The Concept of Domino Reactions: An Approach to the Ideal Synthesis

Lutz F. Tietze

Institute of Organic and Biomolecular Chemistry, Georg-August-University Göttingen, Tammanstr. 2, D-37077 Göttingen, Germany,
Email: ltietze@gwdg.de

The efficient synthesis of natural products, drugs, agrochemicals and materials is a very important aspect in academia and industry. To permit an ecologically and economically favourable approach the former stepwise procedures must be replaced by domino reactions which allow the preparation of complex molecules starting from simple substrates in a straightforward way. Thus, the increase of complexity in correlation to the number of steps is a valuable criterion for the quality of a modern synthesis. Domino reactions allow the reduction of the amount of waste being formed and the preservation of our resources. Moreover, the reactions can proceed via unstable intermediates which is hardly possible in a stepwise approach.

Some new examples of the usefulness of domino reactions are the synthesis of the fungal metabolites diversonol\(^2\) and blennolide A\(^3\) using an enantioselective domino-Wacker/carbonylation/methoxylolation reaction as well as of the natural arylhydronaphthalene lignan linoxepine\(^4\) employing a domino-carbopalladation/Heck reaction. The approach has also been applied for the synthesis of novel materials such as molecular switches using a domino-Sonogashira/carbopalladation/CH-activation.\(^5\)

Synthesis of Natural Products, Drugs and Agrochemicals by Multiple Pd-Catalyzed Transformations and other Efficient Methods

Lutz F. Tietze

Institute of Organic and Biomolecular Chemistry, Georg-August-University Göttingen,
Tammannstr. 2, D-37077 Göttingen, Germany,
e-mail: ltietze@gwdg.de

We have used multiple Pd-catalyzed transformations and other efficient reactions for the synthesis of desogestrel, an important contraceptive, of analogues of the insecticidal spinosyns, as well as of natural products. Catalytic processes are very valuable not only in the synthesis of bulk chemicals but also for the preparation of fine chemicals. The combination of two or more catalytic reactions in a sequential mode even increases the efficiency of this approach.


Novel Drugs and Targets for a Selective Treatment of Cancer
Lutz F. Tietze

Institute of Organic and Biomolecular Chemistry
Georg-August-University Göttingen, Tammanstr. 2
D-37077 Göttingen (Germany)
E-mail: ltietze@gwdg.de

Anticancer therapy is hampered by an insufficient differentiation of normal and malignant cells by the known antiproliferant agents, resulting in severe side effects. Tumor-selective chemotherapy must therefore be based on the exploitation of phenotypic or genetic differences of malignant and normal cells.

The Antibody Directed Enzyme Prodrug Therapy (ADEPT) using a prodrug as well as a conjugate of a monoclonal antibody and an enzyme allows a selective liberation of a highly cytotoxic compound from a prodrug with reduced cytotoxicity in the cancer tissue. The recently developed novel glycosidic prodrugs 2 based on the natural antibiotic duocarmycin 1 are up to almost one million times less toxic than the prodrugs in the presence of galactosidase. The IC_{50}-value of the formed drugs such as 3 is as low as 150 fM. The mode of action of these compounds could be elucidated using mass spectrometry, volume computer tomography (VCT) and fluorescence measurements. They do not attack DNA as found for 1, but aldehyde dehydrogenase 1 as a new target in cancer therapy.