Difluoromethyl Phenyl Sulfone, a Difluoromethylidene Equivalent: Use in the Synthesis of 1,1-Difluoro-1-Alkenes

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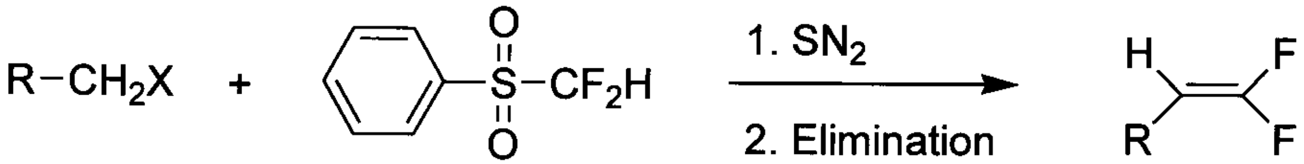


Outline

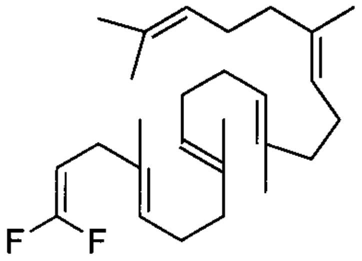
- Difluoroalkene Introduction
- Biological Activity of Difluoroalkenes
- Synthesis of Difluoroalkenes
- Reactivity of Difluoroalkenes
- Early Work from the Prakash group
- Current Paper
- Conclusion

Difluoroalkene Introduction

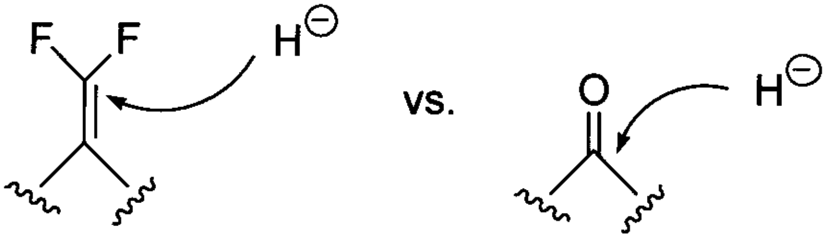
- Aliphatic fluorine
  - C-F bond mimics C-H bond because of similar bond distance
  - Difluoromethylene unit is isosteric and isopolar to ethereal oxygen
- Difluoroalkenes
  - Potential bioisosteres for carbonyl
    - Electronegativity comparable to carbonyl
    - Both serve as H-bond acceptors
  - Difference between difluoroalkene and carbonyl
    - Because of repulsion between fluorines and anionic center, α anions are not formed

Biological Activity of Difluoroalkenes

- Terminal difluoroalkene analogues of Squalene inhibit Squalene Epoxidase (J.A.C.S. **1992**, *114*, 360)

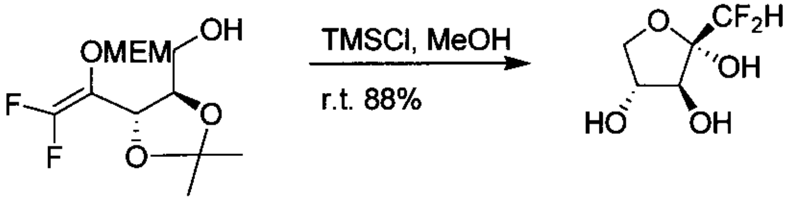


- Difluoroalkenes reverse regiospecificity of NAD(P)H-Dependent hydride transfer. (J.A.C.S. **2003**, *125*, 6348)

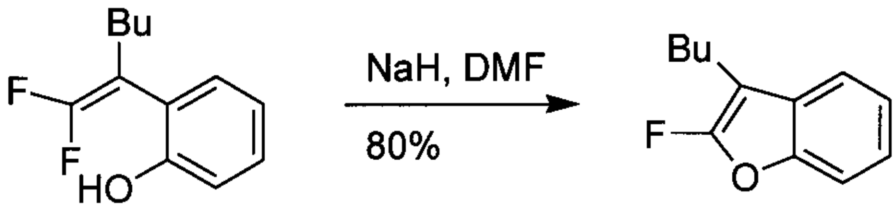


Reactions with Difluoroalkenes

- Cyclization (Org. Lett. **2003**, *5*, 337)

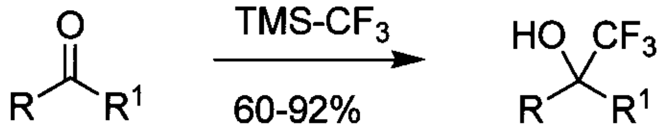


- 5-Endo-Trigonal Cyclizations (J.O.C. **2004**, *69*, 4203)

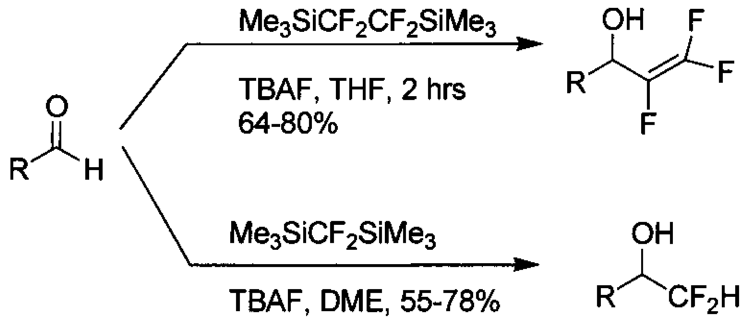


Early Work from the Prakash Group

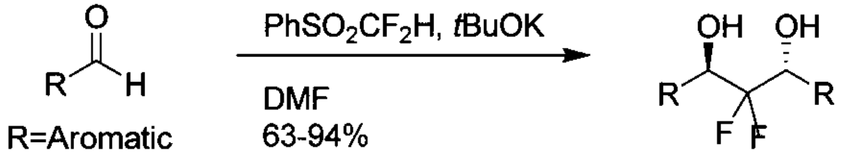
- TMS-CF_3 addition into carbonyl (J.A.C.S. **1989**, *111*, 393)



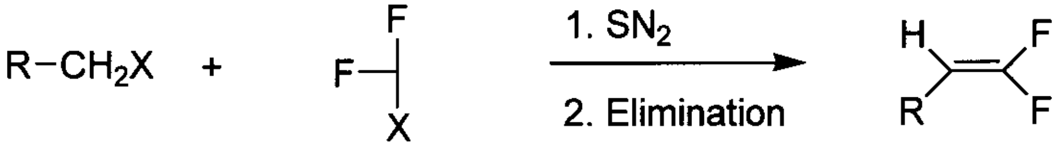
- Fluoroalkylation and perfluorovinylation (J.A.C.S. **1997**, *119*, 1573)



- Difluoromethyl Phenyl Sulfone as dianion Equivalent (Angew. Chem. Int. Ed. **2003**, *42*, 5216)

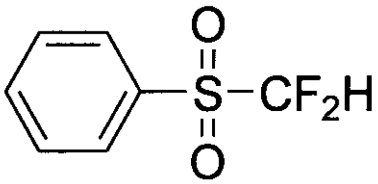


Current Paper



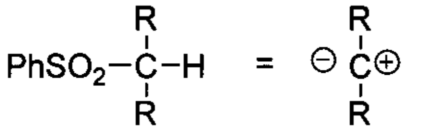
Goal: Convert primary iodides into difluoroalkenes

- A trifluoromethane anion is too hard of a nucleophile to add into a soft alkyl iodide electrophile
- Solution: attenuate nucleophile
  - Benzene sulfonyl group ("chemical chameleon") can increase the softness of the nucleophile to react with alkyl iodides



“Chemical Chameleon”

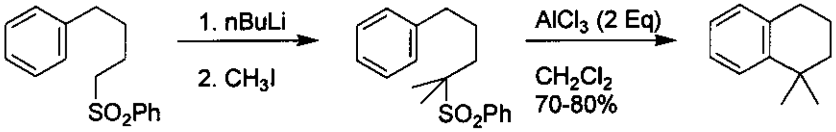
- Trost dubbed sulfones as chemical chameleons because they can behave as 1,1-dipoles
  (J.A.C.S. **1984**, *106*, 7260)



$$PhSO_2-\overset{R}{\underset{R}{C}}-H \;=\; \ominus\,\overset{R}{\underset{R}{C}}\oplus$$

1,1-dipole

- Sulfones can serve as nucleophilic or electrophilic species depending on their chemical environment
  (J.A.C.S. **1984**, *106*, 7260)



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Optimization

Run	Equiv. F	Iodide (Equiv)	Base (equiv)	Solvent	Temp	t (hours)	Yield
1	1	n-pentylbromide (2.1)	*t*BuOK (1.0)	DMF	-50-25	1	34
2	1	n-pentylbromide (2.1)	tBuOK (1.0)	DMF	-50-25	16	29
3	1	n-pentylbromide (2.1)	tBuOK (2.0)	DMF	-50-25	1	52
4	1	n-pentylbromide (4.0)	tBuOK (2.0)	DMF	-50-25	1	61
5	1	n-pentyliodide (4.0)	NaOH (25.0)	DMF	-50-25	1	85
6	1	n-pentylbromide (10.0)	tBuOK (2.0)	DCM	25	20	1
7	1	ethyl iodide (4.0)	tBuOK (2.0)	DMF	-50	1	65
8	1	ethyl iodide (4.0)	tBuOK (2.0)	THF	-50	1	0
9	1	2- iodobutane (4.0)	tBuOK (2.0)	DMF	-50	1	0
10	1	methyl triflate (4.0)	tBuOK (2.0)	DMF	-50	1	0
11	1	methyl triflate (4.0)	tBuOK (2.0)	THF	-50	1	0

- Iodides gave higher yields than bromides (5 vs. 4)
- Triflates gave no isolated product (10 and 11)
- Best results were obtained with 4 Equivalent of Iodide, 2 Equivalent of base, DMF and -50 degrees

Elimination

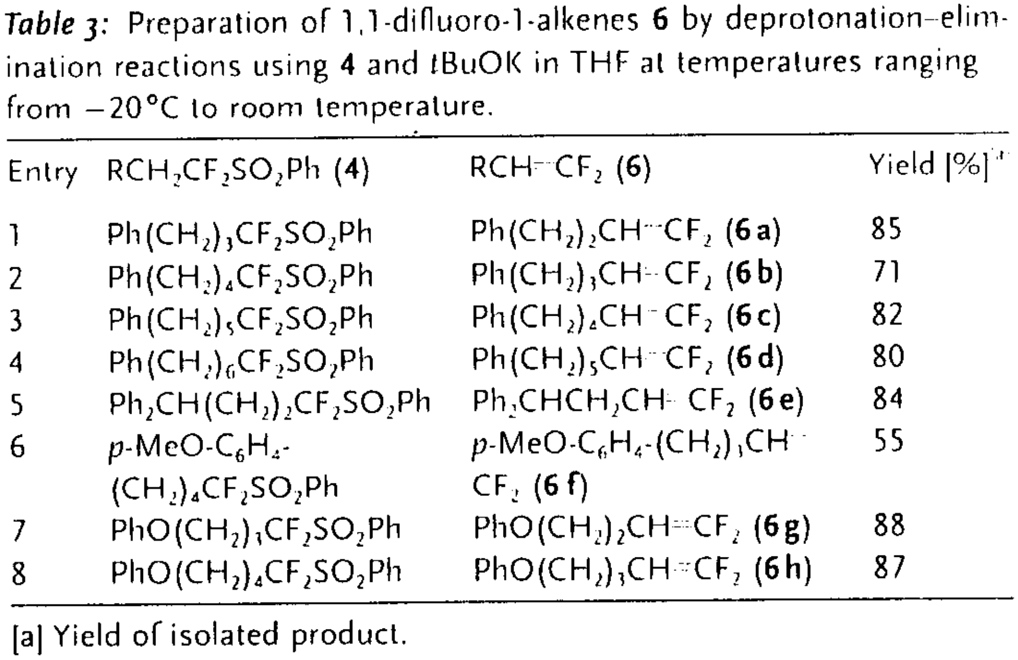

Table 3: Preparation of 1,1-difluoro-1-alkenes **6** by deprotonation–elimination reactions using **4** and *t*BuOK in THF at temperatures ranging from −20°C to room temperature.

Entry	$RCH_2CF_2SO_2Ph$ (**4**)	$RCH{=}CF_2$ (**6**)	Yield [%][a]
1	$Ph(CH_2)_3CF_2SO_2Ph$	$Ph(CH_2)_2CH{=}CF_2$ (**6a**)	85
2	$Ph(CH_2)_4CF_2SO_2Ph$	$Ph(CH_2)_3CH{=}CF_2$ (**6b**)	71
3	$Ph(CH_2)_5CF_2SO_2Ph$	$Ph(CH_2)_4CH{=}CF_2$ (**6c**)	82
4	$Ph(CH_2)_6CF_2SO_2Ph$	$Ph(CH_2)_5CH{=}CF_2$ (**6d**)	80
5	$Ph_2CH(CH_2)_2CF_2SO_2Ph$	$Ph_2CHCH_2CH{=}CF_2$ (**6e**)	84
6	*p*-MeO-C_6H_4-$(CH_2)_4CF_2SO_2Ph$	*p*-MeO-C_6H_4-$(CH_2)_3CH{=}CF_2$ (**6f**)	55
7	$PhO(CH_2)_3CF_2SO_2Ph$	$PhO(CH_2)_2CH{=}CF_2$ (**6g**)	88
8	$PhO(CH_2)_4CF_2SO_2Ph$	$PhO(CH_2)_3CH{=}CF_2$ (**6h**)	87

[a] Yield of isolated product.

Conclusion

- Difluoroalkenes can serve as isosteres of carbonyl compounds inviting various applications to biological systems and biologically active drugs
- There have been several different methods developed for the generation of difluoroalkenes (Wittig, etc)
- Prior to this paper, there were no reports of the conversion of alkyl iodides into difluoroalkenes
- The Prakash group has reported to the synthesis of difluoroalkenes from readily available starting materials. One major limitation, however, at this time is the large excess of iodide necessary to achieve high yields.