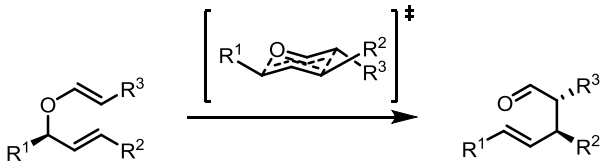
Synteza produktów naturalnych i modyfikacja leków

Prof. Bartłomiej Furman

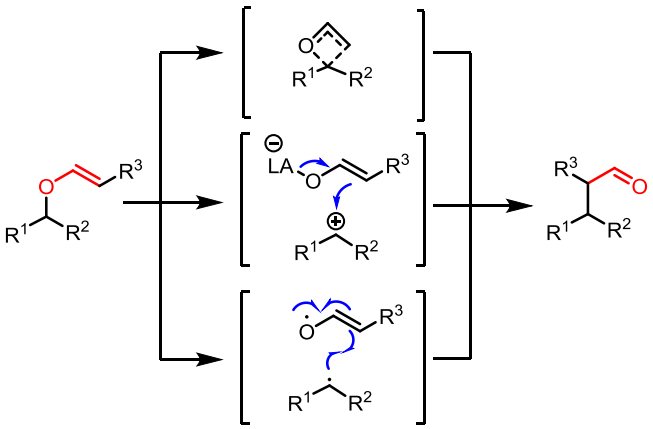
Studies on the rearrangement of vinyl ethers and alkoxydienes

The formation of C-C bond is one of fundamental transformation of organic chemistry. Particularly important and highly desired are methods that allow for formation of new C-C bond in highly stereoselective manner. The Claisen rearrangement is one of classical synthetic method that enables this kind of chemical transformation via [3,3] sigmatropic rearrangement. Another powerful, but less popular, method of construction of a new C-C bond by the breaking C-O one, is [1,3] rearrangement reaction of vinyl ethers (O→C rearrangement). The molecules, bearing latent electrophilic and nucleophilic moieties rearrangement to the product by formation of a new carbon-carbon bond. The most prevalent oxygen-to-carbon rearrangements are those whereby the positive charge at the electrophilic species can be stabilized by heteroatom, for instance oxygen.

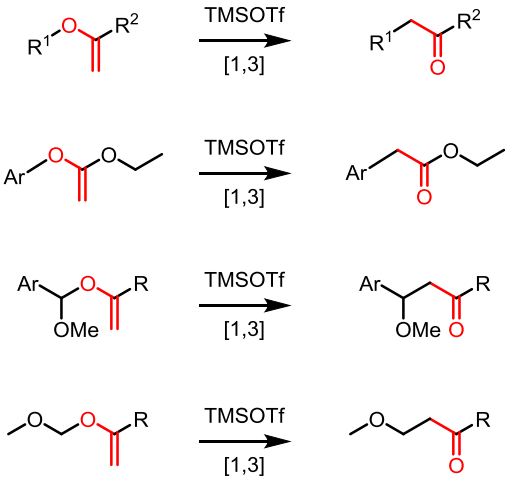
[3,3]-sigmatropicrearrangement



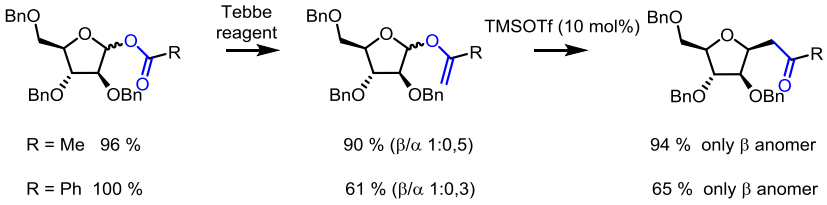
[1,3]-sigmatropicrearrangement

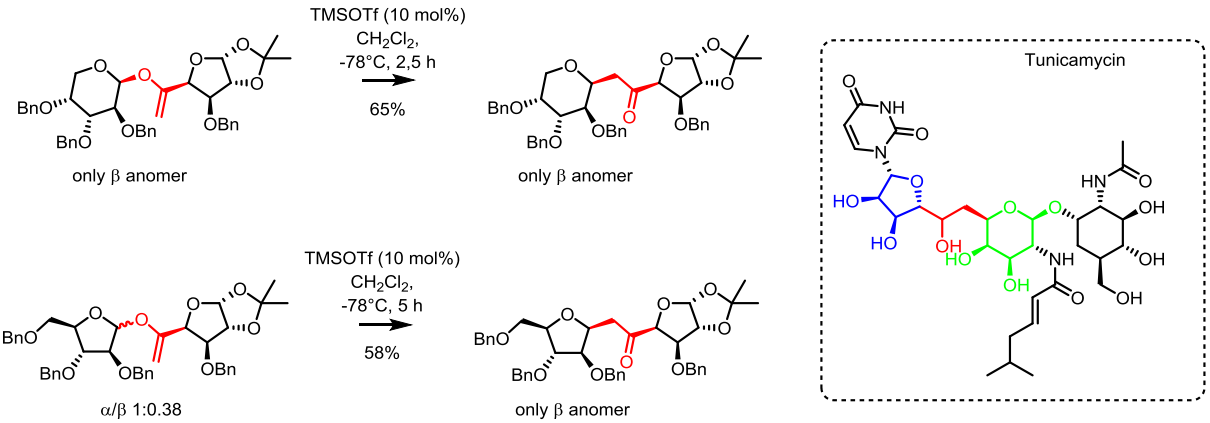


Our group has very recently discovered that substituted vinyl ethers and unsymmetrical ketene acetals undergo smooth conversion to chain-extended ketones or esters with a catalytic amount of trimethylsilyl triflate.[1]

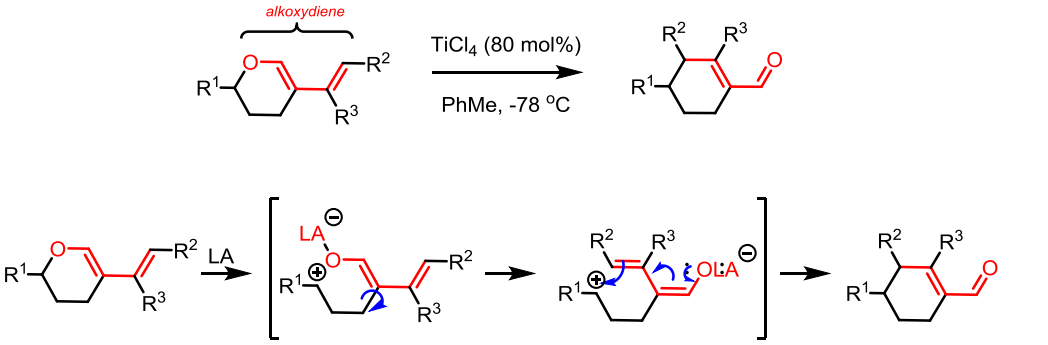


Further examination showed that the developed reaction conditions can be applied to the transformation of sugar-derived anomeric vinyl ethers.[2] This highly stereoselective transformation opens an access to C-glycosides and C-disaccharides – important, acid hydrolysis-resistant C nucleoside analogues.





Very recently, we have found that *O*-1,3-alkoxydienes undergo a smooth vinylogous Ferrier-Petasis-type reaction when treated by a catalytic amount of titanium(IV) chloride. This rearrangement reaction proceeds with good chemical yield and regioselectivity to afford the corresponding cyclohexene carbaldehydes which are important structural synthons for the synthesis of numerous biologically active molecules .



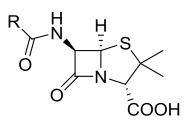
1. Maziarz, E.; Furman, B., *Tetrahedron* **2014**, 70, 1651-1658

2. A. Domżalska, E. Maziarz, B. Furman, *submitted*

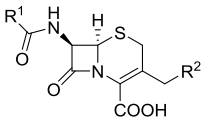
Kinugasa Reaction as a Stereoselective Method of β-Lactams Synthesis: Advanced Applications

β-Lactam ring is a key structural element of vast pharmacologically active compounds, including penicillins, cephalosporins, carbapenems, nocardicines or modern cholesterol lowering agents (e.g. ezetimibe). Bioactivity of β-lactamic derivatives is a driving force for search of new bioactive compounds, as well as, for the development of new strategies of the 2-azetidinone ring formation.

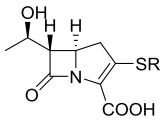
β-Lactam antibiotics



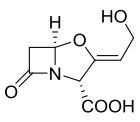
penicillines



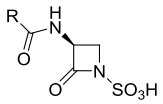
cephalosporines



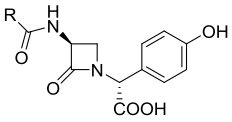
carbapenems



clavulanic acid

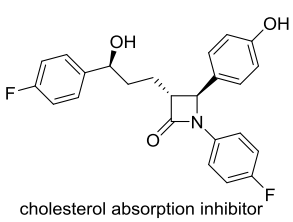


monobactams

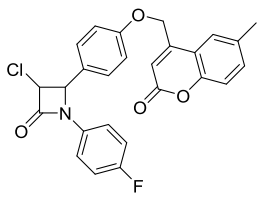


nocardicines

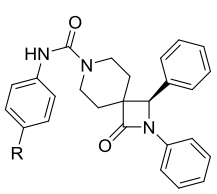
Non-antibiotic β-Lactams:



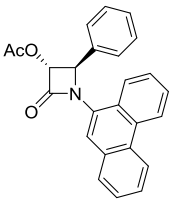
cholesterol absorption inhibitor (ezetimibe)



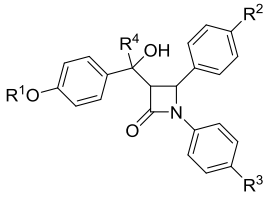
antifungal



analgestic

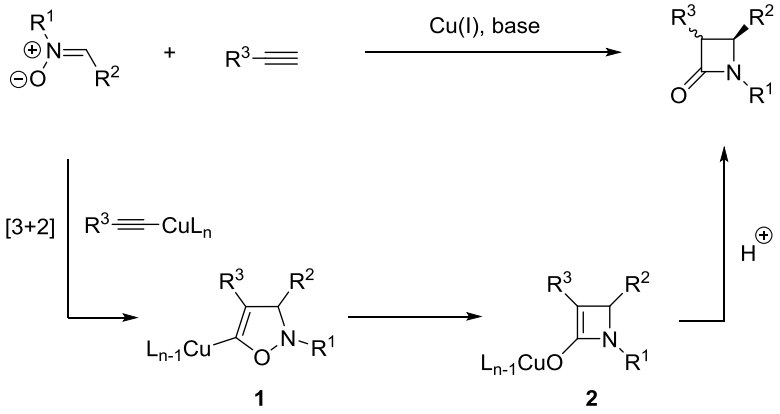


anticancer



selective estrogen receptor modulators

One of the rarely used method of β-lactams formation is Cu(I)-catalyzed reaction of terminal alkynes and nitrones (Kinugasa reaction).



Although the Kinugasa reaction was discovered 30 years ago, it received more attention in last years. Significant part of this come-back is due to our pioneering works which have been initiated nine years ago. Recently, we demonstrated that bicyclic framework of carbapenam antibiotics can be obtained efficiently and stereoselectively by the reaction of terminal alkynes and chiral cyclic nitrones.[1] The culmination of this part of our work was the use of Kinugasa in the synthesis of ezetimibe (commercially available

cholesterol absorption inhibitor)[2], Kaneka β-lactam[3] (chiral industrial precursor of synthetic carbapenems), and elaboration of a strategy leading to thienamycin[4] and related antibiotics.

1. (a) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M., J. Org. Chem. 2008, 73, 7402-7404; (b) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M., J. Org. Chem. 2009, 74, 3094-3100; (c) Mames, A.; Stecko, S.; Mikołajczyk, P.; Soluch, M.; Furman, B.; Chmielewski, M., J. Org. Chem. 2010, 75, 7580-7587; (d) Woźnica, M.; Masnyk, M.; Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M.; Frelek, J., J. Org. Chem. 2010, 75, 7219-7226; (e) Kabala, K.; Grzeszczyk, B.; Stecko, S.; Furman, B.; Chmielewski, M., J. Org. Chem. 2015, 80, 12038–12046.

2. Michalak, M.; Stodulski, M.; Stecko, S.; Mames, A.; Panfil, I.; Soluch, M.; Furman, B.; Chmielewski, M., J. Org. Chem. 2011, 76, 6931-6936.

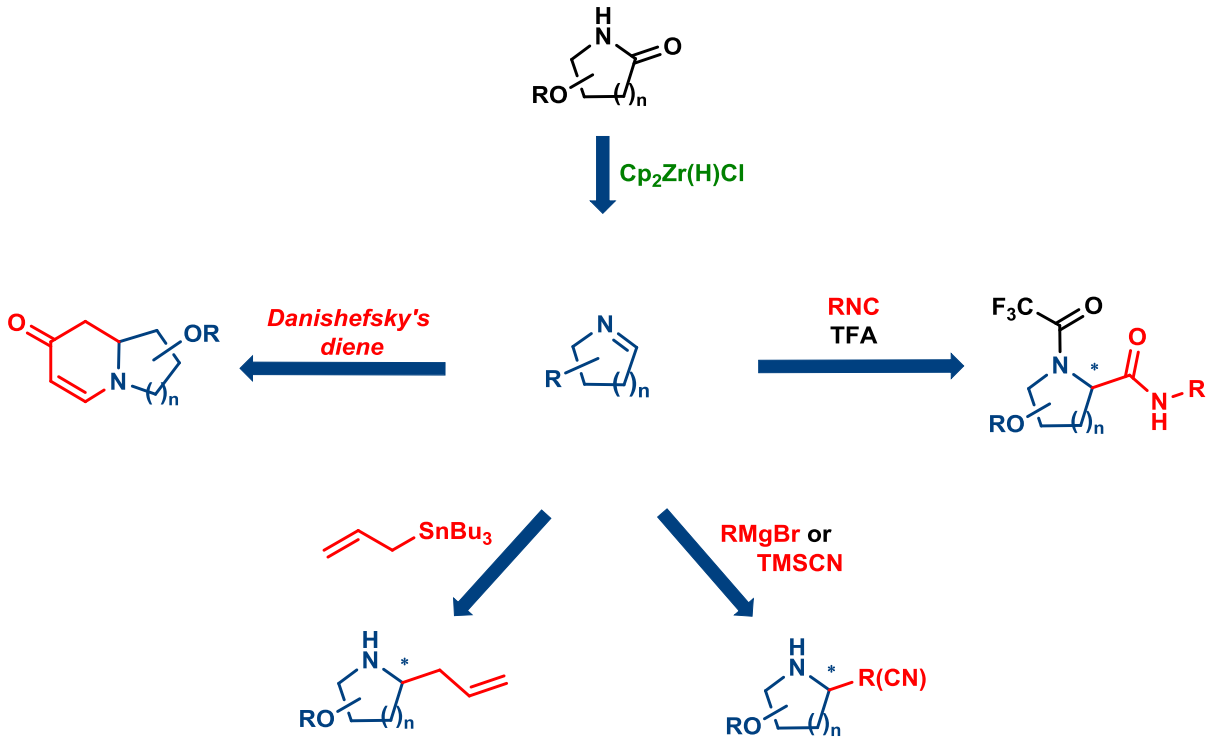
3. Grzeszczyk, B.; Stecko, S.; Mucha, L.; Staszewska-Krajewska, O.; Chmielewski, M.; Furman, B., J. Antibiot. 2013, 66, 161-163.

4. Grzeszczyk, B.; Staszewska-Krajewska, O.; Chmielewski, M.; Furman, B., J. Antibiot. 2016, 69, 164-168.

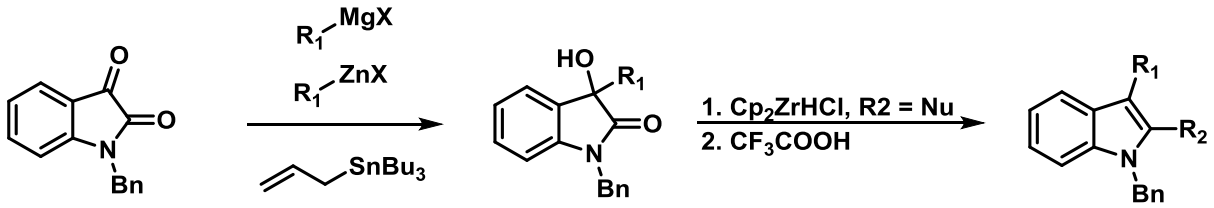
Chemoselective activation of amide carbonyls towards nucleophilic reagents

Amides represent an important class of compounds in chemistry, chemical biology and pharmaceutical industry. Their broad utility in many fields is closely tied to the structure of the amide moiety which endows these compounds with unique features. The low reactivity of amide carbonyls towards nucleophiles is a major obstacle to their further functionalization. Selective activation of amides and lactams enables access to novel reactivity pathways and opens up intriguing perspectives in synthesis.

Recently, we have demonstrated that upon treatment with $Cp_2Zr(H)Cl$ (Schwartz's reagent), five- and six-membered lactams, including sugar- and hydroxy acid-derived lactams,[1] can be easily converted into imines under mild conditions. In addition, as was also shown, in situ generated cyclic imines can be directly subjected to further reactions with nucleophilic reagents such as allyltributylstannane,[1b] Grignard reagents,[1b] enolates[1b] or Danishefsky's diene[1a] to afford α-functionalized pyrrolidines, piperidines and polyhydroxylated pyrrolidine peptidomimetic[1c] scaffolds in a one-pot manner. The key advantage of the presented approach is the simplicity and convenience of generation of sugar-derived imines from readily available starting materials: sugar-derived lactams. The use of sugar-derived lactams as cyclic imine precursors is crucial to the efficiency of the described synthetic method. These compounds are more readily prepared, handled, and stored than the alternative precursors of cyclic imines such as nitrones, *N*-chloroamines or azido aldehydes.



Very recently, by selectively activating the amide carbonyl in isatin-derived oxindoles, we obtained a number of the 2,3-disubstituted indoles in a regiospecific and functional group-tolerant manner.[2] The methodology is normally characterized by excellent yields. The reaction proceeds by chemoselective partial reduction of the amide moiety to an iminium salt and a subsequent nucleophilic addition followed by dehydration, which furnishes the target indole. A number of nucleophiles, including C- and S-nucleophiles, have been examined. The obtained compounds were studied towards acetylcholinesterase inhibitory activity and concurrently considered using a molecular docking approach.



Our current work focuses on a synthesis of previously inaccessible imines from readily available amides.

1. (a) Szcześniak, P.; Stecko, S.; Maziarz, E.; Staszewska-Krajewska, O.; Furman, B. *J. Org. Chem.* **2014**, *79*, 10487−10503, (b) Szcześniak, P.; Stecko, S.; Staszewska-Krajewska, O.; Furman, B. *Tetrahedron* ***2014***, *70*, 1880−1888, (c) Szcześniak, P.; Stecko, S.; Maziarz, E.; Furman, B. *J. Org. Chem.* **2015**, *80*, 3621–3633.
2. A. Ulikowski, B. Furman *Org. Lett*. **2016**, *18*, 149-153.