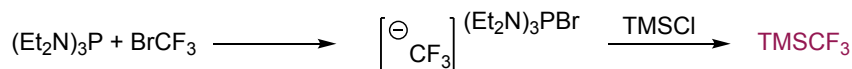


## History:

Introduced by Ruppert in 1984 alongside (CF<sub>3</sub>)<sub>2</sub>SiR<sub>2</sub> and other trifluoromethyl substituted silanes

DIE ERSTEN CF<sub>3</sub>-SUBSTITUIERTEN ORGANYL (CHLOR) SILANE

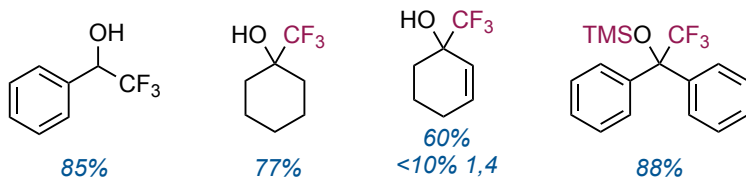
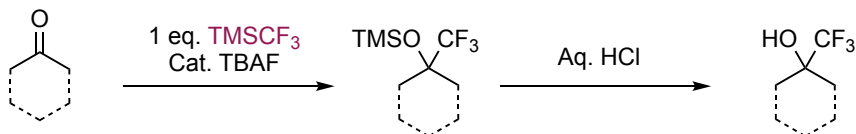
Ingo Ruppert,\* Klaus Schlich und Wolfgang Volbach



Popularized by Prakash who first published its use as a trifluoromethide equivalent

### Fluoride-Induced Trifluoromethylation of Carbonyl Compounds with Trifluoromethyltrimethylsilane (TMS-CF<sub>3</sub>). A Trifluoromethide Equivalent<sup>1</sup>

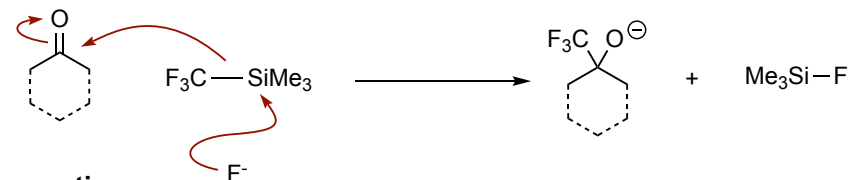
G. K. Surya Prakash,\* Ramesh Krishnamurti, and George A. Olah\*



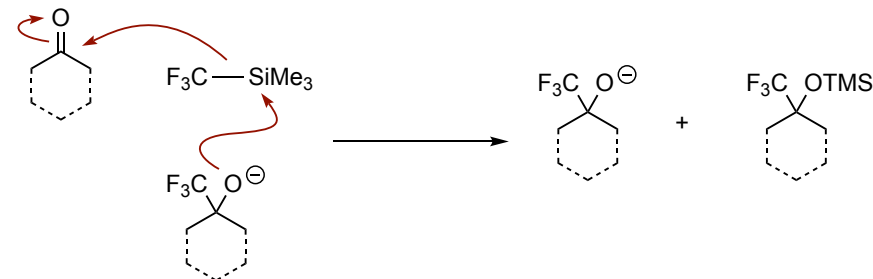
## Mechanism:

Initially proposed to go through an anionic chain mechanism

### Initiation:



### Propagation:

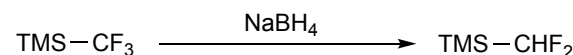


*t*BuOK is also a viable initiator for the reaction (evidence for propagation step)

They note that when wet TBAF is used, no adverse reactivity is observed until large loadings (upwards of 50 mol %) is used. In this case, hydrolysis of the silyl ether occurs during the reaction and CF<sub>3</sub>H is generated

## Fun Fact!

The Ruppert–Prakash reagent is also useful as a precursor to difluoromethide equivalents!

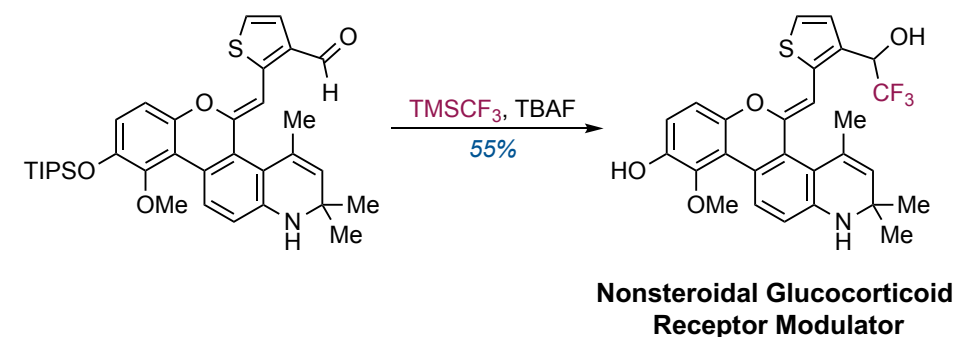
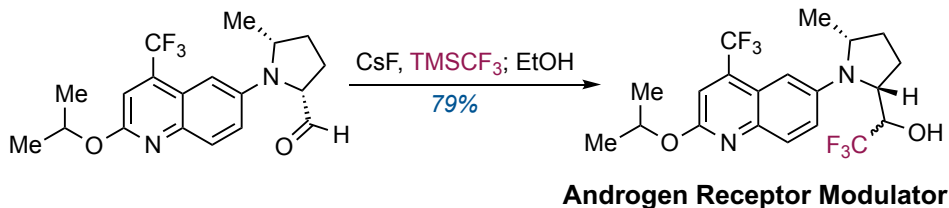
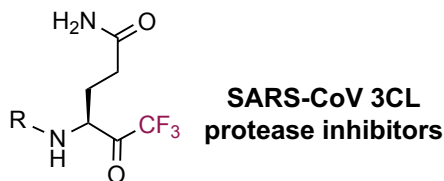
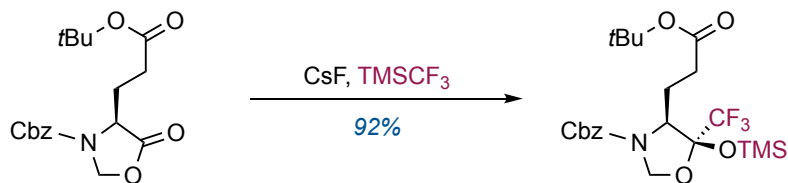


These behave the same as the Ruppert–Prakash reagent  
Alternatively, NaBH<sub>4</sub> after 1,2-addition can generate difluoromethyl groups

Eros (Difluoromethyl)trimethylsilane <https://doi.org/10.1002/047084289X.rn01650.pub2>

## Application in Medicinal Chemistry:

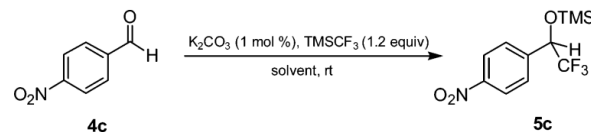
The Ruppert–Prakash reagent is most often used in MedChem contexts where the CF<sub>3</sub> group can be used in place of methyl groups



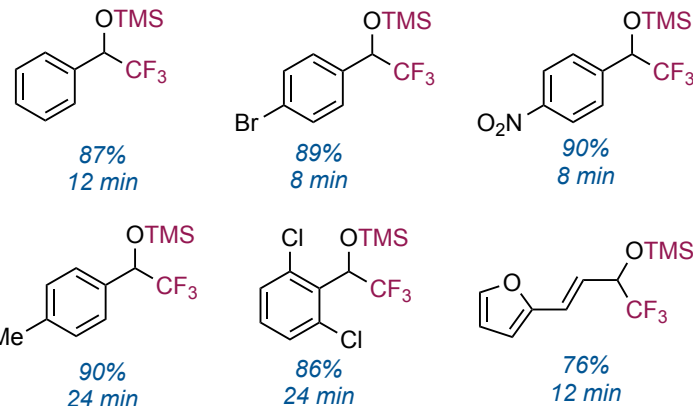
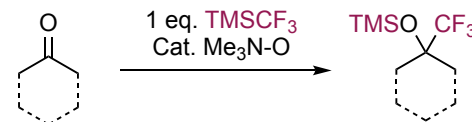
## Modifications:

When using CsF as an initiator, water must be avoided to maintain efficiency. Also, nucleophilic fluorides remove silyl protecting groups

N-Oxides or K<sub>2</sub>CO<sub>3</sub> in DMF can initiate the reaction without fluoride sources



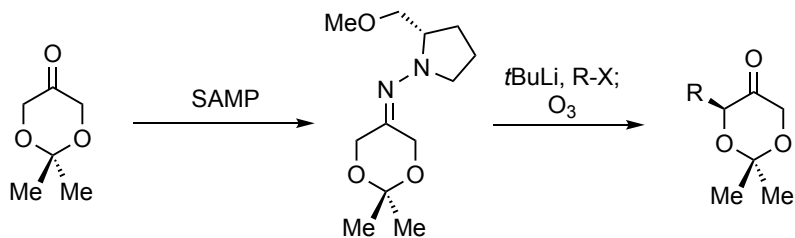
entry	solvents	time	conv. (%)	yield (%)
i	DMF	5 min	100	86
ii	THF	overnight	60	
iii	THF + DMF (4:1)	10 h	100	80
iv	DCM	48 h	<5	
v	DCM + DMF (4:1)	1 h	100	78
vi	DMSO	5 min	100	78



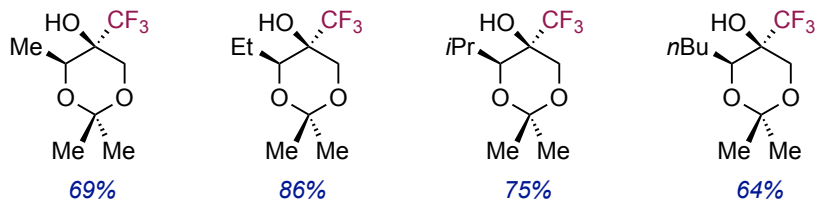
Tet. 2006, 62, 8601, <https://doi.org/10.1016/j.tet.2006.06.052>  
 J. Med. Chem. 2007, 50, 5049 <https://doi.org/10.1021/jm070231h>  
 J. Med. Chem. 2007, 50, 4699 <https://doi.org/10.1021/jm070370z>

J. Org. Chem. 2006, 71, 6806 <https://doi.org/10.1021/jo060835d>

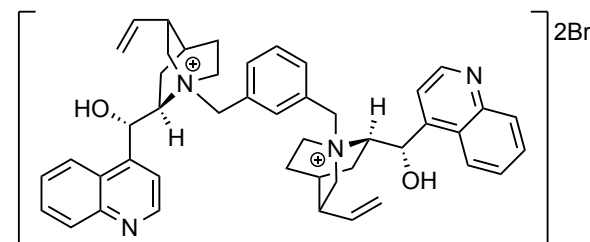
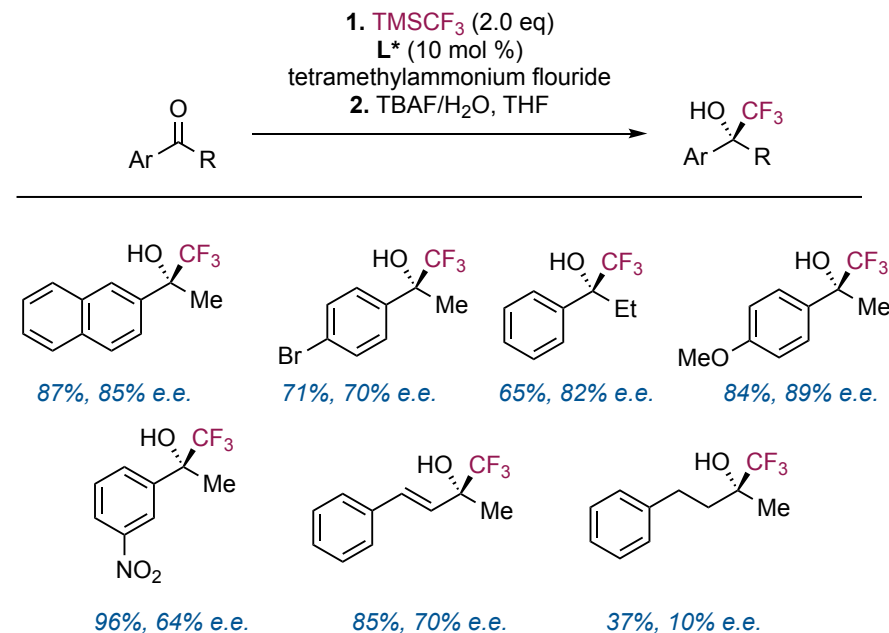
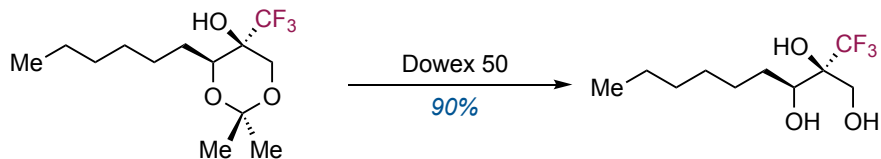
## Enantioselective Trifluoromethylation



55-70% yield over 3 steps, e.e. > 92%



Single diastereomer (by <sup>1</sup>H NMR) in all cases



## Further Reading:

The Ruppert–Prakash reagent has recently been used in organometallic reactions as a difluorocarbene precursor  
*ACIE* **2018**, 57, 13211 <https://doi.org/10.1002/anie.201807873>.

The mechanism is also more complicated than it may seem. The Lloyd–Jones group has published a full study on the mechanism and the various ways that the reaction can be inhibited (by water or even by the CF<sub>3</sub> anion itself)  
*J. Am. Chem. Soc.* **2018**, 140, 11112 <https://doi.org/10.1021/jacs.8b06777>