


Langlois Reagent: An Efficient Trifluoromethylation Reagent

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Abstract **Key words** Langlois reagent, trifluoromethylation, free radical, fluoroorganic synthesis, sodium trifluoromethanesulfinate or sodium triflinate

The fluorine atom has a grand reception in pharmaceutical, material, and agrochemical industries as it dramatically alters the physical, chemical, and metabolic properties of organic compounds in its presence. Hence, its incorporation as an atom or fluorine-containing functional groups in organic molecules remains a huge interest among the organic chemists.¹ Among the fluorine-containing functional groups, the trifluoromethyl (CF₃) group is the most common group that could improve molecular properties and hence predominantly found in pharmaceutical substances. Therefore, the development of novel methods to build the C–CF₃ bond is of great interest, and several other reagents have been developed.²

Among the other available trifluoromethylating reagents, such as Togni, Umemoto, Ruppert–Prakash reagents, etc., Langlois reagent (CF₃SO₂Na) has been extensively focused in the past few decades due to its commercial availability, inexpensiveness, stability, and, importantly, its capability of transferring the CF₃ group into a large variety of substrates via both electrophilic and free-radical mechanistic pathways.^{3,4} Interestingly, this reagent can also be used to install SCF₃, SOCF₃, etc. functions into organic compounds.⁵



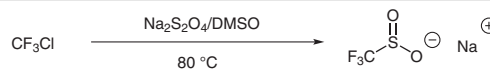
Anusha K. (first from left) and **Megha Mahesh** (second from left) are undergraduate life science students, and **Shikha** is an undergraduate chemistry honors student in the Department of Chemistry at Sri Venkateswara College.

Prof. Sharda Pasricha (first from right) is currently working as professor in the Department of Chemistry, Sri Venkateswara College, University of Delhi, India. She has nearly 25 years of teaching experience at the undergraduate level. She has published nearly 20 research articles in journals of national and international reputation. She was a recipient of the prestigious ‘Distinguished Teacher Award’ from University of Delhi in 2009. She has authored two books and several e-modules for UG students. Her current research interests include green chemistry, heterogeneous catalysis, and synthesis of biologically relevant heterocycles.

Dr. T. M. Rangarajan is currently working as assistant professor of chemistry and has nearly 10 years of research experience and 5 years of teaching experience. He has published 23 research articles of international repute and has three national patents and one international patent to his name. His research interests include electrochemical perfluorination, electro-organic synthesis, organic synthesis, cross-coupling methodologies, and medicinal chemistry.

In 1991, the sodium trifluoromethanesulfinate (NaSO₂CF₃) reagent was first introduced by the Langlois group for the introduction of the trifluoromethyl group in an aromatic system and the reagent was first prepared from trifluoromethylchloride and sodium dithionite⁶ as shown in Scheme 1. However, this reagent was unexplored for fifteen years. In


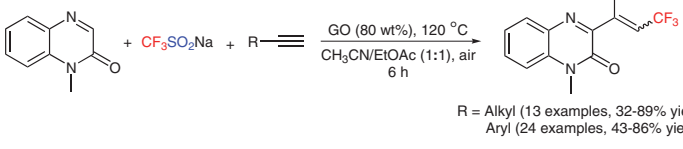
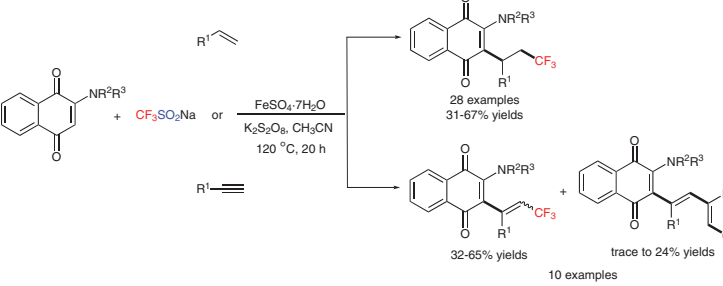
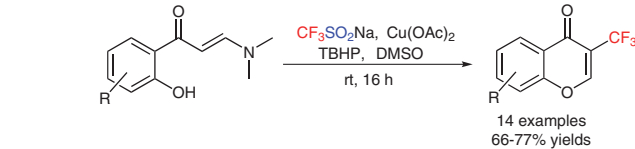
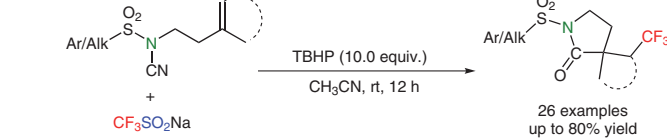
2011, Baran *et al.* successfully developed the trifluoromethylation of heteroaromatic systems using various trifluoromethylating agents along with sodium trifluoromethanesulfinate and first named it as Langlois reagent for the success of the method.⁷ After the pioneering work of Baran *et al.*, the applications of this reagent boomed into several areas of organic synthesis (Table 1).



Scheme 1 Synthesis of Langlois reagent

Table 1 Recent Applications of Langlois Reagent ($\text{CF}_3\text{SO}_2\text{Na}$)

<p>Zha and coworkers introduced a transition-metal-free method for the incorporation of $-\text{SCF}_3$ and $-\text{SOCF}_3$ to an electron-rich indole system using Langlois reagent in the presence of PCl_3, afforded target molecules with 23–86% yields. PCl_3 was used as a reducing and chlorinating agent for the first time.⁵</p>	
<p>Liao <i>et al.</i> demonstrated the first-ever method for utilization of SO_2 from $\text{CF}_3\text{SO}_2\text{Na}$ with simultaneous insertion of $-\text{CF}_3$ and $-\text{SO}_2$ groups in <i>N</i>-cyano-alkenes via electrolysis (anodic oxidation) leading to the cyclic <i>N</i>-sulfonylimines with 15–64% yield.⁸</p>	
<p>Cui <i>et al.</i> reported an interesting method to access the halo-trifluoromethylation of alkenes via free-radical addition mechanism mediated by $\text{Mn}(\text{OAc})_3 \cdot 2\text{H}_2\text{O}$. The addition products were achieved by Langlois reagent accompanied by perhalocarboxylic acids with excellent yields.⁹</p>	
<p>Wan <i>et al.</i> demonstrated a combination of iodine and Langlois reagent mixture for the introduction of perfluoroalkylsulfonyl group at the α-position of (<i>E</i>)-enaminones via a free-radical mechanism. Interestingly, the products were achieved stereoselectively via an unprecedented C–H elaboration and C=C configuration inversion under mild reaction conditions with 38–83% yields.¹⁰</p>	
<p>Akondi <i>et al.</i> developed an environmentally benign three-component reaction strategy for the synthesis of trifluoromethylated alkenes under visible-light conditions through trifluoromethyl-alkenylation of unactivated alkenes, with Langlois reagent, and nitroalkene.¹¹</p>	

<p>Lili <i>et al.</i> demonstrated the formation of trifluoromethylated dimerized products from styrenes and Langlois reagent in the presence of cyanoarenes (PC1: 2,4,6-tris(diphenylamino)-5-fluoroisophthalonitriles or 3DPAFIPN) as an efficient organic photocatalyst under blue LED irradiation. The scope and mechanism of the reaction with the experimental supports were elaborated on in this study. This method afforded the products with 30–80% yields.¹²</p>	 <p>15 examples 30-80% yields</p> <p>PC1 : 2,4,6-Tris(diphenylamino)-5-fluoroisophthalonitrile</p>
<p>Liu <i>et al.</i> developed a transition-metal-free, graphene oxide (GO) catalyzed direct C–H trifluoromethylation of alkynes and quinoxalinones with Langlois reagent that afforded the trifluoromethylated quinoxalin-2(1<i>H</i>)-one product under ambient atmosphere.¹³</p>	 <p>R = Alkyl (13 examples, 32-89% yields), Aryl (24 examples, 43-86% yields)</p>
<p>Tang <i>et al.</i> have demonstrated the first Fe-catalyzed regioselective perfluoromethylalken- and alkynylation of 1,4-naphthoquinones using NaSO₂CF₃ and K₂S₂O₈ as an oxidant. This method has been displayed as high regioselectivity and functional group tolerance.¹⁴</p>	 <p>28 examples 31-67% yields</p> <p>32-65% yields</p> <p>10 examples trace to 24% yields</p>
<p>Behera and co-workers developed an efficient and scalable protocol for the synthesis of trifluoromethylated chromones from readily accessible <i>o</i>-hydroxyphenyl enaminones. The transformation is affected by the Langlois reagent in DMSO with a catalytic amount of Cu(OAc)₂ and TBHP oxidant at room temperature.¹⁵</p>	 <p>14 examples 66-77% yields</p>
<p>Li <i>et al.</i> reported an efficient methodology to access trifluoromethylated γ-lactams in good yields via radical tandem cyclization from <i>N</i>-cyano alkenes using CF₃SO₂Na, and the reaction was initiated by TBHP, thus involving a CF₃-radical-triggered tandem cyclization with subsequent hydrolysis. The methodology provides a broad substrate scope with various substituted substrates, good functional group tolerance, and easy scalability.¹⁶</p>	 <p>26 examples up to 80% yield</p>

In summary, Langlois reagent is an efficient trifluoromethylating or fluoroalkylating reagent with diverse functionalization, a broad substrate scope, and ease of handling due to its solid nature among other fluorinating agents. Recently, much attention has been paid to this reagent as the CF₃-incorporated organic compounds, which display a variety of applications in several areas of chemistry. However, the preparation of the reagent requires fluoroalkyl halides which pose an environmental threat and requires an alternative route to address the issue.

Conflict of Interest

The authors declare no conflict of interest.

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