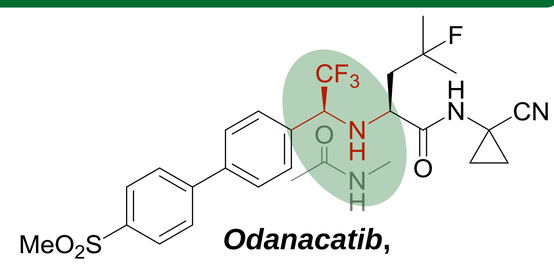
Synthesis of novel and highly functionalized CF_3-containing scaffolds for *MedChem* applications

Andreas Baumann[a]; Amrei Deutsch[a]; Ursula Hülsmann[a]; Dr. Carl Deutsch[b] and Prof. Dr. Anja Hoffmann-Röder*[a];
[a]Center For Integrated Protein Science Munich (CIPS[M]) at the Department of Chemistry, Ludwig-Maximilians-University, Munich; [b]Medical Chemistry, Merck, Darmstadt.

Introduction

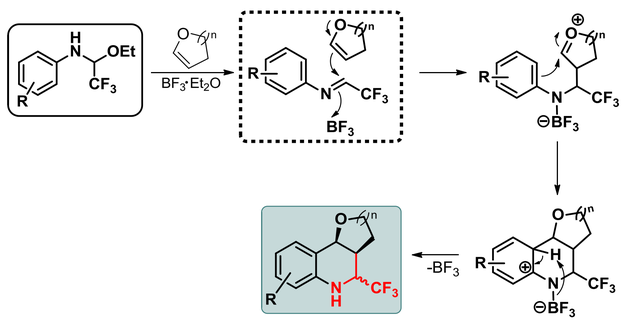
The excellent pharmacological profile of fluorinated drugs has made the incorporation of fluorine atoms a standard method in medicinal chemistry development processes.[1,2] In this regard, we have recently devised a synthetic route towards trifluoromethylated aldimines, which were prepared *in situ* starting from hemiaminal ethers.[3] Using similar compounds, we herein present the preparation of a broad variety of trifluoromethylated amine and imidazole structures for future applications in medicinal chemistry and lead optimization studies. For instance, an illustrative example for a successful incorporation of a trifluoroethyl amine to work as an amide bioisostere is given by *Odanacatib*, a highly potent drug candidate for the inhibition of *Cathepsin K*.



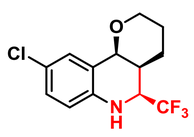
***Odanacatib*,**
MSD Sharp&Dohme, treatment of osteoporosis and bone metastasis
Y. Gauthier *et al.*, *Bioorg. Med. Chem. Lett.* **2008,** 18, 923.

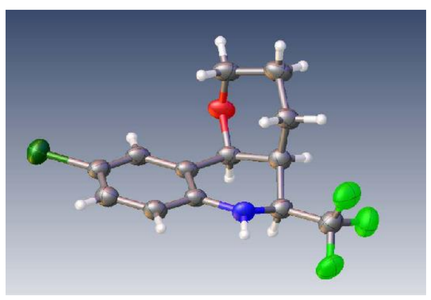
2-CF_3-Tetrahydroquinoline-derivatives *via* Povarov Cycloaddtion

The synthesis of hemiaminal ethers starts from the corresponding amine and **trifluoro-acetaldehyde ethyl hemiacetal (TFAE)**. Substituted **2-CF_3-tetrahydroquinolines** are obtained by reacting hemiaminal ethers, which are converted *in situ* to the appropriate imine, with electron-rich alkenes *via* a Lewis-acid catalyzed [4+2]-cycloaddition.[4]



Selected X-ray structure of

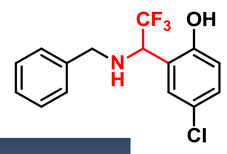


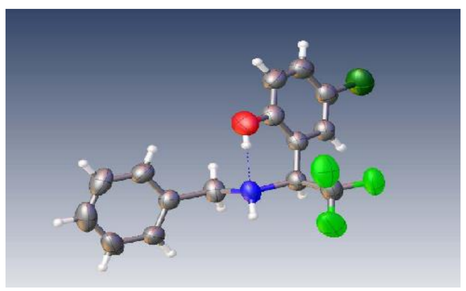


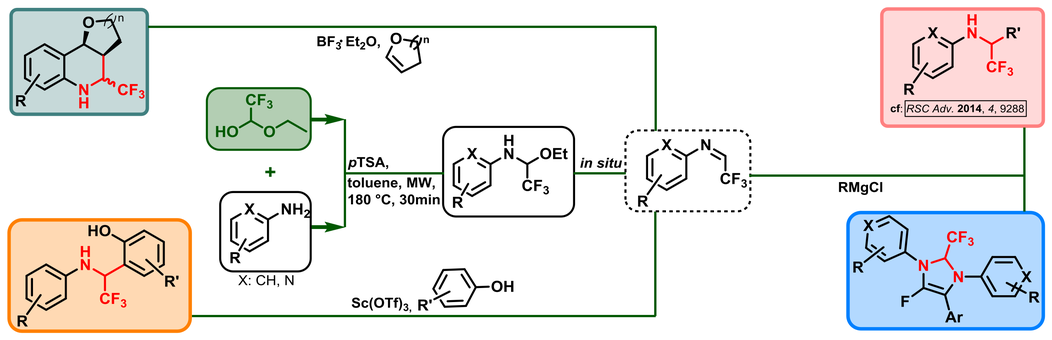
Trifluoroethyl amines *via* Fries Rearrangement

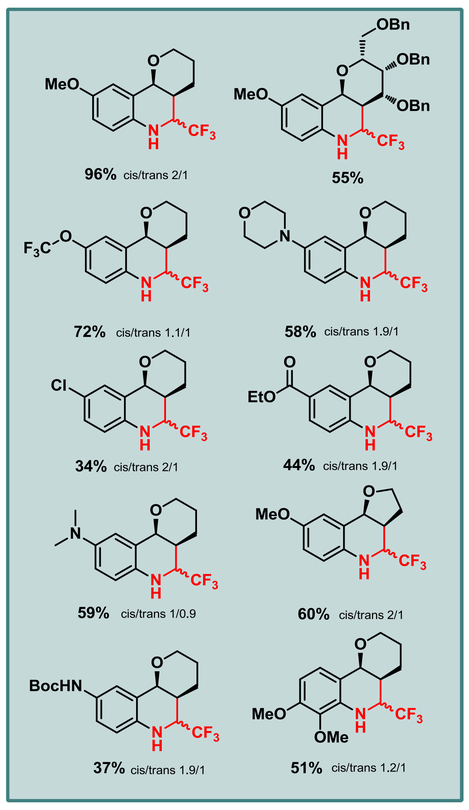
Trifluoroethyl amines of various phenol derivatives can be obtained *via* Fries-Rearrangement and in a *one-pot-procedure*. Thus, treatment of phenols with the corresponding amines in neat **TFAE** under $Sc(OTf)_3$-catalysis led to the desired products.

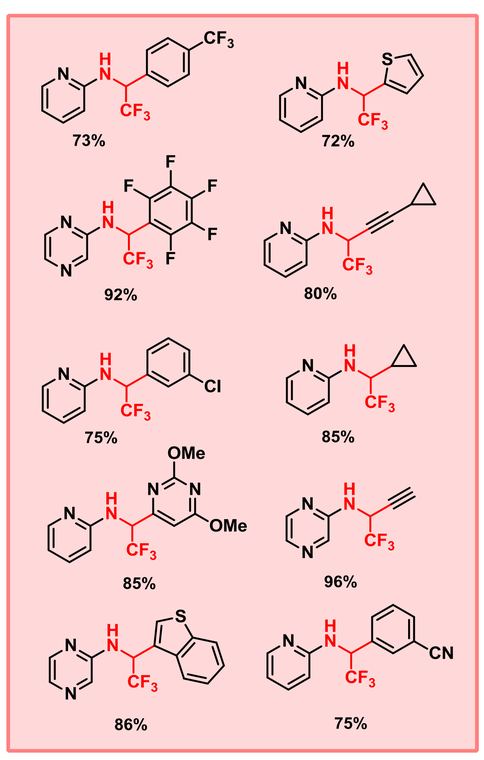
Selected X-ray structure of

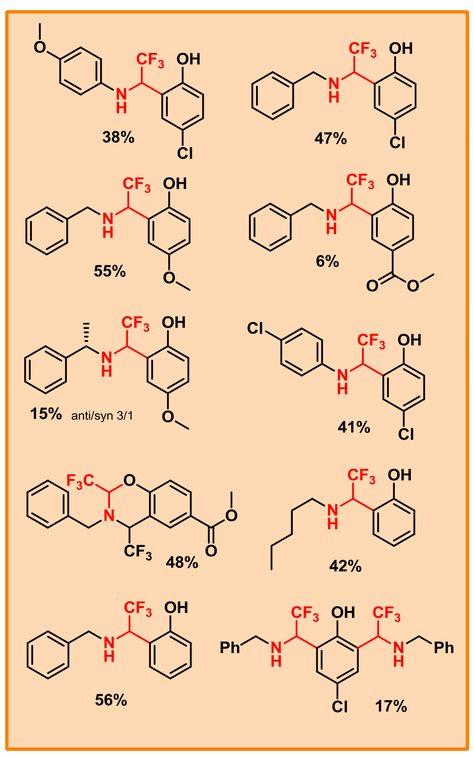


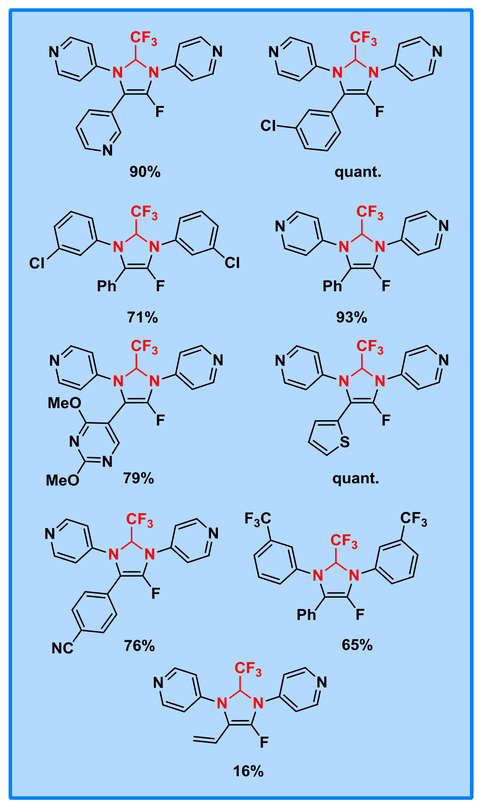






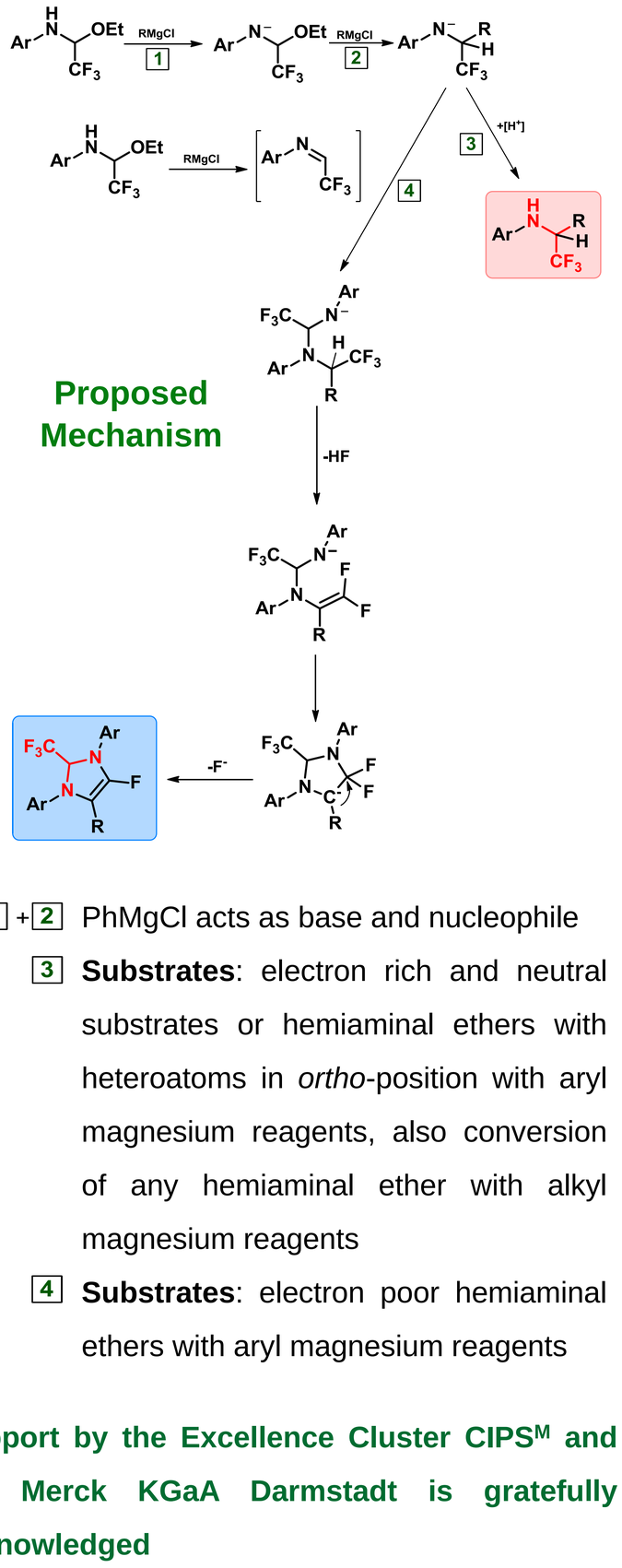






CF_3-imidazoles and trifluoroethyl amines *via* Grignard-Reaction

Trifluoromethylated imidazoles and **trifluoroethyl amines** are also accessible from amines and **TFAE** *via* the corresponding hemiaminal ethers. The latter can then be converted into **trifluoromethylated imidazoles** or **trifluoroethyl amines**[5] by addition of Grignard reagents.



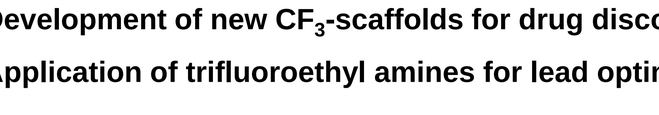
Proposed Mechanism

1 + **2** PhMgCl acts as base and nucleophile

3 **Substrates**: electron rich and neutral substrates or hemiaminal ethers with heteroatoms in *ortho*-position with aryl magnesium reagents, also conversion of any hemiaminal ether with alkyl magnesium reagents

4 **Substrates**: electron poor hemiaminal ethers with aryl magnesium reagents

- **Development of new CF_3-scaffolds for drug discovery**
- **Application of trifluoroethyl amines for lead optimizations**



nicotinamid analog DIMN[5]

Trifluoroethyl amine bioisostere

Support by the Excellence Cluster CIPS[M] and the Merck KGaA Darmstadt is gratefully acknowledged

References: [1] Gouverneur *et al.*, *Chem. Soc. Rev.* **2008**, *37*, 320. [2] Müller, *ChemMedChem* **2007**, *2,* 1100. [3] Deutsch *et al.*, *RSC Advances* **2014**, *4*, 9288. [4] Kouznetsov, *Tetrahedron* **2009**, *65*, 2721. [5] Cho *et al.*, *J. Med. Chem.* **2013**, *56*, 3414−3418.