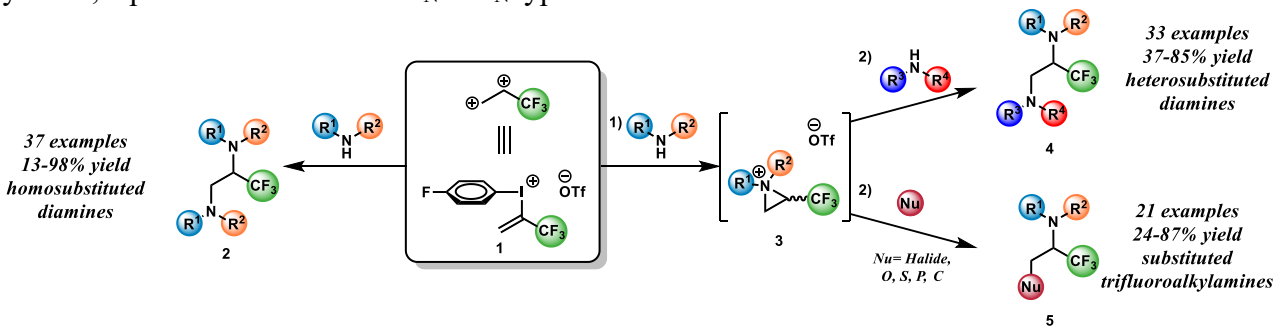
Platform synthesis of trifluoroalkylamines by difunctionalization of carbon-carbon double bond

Ferenc Béke[a], Ágnes Tóth[a], Ádám Mészáros[a], Bence Béla Botlik[a], Zoltán Novák[a]
[a] *ELTE Catalysis and Organic Synthesis Research Group, Eötvös Loránd University, Institute of Chemistry, 1117 Budapest, Pázmány Péter stny. 1/A*
E-mail: bekef@zng.elte.hu, novakz@elte.hu

High structural diversity can be achieved via difunctionalization reactions of alkene double bonds, in one synthetic step. Considering the reaction mechanisms, current transformations operate under A_E + A_N, A_N + A_E, A_R or simultaneous (2+n) cycloaddition mechanism. The addition of two nitrogen nucleophilic species across the C-C double bond requires oxidative[1] and/or transitionmetal catalyzed[2] conditions, which enable the intra- and intermolecular difunctionalizations. Avoiding transitionmetals and external oxidants, only difunctionalizations of vinyl-sulfonium salts are known via the A_N + A_N type mechanism, which permits intramolecular reactions.[3] Resembling to these sulfonium salts, the alkenyl-iodonium salts have not gained any application in this type of transformation. Recently, the synthesis of the alkenyl-iodonium salt **1** have been developed[4], which contains a 1,1-disubstituted alkene moiety. This alkene moiety can be interpreted as a 1,2-dicationic synthon, a perfect candidate for A_N + A_N type difuctionalization reaction.



At the beginning of our study, we have developed appropiate conditions for the difunctionalization reaction of **1** using simple secondary amines, which afforded the corresponding homosubstituted vicinal diamines.[5] Using the optimized conditions, we have evaluated the reactivity of aliphatic, aromatic and cyclic amines with different steric bulk and subtituents with different electronic properties. We have uncovered the reaction intermediates by ^{19}F-NMR spectroscopy and have identified their structure as aziridinium ions (**3**).

The generation and regioselective ringopening of the **3** aziridinium intermediate have been optimized by two different secondary amines, which afforded the formation of heterosubstituted vicinal diamines (**4**). We have developed the scope of reaction using various aliphatic and cyclic secondary amines at the first stage of the reaction and different primary and secondary amines and *N*-heterocycles. Applying various halides, *O*-, *S*-, *P*-, *C*-nucleophiles at the second stage of the reaction, led to the formation of the corresponding trifluoroalkylamines (**5**).

The *vicinal*-diamine backbone can be found in several top selling pharmaceutical API[6], while the trifluoroethylamine derivatives (**5**) functions as amide bond bioisostere.[7]

References

1) K. Muñiz, *Acc. Chem. Res.* 2018, *51*, 1507–1519.
2) F. Cardona, A. Goti, *Nat. Chem.* **2009**, *1*, 269–275.
3) D. Kaiser, I. Klose, R. Oost, J. Neuhaus, N. Maulide, *Chem. Rev.* **2019**, *119*, 8701–8780.
4) Mészáros, Á.; Székely, A.; Stirling, A.; Novák, Z. *Angew. Chem. Int. Ed.* **2018**, *57*, 6643-6647.
5) Béke, F.; Mészáros, Á.; Tóth, Á.; Botlik, B. B.; Novák, Z. *Nat. Commun.* **2020**; *11*, 5924.
6) N. A. McGrath, M. Brichacek, J. T. Njardarson, *J. Chem. Educ.* **2010**, *87*, 1348–1349. (Top 200 SMALL Molecule Drugs by Sales in 2018, lásd Promethazine, Osimertinib, Suntinib, Oseltamivir)
7) J. Y. Gauthier, N. Chauret, W. Cromlish, S. Desmarais, L. T. Duong, J.-P. Falgueyret, D. B. Kimmel, S. Lamontagne, S. Léger, T. LeRiche, et al., *Bioorg. Med. Chem. Lett.* **2008**, *18*, 923–928.