Hydroelementation of SF_5-Alkynes and further functionalizations, a fully Regio- and Stereoselective Pathway Supported by DFT Calculations

Lucas Popek,[a] Jorge-Juan Cabrera-Trujillo,[b] Vincent Debrauwer,[a] Nicolas Blanchard,[a] Karinne Miqueu,[b]* Vincent Bizet[a]*

[a] Université de Haute-Alsace, Université de Strasbourg, CNRS, LIMA, UMR 7042, 68100 Mulhouse – France
[b] CNRS, Université de Pau et des Pays de l'Adour, IPREM UMR 5254, 64053 Pau cedex 09 – France.
vbizet@unistra.fr – Group website: bsm.unistra.fr

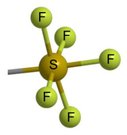
Published in : *Angew. Chem. Int. Ed.*, **2023**, *62*, e202300685

Why SF_5 is of interest ?

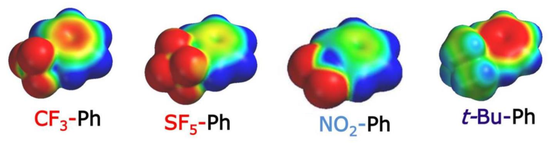
SF_5 Among the so-called "emerging" fluorinated groups, the pentafluorosulfanyl group (SF_5) is of growing interest in heterocyclic synthesis, materials science, and medicinal chemistry and drug development are in progress.[1] All of the properties showed bellow make SF_5 an interesting alternative to the CF_3 group as a bioisostere, especially in drug development.[2]

High dipole moment : 3.56 D for **SF_5** vs 2.59 D for CF_3

Octahedral structure



Hammet constants :

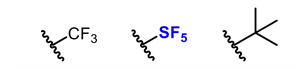


	CF_3-Ph	SF_5-Ph	NO_2-Ph	*t*-Bu-Ph
σ_p =	0.54	0.68	0.78	- 0.20

Hansch lipophilicity constant :

	CF_3	OCF_3	SF_5	SCF_3
π =	0.88	1.04	**1.23**	1.44

Large volume :

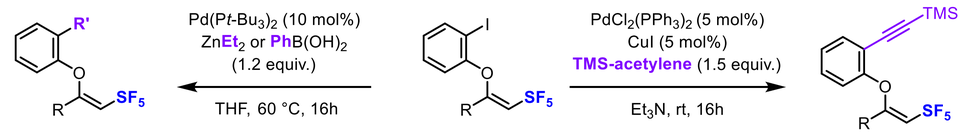


	CF_3	SF_5	*t*-Bu
V =	34.6 Å^3	**55.4 Å^3**	76.9 Å^3

- Polar and lipophilic
- Strong electron acceptor
- Thermally stable
- Hydrolytically stable

Downstream functionalization

A. Cross-coupling reactions (R = *p*-Ph-C_6H_4)

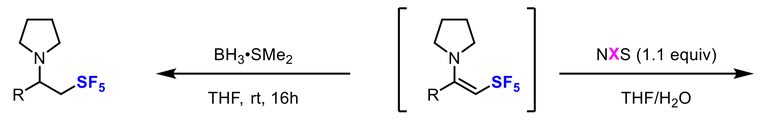


R' = Et, 49% **9aa**
R' = Ph, 75% **9ab**

6abb

57% **9ac**

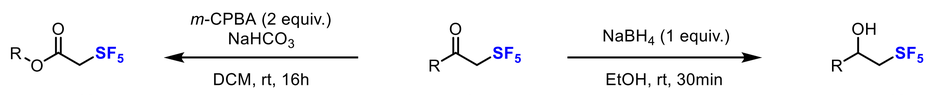
B. Reduction and halogenation reactions of enamine



55% **11**

4at

C. Bayer-Villiger reaction and reduction of the ketone

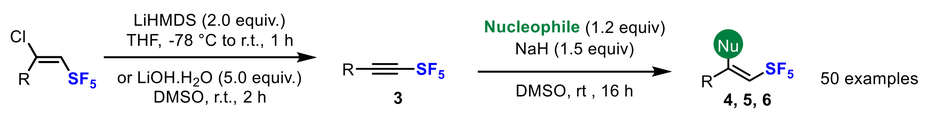


71% **13**

8a

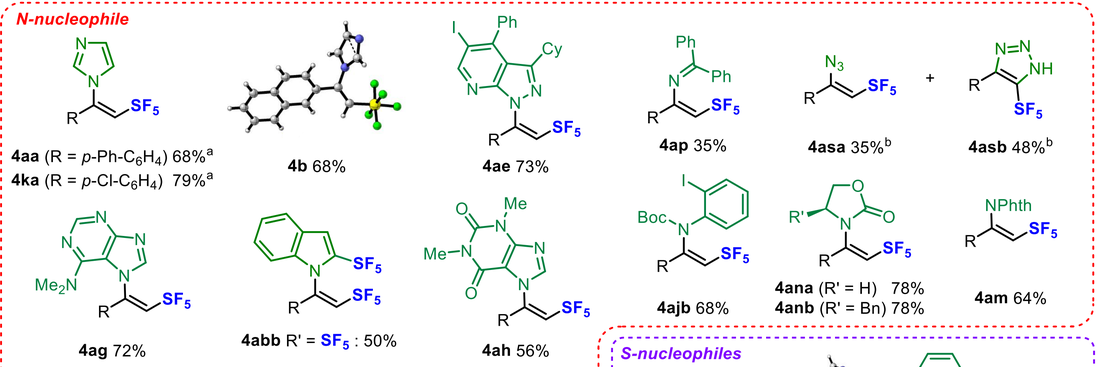
94% **12**

Hydroelementation of SF_5-alkynes (Selected examples)



3 **4, 5, 6**

N-nucleophile



4aa (R = *p*-Ph-C_6H_4) 68%[a]
4ka (R = *p*-Cl-C_6H_4) 79%[a]

4b 68%

4ae 73%

4ap 35%

4asa 35%[b]

4asb 48%[b]

4ag 72%

4abb R' = SF_5 : 50%

4ah 56%

4ajb 68%

4ana (R' = H) 78%
4anb (R' = Bn) 78%

4am 64%

4ae 53%[b]

4ae' 7%[b]

4ao 59%

4aib (R' = Ms) 58%
4aic (R' = Ac) 51%
4aid (R' = Ts) 38%

4aka R' = H 0%
4akb R' = Ts 42%

4aq 45%[a,c]

S-nucleophiles

5a 85%

5b 58%

5c 39%

O-nucleophiles

6af (R' = Me) 45%[d]
6ag (R' = ^{t}Bu) 40%

6aba (R' = Br) 83%
6abb (R' = I) 84%

6ae 60%

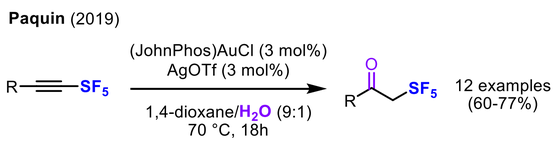
Unless otherwise stated, R = *p*-Ph-C_6H_4 [a] THF was used instead of DMSO with 2 equiv. of nucleohile [b] Both products were obtained from the reaction with the nucleohile [c] KOH was used instead of NaH [d] A 50:50 *E*:*Z* mixture was obtained but only *Z* isomer could be isolated.

An easy access to alpha-SF_5 ketones

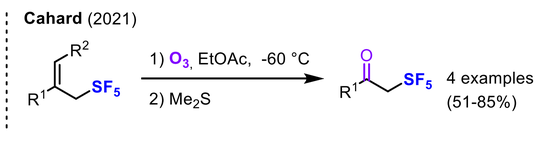
SF_5 Several methods have been reported in the literature for the synthesis of α-SF_5 ketones.[3] Herein, we propose an alternative strategy by hydroamination of SF_5-alkynes followed by acidic aqueous hydrolysis.

State of the art:

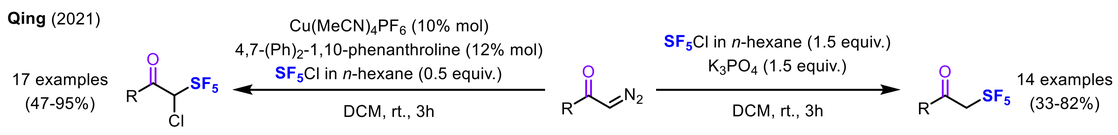
Paquin (2019)



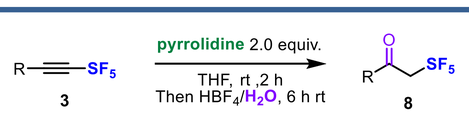
Cahard (2021)



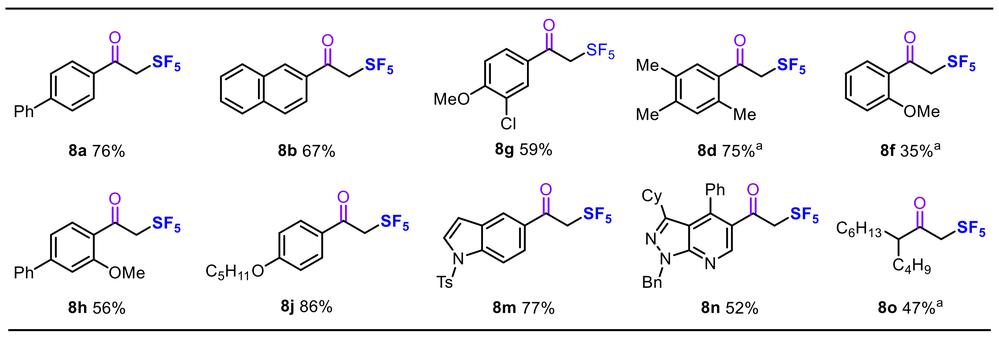
Qing (2021)



This work:



3 **8**

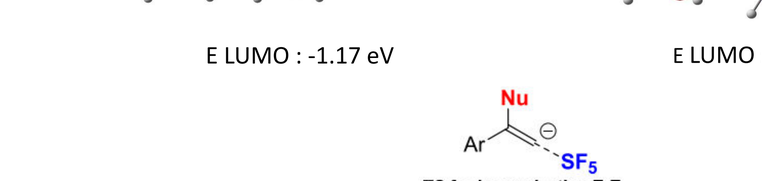


8a 76%
8b 67%
8g 59%
8d 75%[a]
8f 35%[a]
8h 56%
8j 86%
8m 77%
8n 52%
8o 47%[a]

a) H_2SO_4 10% was used instead of HBF_4

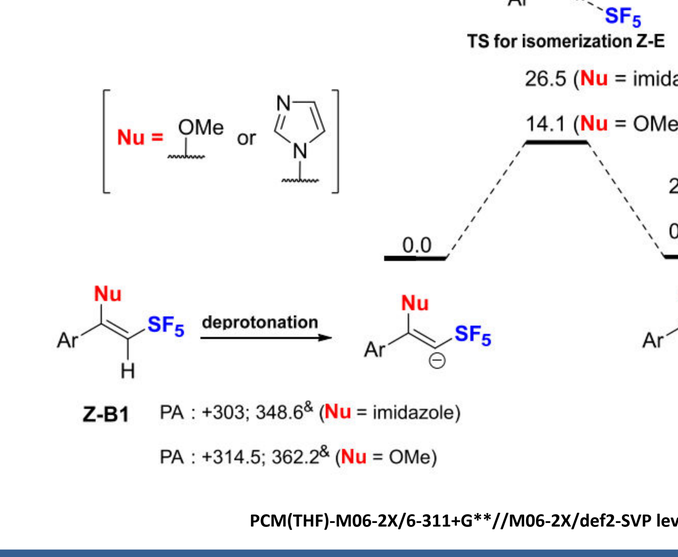
Computational study : Difference of selectivity SF_5 *vs* CF_3

SF_5 Hydroamination reaction over CF_3-alkynes has been previously reported,[4] but a mixture of α- and β-regioisomers (**A1**/**B1**) was obtained and the presence of a base was essential (conditions **Y**). In sharp contrast, a total β-regioselectivity was observed with SF_5-alkynes regardless of the conditions (**X** or **Y**). Our DFT study for the hydroamination reaction over CF_3/SF_5-alkynes (conditions **X**) confirms that the reaction is kinetically and thermodynamically favored with SF_5-alkynes. β-selectivity can also be rationalized in terms of polarization, activation barriers difference computed for **TS-A1** and **TS-B1** ($\Delta\Delta G^{\ddagger}$= 2.9 kcal) and lower steric repulsion (ΔE_{Pauli}). In addition, the lower activation barriers calculated for SF_5 support that reaction occurs without base assistance thanks to better orbital interaction between the nitrogen lone pair of the imidazole and the empty π*CΞC.



Conditions **X**: imidazole (2 equiv.) THF, r.t., 2h

Conditions **Y**: imidazole (1.5 equiv.) KOH (20 mol%) MeCN, r.t., 24h



PCM(THF)-M06-2X/6-311+G**//M06-2X/def2-SVP

➢ Pauli repulsion (Steric repulsion)

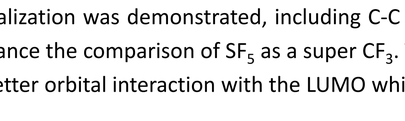
Alkyne-SF_5 (2a) + imidazole		
	C_β attack	C_α attack
ΔE_{Pauli}	**115.9**	**124.4**

➢ Polarisation of R^f-alkynes

	Alkyne-SF_5 (2a)	Alkyne-CF_3 (2a')
qC_α	-0.298	-0.149
qC_β	0.090	0.066
Δq	**0.39**	**0.22**

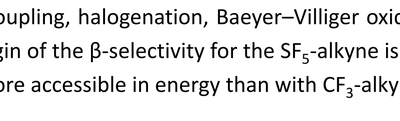
➢ Energetic position of R^f-alkynes

SF_5-alkyne **2a**

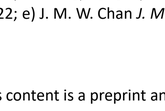


E LUMO : -1.17 eV

CF_3-alkyne **2a'**



E LUMO : -1.04 eV



TS for isomerization Z-E

PCM(THF)-M06-2X/6-311+G//M06-2X/def2-SVP level and in gas phase (&)**

Conclusion

SF_5 On this poster is presented an efficient hydroelementation reaction on SF_5-alkynes. The reaction tolerates N, O and S nucleophiles with a wide range of functional groups. The corresponding adducts are isolated in good to high yields as a single regio- and stereoisomer. A new synthesis of α-SF_5-ketone is proposed in very mild condition. A selection of downstream functionalization was demonstrated, including C-C cross coupling, halogenation, Baeyer–Villiger oxidation and reduction. DFT calculations were performed to better understand the impact on reactivity of the SF_5 compared to the CF_3 group, which nuance the comparison of SF_5 as a super CF_3. The origin of the β-selectivity for the SF_5-alkyne is related to a lower steric repulsion (ΔE_{Pauli}) upon attack at C_β. Nucleophilic attack of imidazole on SF_5-alkyne occurs in the absence of base thanks to better orbital interaction with the LUMO which is more accessible in energy than with CF_3-alkyne.

References:

1) a) P.R. Savoie, J. T. Welch *Chem. Rev.* **2015**, *115*, 1130; b) P. Das, E. Tokunaga, N. Shibata *Tetrahedron Lett.* **2017**, *58*, 4803; c) G. Haufe *Tetrahedron* **2022,** *109*, 132656; d) L. Popek, T. M. Nguyen, N. Blanchard, D. Cahard, V. Bizet *Tetrahedron* **2022,** *117-118*, 132814,
2) a) M. Inoue, Y. Sumii, N. Shibata *ACS Omega* **2020,** *5*, 10633; b) M. F. Sowaileh, R. A. Hazlitt, D. A. Colby *ChemMedChem* **2017**, *12*, 1481; c) S. Altomonte, M. Zanda *J. Fluorine Chem.* **2012**, *143*, 57; d) N. A. Meanwell *J. Med. Chem.* **2018**, *61*, 5822; e) J. M. W. Chan *J. Mater. Chem. C* **2019**, *7*, 12822.
3) a) M. Cloutier, M. Roudias, J.-F. Paquin, *Org. Lett.* **2019**, *21*, 3866; b) F.-F. Feng, J.-A. Ma, D. Cahard, *J. Org. Chem.* **2021**, *86*, 13808; c) F.-L. Qing, J.-Y. Shou, X.-H. Xu, *Angew. Chem. Int. Ed.* **2021**, *60*, 15271.
4) B. A. Trofimov, L. V. Andriyankova, L. P. Nikitina, K. V. Belyaeva, A. G. Mal'kina, A. V. Afonin, I. A. Ushakov, V. B. Kobychev, V. Muzalevskiy, V. G. Nenajdenko *J. Fluorine Chem*. **2016**, *188*, 157.
5) For nucleophilic addition of methanol on SF_5-acetylene, see: F.W. Hoover, D.D. Coffman. *J. Org. Chem*. **1964**, *29*, 3567–3570.
6) For similar works developed at the same time, see: a) J. O. Wenzel, F. Jester, D. Rombach *ChemRxiv* **2022**, DOI 10.26434/chemrxiv-2022-brg1w; b) H. Kucher, J. O. Wenzel, D. Rombach, *ChemRxiv* **2022**, DOI 10.26434/chemrxiv-2022-01jhn. This content is a preprint and has not been peer-reviewed.