

GOLD-CATALYZED SYNTHESIS OF FLUORINATED 2,5-DIHYDROFURANS

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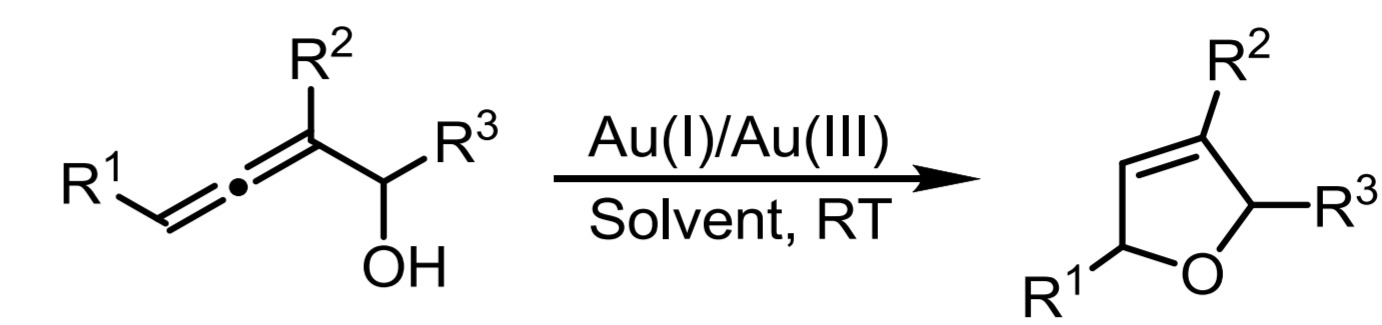


Introduction

The enormous potential of fluorine-substituted molecules in organic chemistry is reflected in a special interest of new synthetic strategies.

Based on the significant change of chemical and physiological properties there exist many pharmaceutical and industrial applications.^[1] These include solubility, lipophilicity, metabolic stability and bioavailability by replacement of hydrogen with fluorine.^[2-3]

The gold-catalyzed cycloisomerization of α -hydroxyallenes forming 2,5-dihydrofurans is a well-known reaction.^[4]

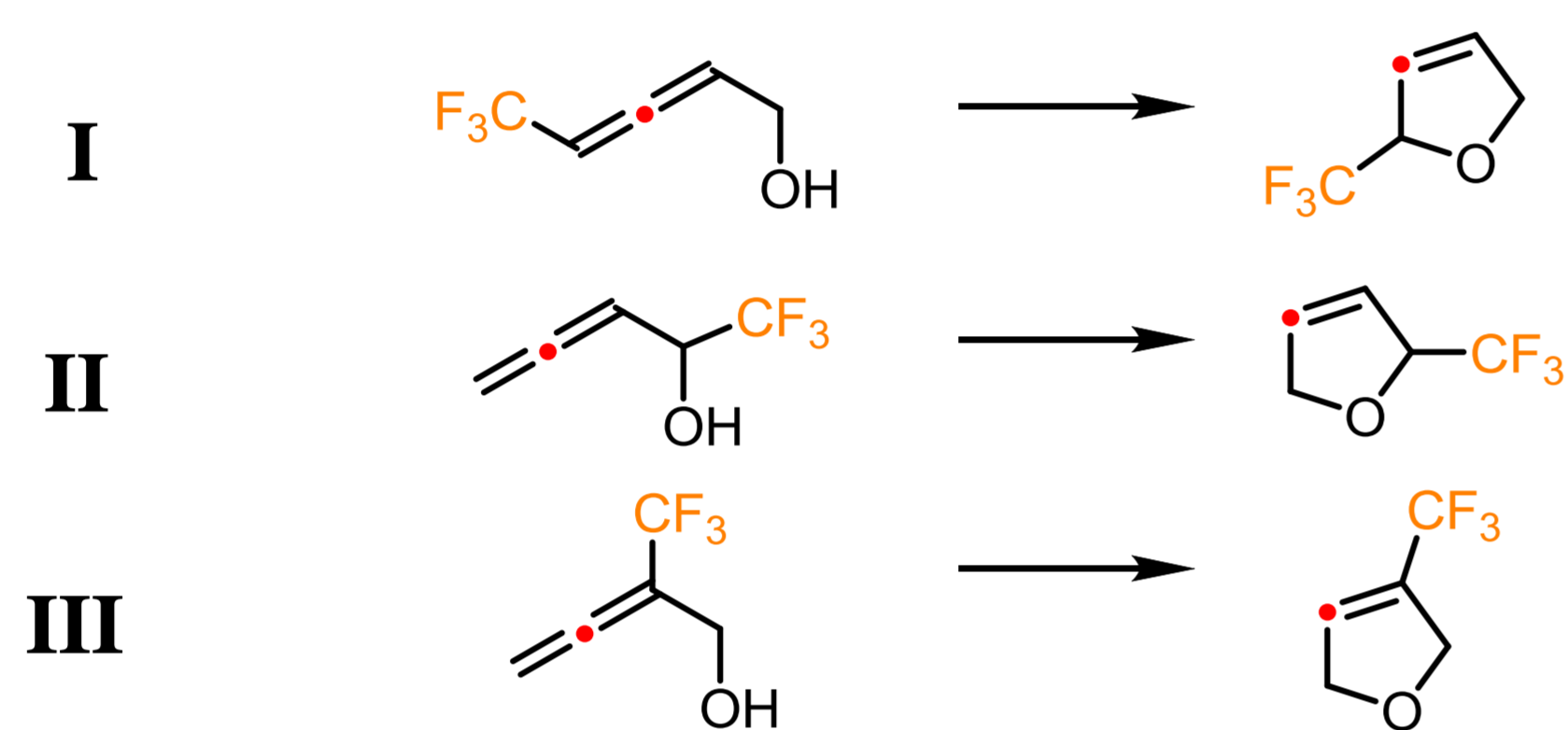


Using this selective formation to prepare fluorinated cycloisomerization products is of particular value for the total synthesis of natural compounds and their derivatives.

In this project, the gold-catalyzed cycloisomerization of fluorinated α -hydroxyallenes is pursued. First results of our investigations and their perspectives are reported.

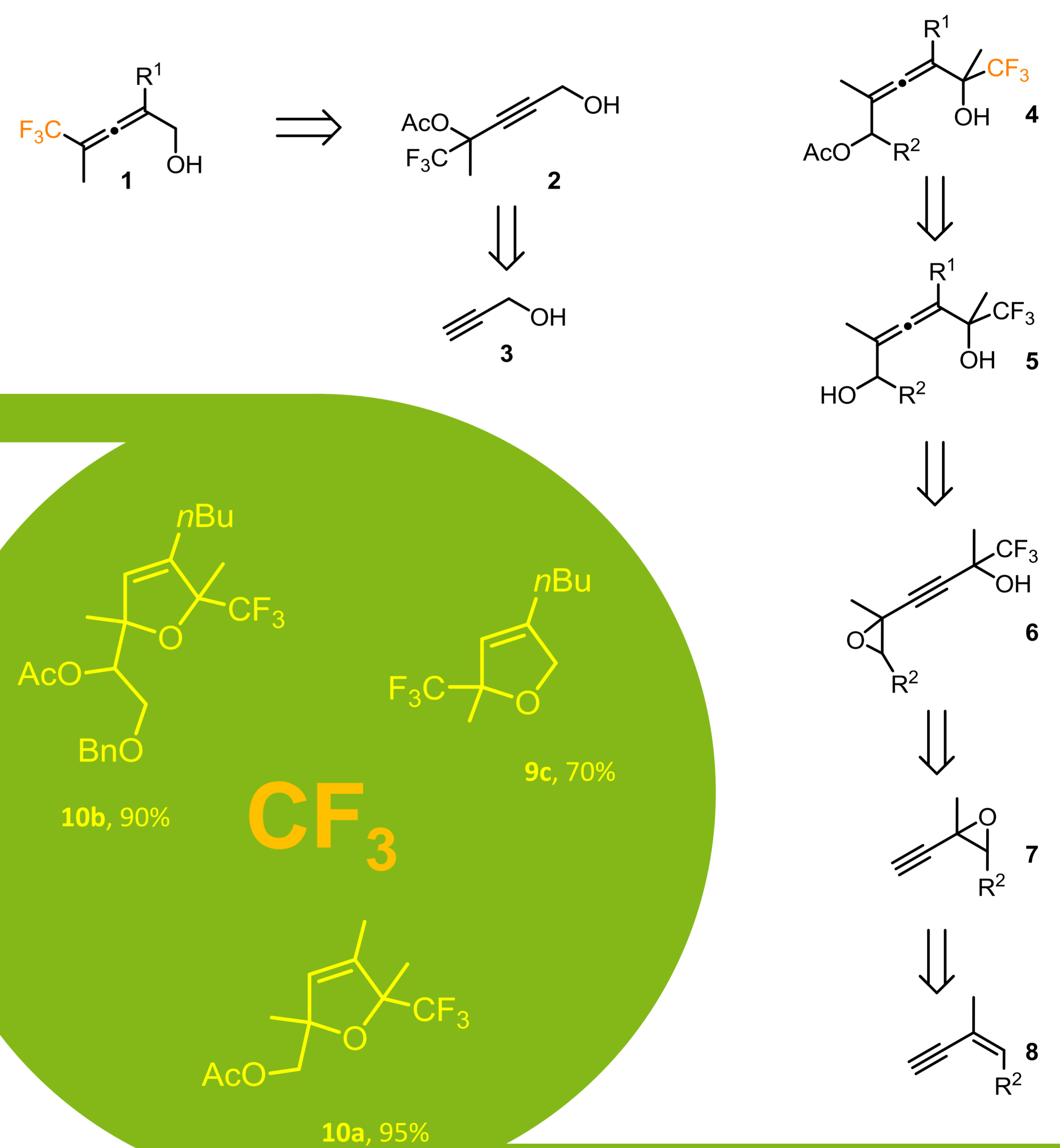
Results and Discussion

The CF_3 -substituent is an interesting target in organic synthesis. For α -hydroxyallenes three different trifluoromethylated regioisomers **I** - **III** are possible.

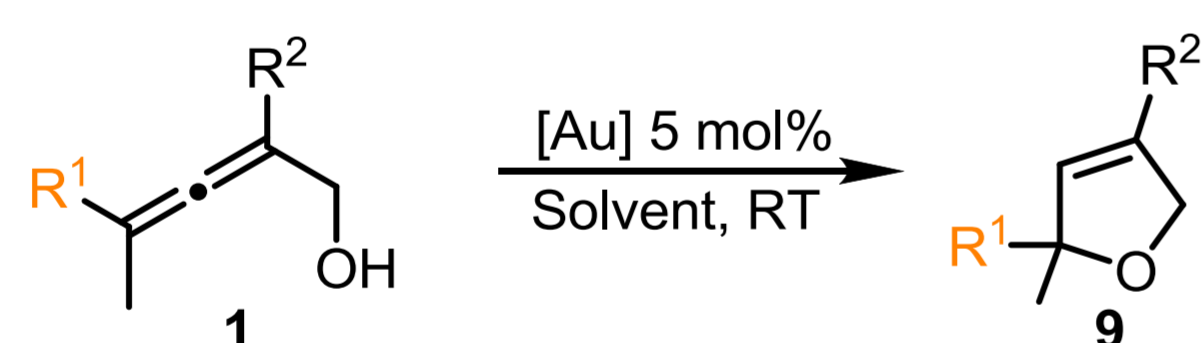


Our first results towards the cycloisomerization of allenes of type **I** and **II** are shown below.

The allenes **1** and **4** can be achieved by Cu-mediated $\text{S}_{\text{N}}2'$ -substitution of the corresponding alkynes **2** and **6**. These can easily be prepared from the terminal alkynes **3** and **7** through addition of trifluoroacetone. Compound **7** was synthesized by epoxidation of **8**. All steps are available in good yields.

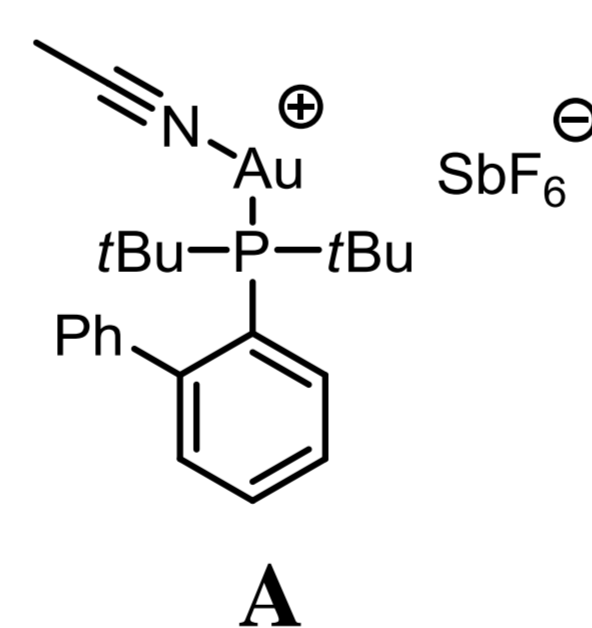


There exists an enormous influence of the CF_3 -group onto the reactivity. While the non-fluorinated allenes **1a** and **1b** easily cyclize with AuBr_3 , for the allene **1c** the more carbophilic Au(I)-catalyst **A** is required.

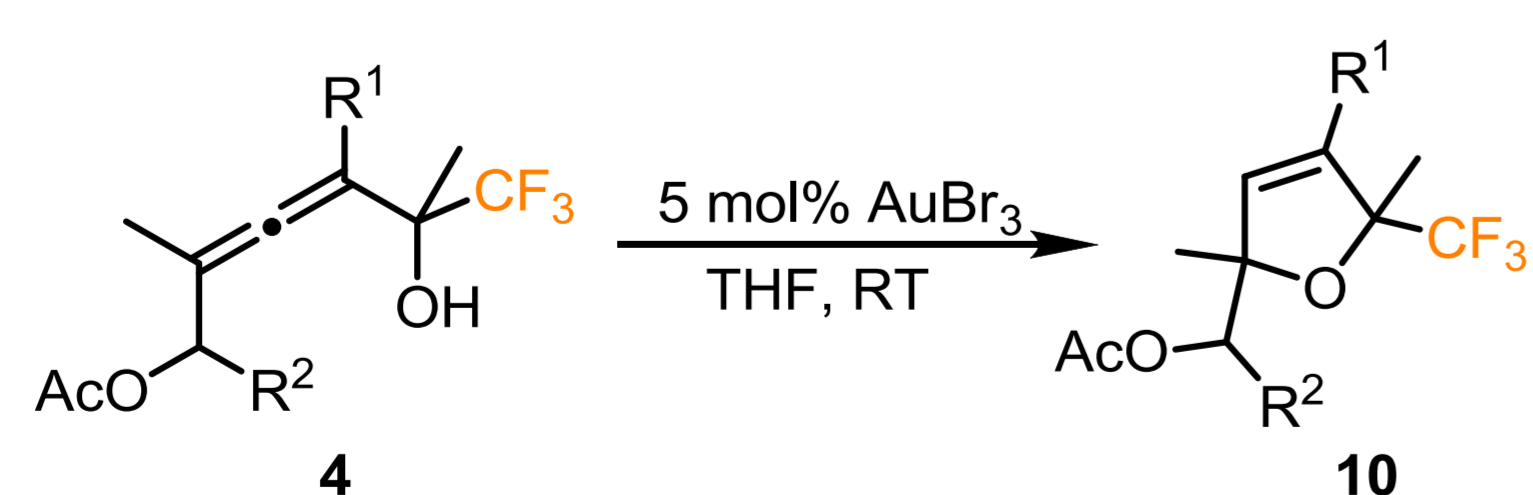


Entry	1	R ¹	R ²	Catalyst	Conditions	Yield
1	1a	Me	Bu	AuBr_3	THF, 5 min	99 %
2	1b	Me	Ph	AuBr_3	THF, 2.5 h	65 %
3	1a	Me	Bu	A	THF, 5 min	99 %
4	1b	Me	Ph	A	THF, 5 min	99 %
5	1c	CF_3	Bu	AuBr_3	THF, 7 d	0 % ^a
6	1c	CF_3	Bu	A	THF, 8 h	70 %

a) the substrate was reisolated



Subjected to the position of the CF_3 -substituent we observed a dramatic effect on the cyclization reaction. While the allene **1c** is less reactive, the allenes **4a** and **4b** respectively react with AuBr_3 in good yields.



Entry	4	R ¹	R ²	Conditions	Yield
1	4a	Me	H	THF, 12 h	95 %
2	4b	Bu	CH_2OBn	THF, 1 d	90 %

Conclusion

We have investigated the gold-catalyzed cycloisomerization of fluorinated allenes on the basis of CF_3 -substituted allenes. The enormous impact of the CF_3 -substituent and its position was demonstrated. Currently, we are investigating allenes of type **III** as well as F-substituted allenes and the use of ionic liquids.

References

- [1] Dolbier Jr., W. R.; *J. Fluorine Chem.* **2005**, *126*, 157-163.
 [2] O'Hagan, D.; *Chem. Soc. Rev.* **2008**, *37*, 308-319.

- [3] Fluorine in Bioorganic Chemistry (Eds.: J.T. Welch, S. Eswarakrishnan); Plenum, New York, **1991**.

- [4] Winter, C.; Krause, N.; *Chem. Rev.* **2011**, *111*, 1994-2009.