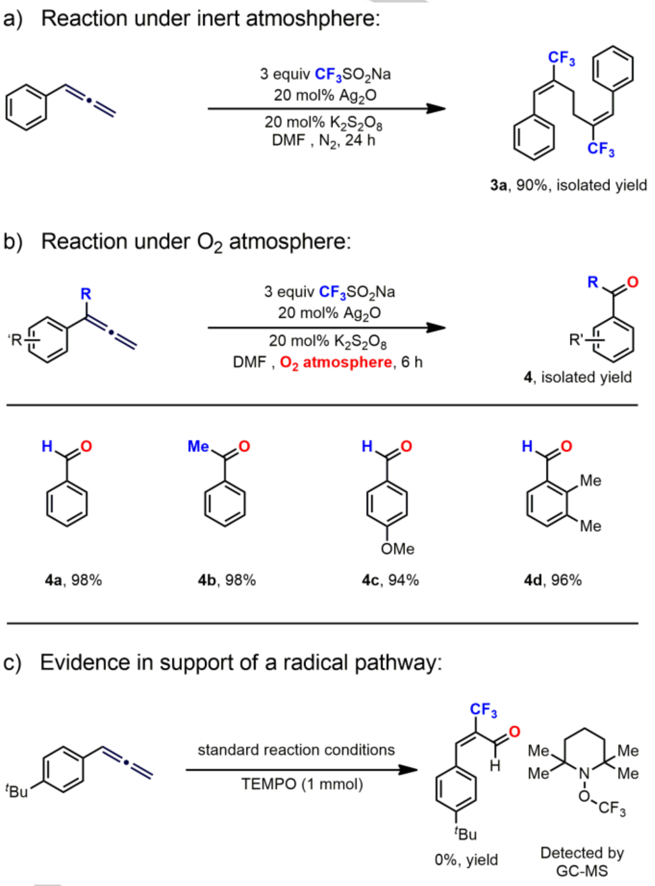
Table 3. Oxidative trifluoromethylation using CF_3SO_2Na



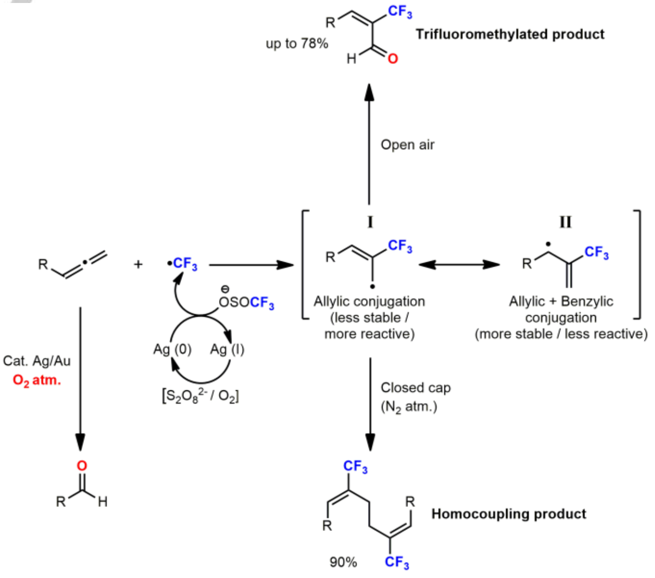
[a] GC–yield.

The reaction between CF_3 radical and the allene proceeds *via* formation of radical intermediates **I** or **II**. In particular, (intermediate **II**) is less reactive due to the allylic and benzylic conjugation. Under the reaction condition, O_2 promotes oxidation of **I** into trifluoromethylated enones. Conversely, closed cap reaction (N_2 atmosphere) afford the homocoupling product (**3a**). To investigate the stability of the radical species involved in the trifluoromethylation reaction, computational calculations were performed in order to observe the spin density on the atom **C1**, **C2** and **C3**. We hypothesize that the benzylic conjugation increases the spin density on the **C1** and the stability of the species **II** (Table 4). Moreover, the presence of electron-donating group (methyl, intermediate **B**) on the arene decreases the spin density on the benzyl carbon (**C1**). On the contrary it was observed that the spin density decreased on **C3** in presence of electron withdrawing group such as bromine or naphthyl. Thus, we can assume that the reactive species involved in the oxidation step is the intermediate **I** because of lower stability induced by lowest spin density on **C3**.

Furthermore the property of the aryl substituents could affect the trifluoromethylation reaction.

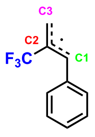


Scheme 2. Mechanistic studies



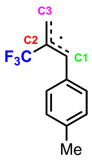
Scheme 3. Proposed Mechanism of trifluoromethylation

Table 4. Spin density on **C1**, **C2** and **C3** involved in trifluoromethylation.

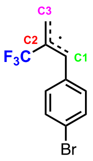


A

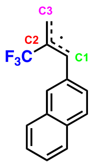
Level of computational theory	spin density C1	spin density C2	spin density C3
6-311++g(d,p)	+0.674	-0.258	+0.506



B



C



D

Level of computational theory	Intermediate	spin density C1	spin density C2	spin density C3
6-311++g(d,p)	**B**	+0.627	-0.247	+0.506
	C	+0.631	-0.247	+0.497
	D	+0.622	-0.249	+0.491

In conclusion, we have developed a direct, efficient, and general method to synthesize α-CF_3-substituted enones from allenes. Various functionalized allenes were employed using an inexpensive trifluoromethylating reagent. Mild reaction condition and easy availability of starting material make this method attractive to generate α-trifluromethylated enones.

Keywords: • Trifluoromethylation • Allenes • Enones • *E*-selective • Thermodynamically controlled product

Acknowledgements

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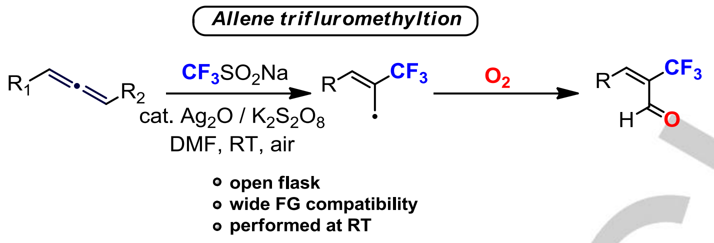
[11] Due to high volatility, the yield of the product was measured by GC-MS of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

COMMUNICATION

A highly regio and sterio selective trifluromethylation of allenes has been developed to afford α-trifluoromethylated acroleins using Langlois's reagent..



M Brochetta, T Borsari, A Gandini, S Porey, A Deb, E Casali, A. Chakraborty, G Zanoni and D. Maiti**

Page No. – Page No.

Triflurommethylation of Allene: An Expedient Access to α – Triflurommethylated Enones at Room Temperature