Scientific Profile of Prof. Dr. Uwe Beifuss

The Beifuss group has a strong interest in the development of synthetic methods for the selective and efficient preparation of heterocycles. Another area of focus involves oxidative transformations, such as phenolic couplings and laccase-catalyzed domino reactions. A third area of interest is the isolation and structure elucidation of natural products. Great emphasis is also placed to the synthesis and development of pressure and temperature sensors.

Development of efficient synthetic methods for heterocycles

The focus of our activities in this field is on the development of new domino reactions. It comprises Cu-catalyzed reactions between bisfunctionalized substrates, the synthesis of heterocycles via cationic intermediates as well as reductive cyclizations of nitro compounds.

Cu(I)-catalyzed cross couplings between aryl halides and *C*-, *N*-, *O*- as well as *S*-nucleophiles offer a powerful tool for the formation of *C*-*C*- as well as *C*-*heteroatom* bonds. The synthetic potential of Cu(I)-catalyzed cross couplings can be significantly extended by combining such couplings with other reactions to new domino processes. Following this approach, the Beifuss group successfully established transformations of *o*-dihalobenzenes (Aljaar et al., 2012), *o*-halobenzyl halides (Malakar et al., 2011; Malakar et al., 2012a; Sudheendran et al., 2013) and –tosylates (Omar et al., 2014a), 1-(2-halophenyl)methanamines (Omar et al., 2014b) and *o*-halobenzaldehydes (Malakar et al., 2012b) with bisfunctionalized nucleophiles, such as 1,3-dicarbonyls, amidines, imidates and 2-mercaptoimidazoles. This resulted in the development of powerful methods for the selective and efficient preparation of a number of carbo- and heterocyclic systems, including dihydrodibenzo[*b*,*d*]furan-1(2*H*)-ones, 4*H*-chromenes und naphthalenes, quinazolines and imidazobenzothiazines.

Another topic is the stereoselective synthesis of heterocycles via cationic intermediates. One aspect of this work is the development of regio- and stereoselective multiple functionalizations of positively charged aromatic *N*-, *O*- and *S*-heterocycles by sequential transformations, which provide efficient access to a great number of relevant classes of compounds, including quinolone alkaloids, acridones, xanthones, pyranones and thioxanthones. Another part of this work consists in studying new aspects of cationic cycloadditions and cationic cyclizations. The Beifuss group has also extensive experience in Mo-catalyzed reductive cyclizations of nitro compounds to different *N*-heterocycles.

Development of oxidative transformations

Regio- and stereoselective phenolic couplings

In nature, enzymatic oxidative phenolic couplings often proceed with excellent regio-, diastereo- and enantioselectivities. In contrast, the importance of phenolic couplings in organic synthesis is only limited. Therefore, the key focus of one of our research topics is the development of oxidative couplings of phenolics with oxygen as oxidant to a highly efficient and selective synthetic method. In addition to structural and mechanistic studies of this central biological process, which aim at getting more insights into the interactions between oxidizing enzymes and so-called dirigent proteins, we focus on the use of transition metal compounds as well as laccases as catalysts for selective oxidative couplings of phenolics and other types of oxidative transformations. Some aspects of this project are studied in collaboration with the research groups of Profs. Schmid, Urlacher, Pleiss and Schaller. As part of these efforts, we were able to discover and characterize the first enantiocomplementary dirigierent protein (Pickel et al., 2010). Further projects were devoted to the oxidative dimerization of (*E*)- and (*Z*)-2-propenylsesamol for the diastereoselective formation of carpanones and benzopyrans (Constantin et al., 2012a), the laccase-catalyzed dimerization of vanillidene derivatives (Constantin et al., 2012b) and the laccase-catalyzed trimerization of sesamol.

Laccase-catalyzed domino reactions

The combination of several enzyme-catalyzed reactions as well as the combination of enzyme-catalyzed reactions with other transformations to new synthetic sequences is of key importance for our group. So far, we have successfully studied the combination of the Hantzsch dihydropyridine synthesis with the laccase-catalyzed oxidation of dihydropyridines to pyridines (Abdel-Mohsen et al., 2012), the synthesis of 6,7-dihydrobenzofuran-4(5*H*)-ones by linking the laccase-catalyzed ring opening of furans to 2-ene-1,4-diones with a Lewis acid-catalyzed annulation (Asta et al., 2013a) and the preparation of 6-hydroxy-(2*H)*-pyran-3(6*H*)-ones by means of the first enzyme-catalyzed Achmatowicz reaction (Asta et al., 2013b). The combinations of laccase-catalyzed oxidations of catechols as well as hydroquinones with 1,4-additions of *C*-, *N*- and *S* nucleophiles proved to be broadly applicable. In addition to substituted catechols (Abdel-Mohsen et al., 2014; Emirdağ-Öztürk et al., 2013) and *p*-benzoquinones (Hajdok et al., 2012) numerous heterocycles can be obtained following this approach. Among them are benzofuro[3,2-*c*]chromen-6-ones and pyrano[4,3-*b*]benzofuran-1-ones (Leutbecher et al., 2011a) as well as benzofuropyridinones, benzofurochinolinones and thiocoumestans (Hajdok et al., 2009), 2-aryl-1*H*-benzimidazoles (Leutbecher et al., 2011b), 7,8-dihydroxy-2*H*-dibenzofuran-1-ones (Hajdok et al., 2007) and pyrimidobenzothiazoles (Abdel-Mohsen et al., 2013).

Isolation and structure elucidation of natural products

Since the characterization of the coenzyme methanophenazine, which turned out to be not only the first phenazine isolated from methanogenic archaea but also the first phenazine derivative with a function in a respiratory chain (Beifuss et al., 2000) we are interested in structure and function of natural products. Our current focus is on the isolation and structure elucidation of secondary metabolites from plants, such as flavonoids (Conrad et al., 2009; Zehl et al., 2011; Braunberger et al., 2013), cyclic oligopeptides (Mongkolvisut et al., 2006), terpenoids (Nareeboon et al., 2006) and carotenoids. Some of these projects are performed in close cooperation with groups from the University of Hohenheim or with partners from abroad. For the structure elucidation of natural products, which often are available in minute amounts only, we rely primarily on the combination of MS based methods, such as HPLC-MS and GC-MS, and NMR spectroscopic methods, including HPLC-NMR.

Pressure sensors and temperature sensors

This project focusses on dyes whose luminescence intensity and luminescence lifetime, resp., depends on the ambient oxygen partial pressure. Immobilized in polymers or attached to surfaces they can be employed for noninvasive pressure measurements on surfaces within the field of aerodynamics. It has been demonstrated that pyrene derivatives immobilized in silicones (Engler et al., 2009) are particular powerful pressure sensors. We are also involved in the synthesis and evaluation of dyes exhibiting temperature dependent luminescence. These compounds find application as temperature sensitive paints (TSPs) for noninvasive temperature measurements. Europium(III)- (Henne et al., 2014) as well as ruthenium(II) complexes immobilized in polymers (Egami et al., 2008) have proved to be outstanding successful. Our sensor projects are conducted in close cooperation with Dr. Klein (DLR, Göttingen) and Dr. Guntermann (ETW, Köln).

References

Abdel-Mohsen HT, Conrad J, Beifuss U (2012). Laccase-catalyzed oxidation of Hantzsch 1,4-dihydropyridines and a new one pot synthesis of pyridines. *Green Chem.* 14: 2686-2690.

Abdel-Mohsen HT, Conrad J, Beifuss U (2013). Laccase-Catalyzed Domino Reaction between Catechols and 6-Substituted 1,2,3,4-Tetrahydro-4-oxo-2-thioxo-5-pyrimidinecarbonitriles for the Synthesis of Pyrimidobenzothiazole Derivatives. *J. Org. Chem.* 78: 7986-8003.

Abdel-Mohsen HT, Conrad J, Beifuss U (2014). Laccase-catalyzed synthesis of catechol thioethers by reaction of catechols with thiols using air as an oxidant. *Green Chem.* 16: 90-95.

Aljaar N, Malakar CC, Conrad J, Strobel S, Schleid T, Beifuss U (2012). Cu-Catalyzed Reaction of 1,2-Dihalobenzenes with 1,3-Cyclohexanediones for the Synthesis of 3,4-Dihydrodibenzo[*b,d*]furan-1(2*H*)-ones. *J. Org. Chem.* 77: 7793-7803.

Asta C, Schmidt D, Conrad J, Frey W, Beifuss U (2013a). Combination of Enzyme- and Lewis Acid-Catalyzed Reactions: A New Method for the Synthesis of 6,7-Dihydrobenzofuran-4(5*H*)-ones Starting from 2,5-Dimethylfuran and 1,3-Cyclohexanediones. *Org. Biomol. Chem.* 11: 5692-5701.

Asta C, Schmidt D, Conrad J, Förster-Fromme B, Tolasch T, Beifuss U (2013b). The first enzymatic Achmatowicz reaction: selective laccase-catalyzed synthesis of 6-hydroxy-(2*H)*-pyran-3(6*H*)-ones and (2*H)*-pyran-2,5(6*H*)-diones. *RSC Adv.* 3: 19259-19263.

Beifuss U, Tietze M, Bäumer S, Deppenmeier U (2000). Methanophenazine: Structure, Total Synthesis, and Function of a New Cofactor from Methanogenic Archaea, *Angew. Chem.* 112: 2583-2585.

Braunberger C, Zehl M, Conrad J, Fischer S, Adhami H-R, Beifuss U, Krenn L (2013). LC-NMR, NMR, and LC-MS identification and LC-DAD quantification of flavonoids and ellagic acid derivatives in *Drosera peltata*. *J. Chromatogr. B* 932: 111-116.

Conrad J, Förster-Fromme B, Constantin M-A, Ondrus V, Mika S, Mert-Balci F, Klaiber I, Pfannstiel J, Möller W, Rösner H, Förster-Fromme K, Beifuss U (2009). Flavonoid Glucuronides and a Chromone from the Aquatic Macrophyte *Stratiotes aloides*. *J. Nat. Prod.* 72: 835-840.

Constantin M-A, Conrad J, Merisor E, Koschorreck K, Urlacher VB, Beifuss U (2012a). Oxidative Dimerization of (*E*)- and (Z)-2-Propenylsesamol with O_2 in the Presence and Absence of Laccases and Other Catalysts: Selective Formation of Carpanones and Benzopyrans under Different Reaction Conditions. *J. Org. Chem.* 77: 4528-4543.

Constantin M-A, Conrad J, Beifuss U (2012b). Laccase-catalyzed oxidative phenolic coupling of vanillidene derivatives. *Green Chem.* 14: 2375-2379.

Egami Y, Fey U, Klein C, Quest J, Beifuss U, Ondrus V (2008). Temperaturempfindliche Farbe für einen erweiterten Temperaturbereich. DE 20 2008 009 006 U1.

Emirdağ-Öztürk S, Hajdok S, Conrad J, Beifuss U (2013). Laccase-catalyzed reaction of 3-*tert*-butyl-1*H*-pyrazol-5(4*H*)one with substituted catechols using air as an oxidant. *Tetrahedron* 69: 3664-3668.

Engler RH, Klein C, Henne U, Beifuss U, Döring F, Ondrus V, Tietze M (2009). Pressure-sensitive paint. DE 10 2009 026 363.

Hajdok S, Leutbecher H, Greiner G, Conrad J, Beifuss U (2007). Laccase initiated oxidative domino reactions for the efficient synthesis of 3,4-dihydro-7,8-dihydroxy-2*H*-dibenzofuran-1-ones. *Tetrahedron Lett.* 48: 5073-5076.

Hajdok S, Conrad J, Leutbecher H, Strobel S, Schleid T, Beifuss U (2009). The Laccase Catalyzed Domino Reaction Between Catechols and Heterocyclic 1,3-Dicarbonyls and the Unambiguous Structure Elucidation of the Products by NMR Spectroscopy and X-ray Crystal Structure Analysis. *J. Org. Chem.* 74: 7230-7237.

Hajdok S, Conrad J, Beifuss U (2012). Laccase-Catalyzed Domino Reaction Between Hydroquinones and Cyclic 1,3-Dicarbonyls for the Regioselective Synthesis of Substituted *p*-Benzoquinones. *J. Org. Chem.* 77*:* 445-459.

Henne U, Klein C, Bruse M, Beifuss U, Ondrus V, Egami Y (2014). Temperaturempfindliche Farbe mit hoher relativer Temperaturempfindlichkeit oberhalb Raumtemperatur und deren Verwendung. DE 10 2010 029 189 B4.

Leutbecher H, Greiner G, Amann R, Stolz A, Beifuss U, Conrad J (2011a). Laccase-catalyzed phenol oxidation. Rapid assignment of ring-proton deficient polycyclic benzofuran regioisomers by experimental ^{1}H-^{13}C long-range coupling constants and DFT-predicted product formation. *Org. Biomol. Chem.* 9: 2667-2673.

Leutbecher H, Constantin M-A, Mika S, Conrad J, Beifuss U (2011b). A new laccase-catalyzed domino process and its application to the efficient synthesis of 2-aryl-1*H*-benzimidazoles. *Tetrahedron Lett.* 52: 604-607.

Malakar CC, Schmidt D, Conrad J, Beifuss U (2011). Cu(I)-Catalyzed Domino Reactions: Efficient and Selective Synthesis of 4*H*-Chromenes and Naphthalenes. *Org. Lett.* 13: 1972-1975.

Malakar CC, Baskakova A, Conrad J, Beifuss U (2012a). Copper-Catalyzed Synthesis of Quinazolines in Water from *o*-Bromobenzylbromides and Benzamidines. *Chem. Eur. J.* 18: 8882-8885.

Malakar CC, Sudheendran K, Imrich H-G, Mika S, Beifuss U (2012b). Cu(I)-catalyzed annulation for the synthesis of substituted naphthalenes using *o*-bromobenzaldehydes and *β*-ketoesters as substrates. *Org. Biomol. Chem.* 10: 3899-3905.

Mongkolvisut W, Sutthivaiyakit S, Leutbecher H, Conrad J, Mika S, Klaiber I, Beifuss U, Rösner H (2006). Integerrimides A and B. Two cyclic heptapeptides from the latex of *Jatropha integerrima*. *J. Nat. Prod.* 69: 1435-1441.

Nareeboon P, Kraus W, Beifuss U, Conrad J, Klaiber I, Sutthivaiyakit S (2006). Novel 24-nor-, 24-nor-2,3-*seco*-, and 3,24-dinor-2,4-*seco*-ursane triterpenes from *Diospyros decandra*: evidences for ring A biosynthetic transformations. *Tetrahedron* 62: 5519-5526.

Omar MA, Conrad J, Beifuss U (2014a). Assembly of 4*H*-chromenes, imidazobenzothiazines and quinazolines via copper-catalyzed domino reactions using 2-halobenzyl tosylates as substrates. *Tetrahedron* 70*:* 5682-5695.

Omar MA, Conrad J, Beifuss U (2014b). Copper-catalyzed domino reaction between 1-(2-halophenyl)methanamines and amidines or imidates for the synthesis of 2-substituted quinazolines. *Tetrahedron* 70: 3061-3072.

Pickel B, Constantin M-A, Pfannstiel J, Conrad J, Beifuss U, Schaller A (2010): Ein enantiokomplementäres dirigierendes Protein für die enantioselektive Laccase-katalysierte oxidative Phenolkupplung. *Angew. Chem*. 122: 207-209.

Sudheendran K, Malakar CC, Conrad J, Beifuss U (2013). Synthesis of Functionalized Naphthalenes by Copper(I)-Catalyzed Annulation between 3-(2-Halobenzyl)pentane-2,4-diones and *β*-Ketoesters, Malonates and Cyanoacetates. *Adv. Synth. Catal.* 355: 2400-2416.

Zehl M, Braunberger C, Conrad J, Crnogorac M, Krasteva S, Vogler B, Beifuss U, Krenn L (2011). Identification and quantification of flavonoids and ellagic acid derivatives in therapeutically important drosera species by LC-DAD, LC-NMR, NMR, and LC-MS. *Anal. Bioanal. Chem.* 400: 2565-2576.