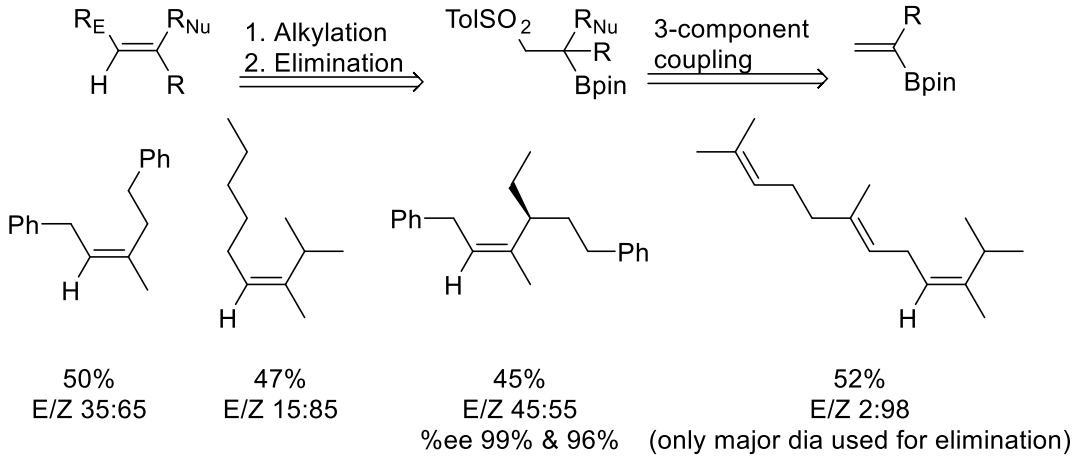
Modular approach to trisubstituted alkenes

Remo Arnold, Manuel Gnägi-Lux, Fabrice Dénès, Philippe Renaud

DCBP, University of Bern, Freiestrasse 3, 3012 Bern, Switzerland
remo.arnold@unibe.ch

In this work, we present a new method for the preparation of trisubstituted alkenes. Starting from vinyl boronic acid pinacol esters various three-component coupling products[1] were prepared, which were used in a specially developed mild protocol to achieve alkylation. Previously, it has be reported that boronic ester can be employed as precursors in olefination reactions[2]. Similarly in this approach, the alkylation products were converted to the trisubstituted alkenes by a strictly *anti* elimination reaction. With the developed protocols, a wide range of electrophiles could be used for alkylation with yields of 40-80% and a dr of up to 1:9. The subsequent olefination reaction proceeded smoothly by addition of TBAF to yield the trisubstituted olefins in yields of 80% to quantitative.



In addition to the wide variety of electrophiles, chiral nucleophiles in the form of enantioenriched boronic acid esters could also be used in the three-component coupling, whose chirality was preserved until olefination and was thus not altered. In addition to the stepwise protocol, a one-pot process was also developed that achieved the same yields but eliminated the time-consuming and tedious purification steps. As an application, the protocol has been successfully used for late-stage functionalization of natural products.

(1) Tappin, N. D. C.; Renaud, P. Radical Reactions of Boron-Ate Complexes Promoting a 1,2-Metallate Rearrangement. *CHIMIA International Journal for Chemistry* **2020**, *74* (1), 33–38. https://doi.org/10.2533/chimia.2020.33.
(2) Armstrong, R.; Aggarwal, V. 50 Years of Zweifel Olefination: A Transition-Metal-Free Coupling. *Synthesis* **2017**, *49* (15), 3323–3336. https://doi.org/10.1055/s-0036-1589046.

Poster presentation 2

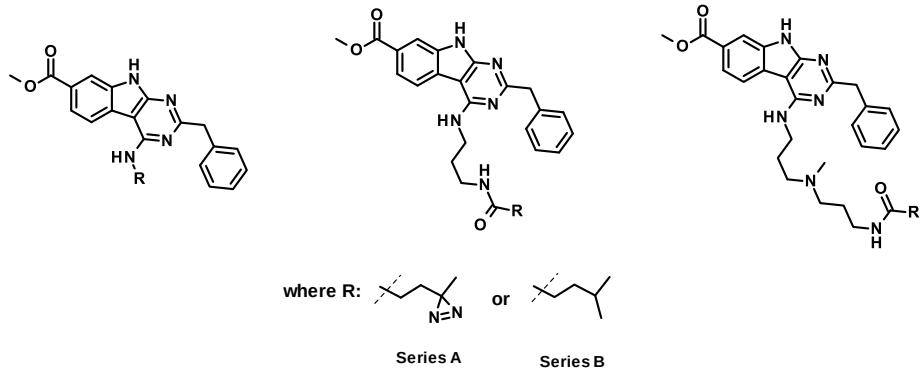
Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Application of photo-crosslinkers for mapping KBTBD4-ligand interaction

Tímea Baló[a,d], Tímea Szabó[a], Virginie Martiny[b], András Herner[a], David Brown[b], Zhuoyao Chen[c], Alex Bullock[c], András Kotschy[a]

[a]Servier Research Institute of Medicinal Chemistry (Záhony street 7., 1031, Budapest, Hungary)
[b] Servier IdRS (Rue Francis Perrin, 91190 Gif-sur-Yvette, France)
[c] Centre for Medicines Discovery Department of Biochemistry, University of Oxford (Old Road Campus Research Building, Roosevelt Drive, Headington, Oxford OX3 7DQ, United Kingdom)
[d] Institute of Chemistry, Eötvös Loránd University (Pázmány Péter sétány 1/A, 1117, Budapest, Hungary)

The ubiquitin proteasome system (UPS) is a major player in the regulation of the natural cycle of proteins in our body. Targeted protein degradation (TPD) through E3 ligases (which is a key element of the UPS) offers a new therapeutic method to cure diseases via the removal of the unwanted or overexpressed proteins responsible for the phenotypic effect.
The KBTBD4 protein is part of the E3 ligase family which has more than 600 members. Since less than 10 out of them is used daily in the TPD, expansion of applicable E3 ligases in this area would be inevitable. Currently, the structure of KBTBD4 protein is unknown, however there is a small molecular binder, namely UM171, which is in phase II clinical trial with oncologic indications [1]. However, the mechanism of action is still not understood completely, the UM171 probably acts as a molecular glue in a ternary complex with KBTBD4 and LSD1-CoRest-complex. To specify and examine the binding mode of this small molecule we designed and synthesized 3H-diazirine based photo-crosslinkers containing UM171 analogues (Series A) as well as negative controls (Series B).



Photoaffinity labeling is widely used to map protein-ligand interactions [2]. While the diazirine is chemically stable precursor, upon UV radiation it decomposes fast to nitrogen and a reactive carbene. Latter can insert even into C-H bond and form a stable covalent bond with the nearest amino acid. We assume that with these photoaffinity probes the binding mode and site will be revealed and gain more structural information about the ligand-protein interaction. This discovery would enable to start a structure-based drug design process.

[1] J.Chagraoui, S. Girard, J. Spinella, L. Simon, E. Bonneil, N. Mayotte, T. MacRae, J. Coulombe-Huntington, T. Bertomeu, C. Moison, E. Tomellini, P. Thibault, M. Tyers, A. Marinier, G. Sauvageau, *Cell Stem Cell,* **2021**, *28*, 48–62.
[2] J. R. Hill, A. A. B. Robertson, *J. Med. Chem.,* **2018**, *61*, 6945-6963.

Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

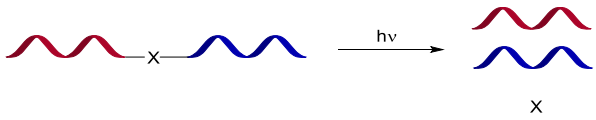
Self-vanishing oligonucleotide

Yan Berset

University of Fribourg, chemin du Musée 9, 1700 Fribourg, Switzerland
yan.berset@unifr.ch

The goal of this project is to synthesize an oligonucleotide made of natural nucleotides and a linker in the middle of the sequence. Under irradiation at a certain wavelength, the cleavage of the photolabile protecting group on the linker would release a phenol which can easily be deprotonated in basic conditions. The phenolate can then trigger a self-immolation and release 2 shorter oligonucleotides and the traceless linker as depicted in Scheme 1 and 2.

Scheme 1: A self-vanishing oligonucleotide.

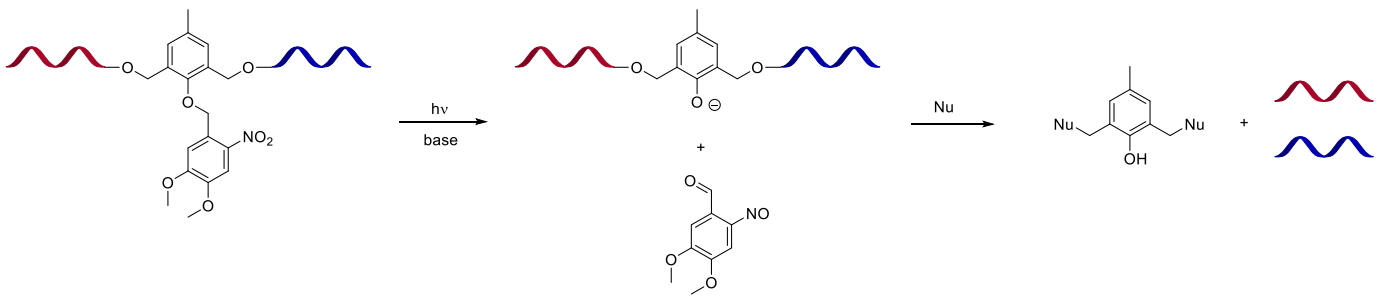


Developed in 1981, self-immolation is the action of a compound (small molecule, polymer, dendrimer,…) to trigger a cascade reaction and release a drug, a signal or any molecule of interest such as 2 shorter oligonucleotide fragments in this project.[1]

Our research group already published a few papers using the self-immolation principle. Kastrati was able to transform a small photochemical input into a large chemical output using a dendritic structure.[2] On the other hand, Janett and Diep used the self-immolation of a *p*-nitrophenol carbonate bound to a DNA single strand, which releases a red *p*-nitrophenolate upon nucleophilic attack on the carbonate.[3] If the nucleophile is bound to a DNA single strand complementary to the sequence linked to the carbonate, this self-immolation can take place in very small concentration thanks to the DNA-hybridization bringing the 2 reactive species in a close proximity.

To afford the desired linker, we designed a *p*-cresol scaffold having the phenol position blocked with a photolabile protecting group (nitroveratrole) that can be cleaved under irradiation at 360 nm and 2 benzyl ethers on both *ortho* positions to the phenol to connect the linker to the oligonucleotide sequence during the solid phase synthesis (Scheme 2). [4]

Scheme 2: Designed linker and photorelease of 2 shorter oligonucleotides.



[1] Gavriel, A. G.; Sambrook, M. R.; Russell, A. T.; Hayes, W. Recent Advances in Self-Immolative Linkers and Their Applications in Polymeric Reporting Systems. *Polym. Chem.* **2022**, *13* (22), 3188–3269. https://doi.org/10.1039/D2PY00414C.

[2] Kastrati, A.; Bochet, C. G. Photochemical Amplifier Based on Self-Immolative Dendritic Spacers. *J. Org. Chem.* **2019**, *84* (12), 7776–7785. https://doi.org/10.1021/acs.joc.9b00651.

[3] Janett, E.; Diep, K.-L.; Fromm, K. M.; Bochet, C. G. A Simple Reaction for DNA Sensing and Chemical Delivery. *ACS Sens.* **2020**, *5* (8), 2338–2343. https://doi.org/10.1021/acssensors.0c00988.

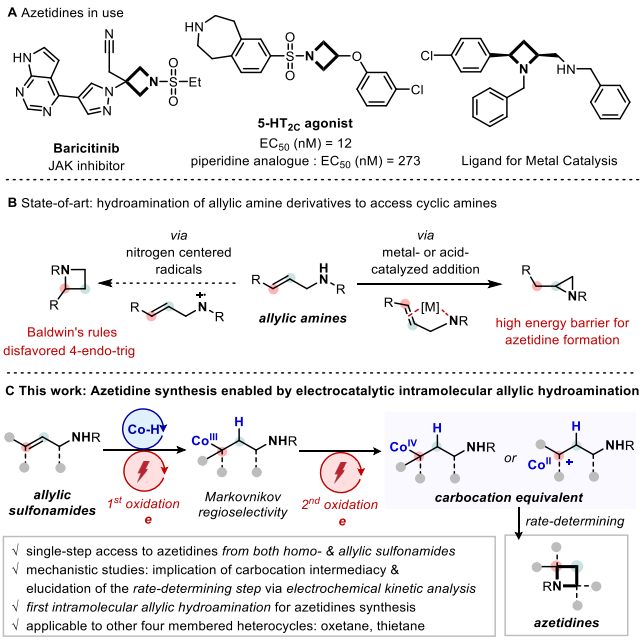
[4] Kessler, M.; Glatthar, R.; Giese, B.; Bochet, C. G. Sequentially Photocleavable Protecting Groups in Solid-Phase Synthesis. *Org. Lett.* **2003**, *5* (8), 1179–1181. https://doi.org/10.1021/ol027454g.

Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Electrocatalytic Access to Azetidines via Intramolecular Al-lylic Hydroamination: Scrutinizing Key Oxidation Steps through Electrochemical Kinetic Analysis

Ahhyeon Choi, Steve H Park, Geunsu Bae, Suyeon Shin, Kwangmin Shin*, Chang Hyuck Choi*, and Hyunwoo Kim*
(Department of Chemistry, Pohang University of Science and Technology (POSTECH), Pohang 37673, Republic of Korea)
dkgus2905@postech.ac.kr

Azetidines are prominent structural scaffolds in bioactive molecules, medicinal chemistry, and ligand design for tran-sition metals. However, state-of-the-art methods cannot be applied to intramolecular hydroamination of allylic amine derivatives despite their underlying potential as one of the most prevalent synthetic precursors to azetidines. Herein, we report an electrocatalytic method for intramolecular hydroamination of allylic sulfonamides to access azetidines for the first time. The merger of cobalt catalysis and electricity enables regioselective generation of key carbocationic intermediates, which could directly undergo intramolecular C-N bond formation. The mechanistic investigations including electrochemical kinetic analysis suggest that either the catalyst re-generation by nucleophilic cyclization or the second electrochemical oxidation to access carbocationic intermediate is involved in the rate-determining step (RDS) of our electrochemical protocol and highlight the ability of electrochemistry in providing ideal means to mediate catalyst oxidation.



[1] Park, S. H.†; Bae, G.†; Choi, A.; Shin, S.; Shin, K.*.; Choi, C. H*.; Kim, H.* Electrocatalytic Access to Azetidines via Intramolecular Allylic Hydroamination: Scrutinizing Key Oxidation Steps through Electrochemical Kinetic Analysis. *J. Am. Chem. Soc*. **2023**, Accepted.

Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Development of a synthetic approach for the synthesis of benzothiazole series as ARNT2 modulators

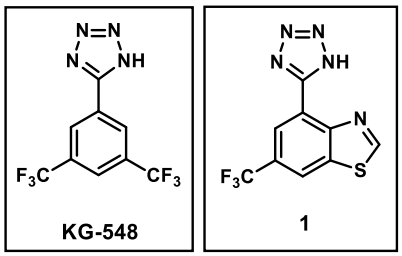
Ian de Toledo[†,‡], Hua Pu[‡], Fraydoon Rastinejad[‡], Paul Brennan[‡]

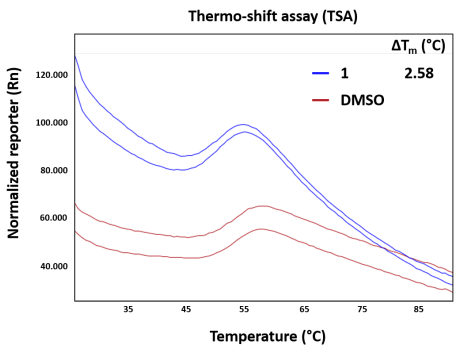
[†] Institute of Chemistry, University of Campinas, 13083-970, Campinas, Brazil
[‡] Nuffield Department of Medicine, University of Oxford, OX3 7BN, Oxford, UK
iandetoledo@outlook.com

ARNT2 is a member of the bHLH-PAS transcription factor (TF) family and is mostly localized in brain and kidneys in murine tissues[1]. It has been linked to neuronal and axonal health and protection and its mutation in humans leads to hypopituarism, post-natal microcephaly, visual and renal anomalies[2]. In 2013, KG-548 was identified as a modulator of the ARNT TF where it interacted with the PAS-B region[3]. Building on that work, our laboratories managed to show binding of KG-548 to ARNT2 in thermal-shift assays (TSA) allowing us to start structure-activity relationships (SAR) studies on this core towards a chemical probe for ARNT2 for unveiling its biological function.

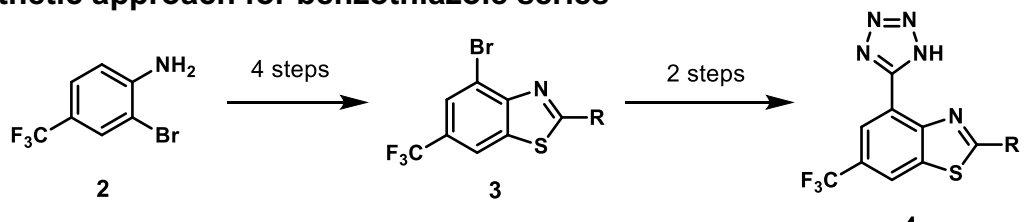
The benzothiazole **1** emerged as a good modulator during SAR investigations, maintaining potency and allowing more vectors of exploration than the hit compound (KG-548). We decided to explore a modular synthetic approach that would allow facile modification of the benzothiazole core in order to synthetise a small library of modulators for potency evaluation. The synthesis of **4** can be achieved in 6 steps and the key intermediate **3** can be synthetized in 4 steps form the commercially available bromoaniline **2**.

1. Initial Hit and ARNT2 thermal-shift assays





2. Synthetic approach for benzothiazole series



[1] Pelto-Huikko, M. T. *et al. J. Histochem Cytochem,* **2003**, 51, 1, 41–54
[2] Dattani, M. T. *et al. Brain,* **2013**, 136, 10, 3096–3105
[3] Gardner, K. H. *et al. ACS Chem. Biol.* **2013**, 8, 3, 626–635

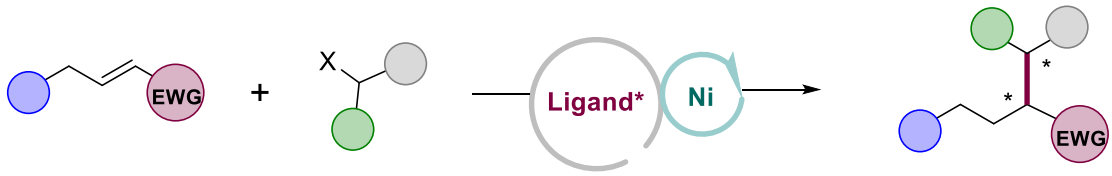
Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Synthesis of Vicinal C(sp^3) Stereocenters by Nickel-Hydride-Catalysed Hydroalkylation of Electron-Deficient Internal Alkenes

Uttam Dhawa

Laboratory of Inorganic Synthesis and Catalysis, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland
uttam.dhawa@epfl.ch

Widespread application of aliphatic carbons in drug discovery has significantly increased the interest in their modular synthesis. The existing methods to synthesis chiral C(sp^3)-rich molecules largely represent limited scope due to their harsh reaction conditions. Moreover, the construction of vicinal C(sp^3) stereocenters is still a daunting challenge. Here we present a step-economical synthesis of one out of the four possible stereoisomers *via* nickel-catalysed enantio- and diastereoselective hydroalkylation of electron-deficient alkenes with racemic alkyl halides under mild conditions.



EWG = Electron withdrawing group

Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

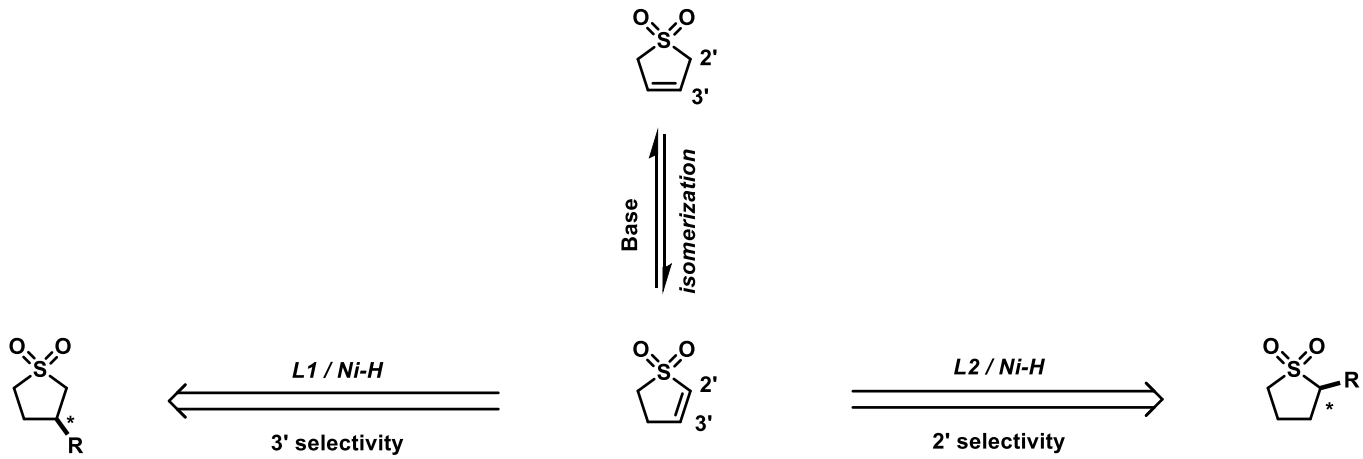
Regiodivergent and Enantioselective Hydroalkylation of Sulfones

Chao Fan, Uttam Dhawa, Xile Hu*

Laboratory of Inorganic Synthesis and Catalysis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, CH 1015 Switzerland
chao.fan@epfl.ch

The impact of the development of sulfur therapeutics is instrumental to the evolution of thepharmaceutical industry. Sulfur-derived functional groups can be found in a broad range ofpharmaceuticals and natural products.[1] However, due to the lack of general ways of building chiral sulfones, very few sulfone, especially chiral alkyl sulfone structure was brought into drug research.[2]

Nickel hydride catalysis has drawn a lot of attention in the recent decade. It has become a streamlined alkylation method using abundant readily available and stable alkene as pro-nucleophiles.[3] Although many improvements have been made using linear alkenes, for cyclic and non-activated alkene, there are still no efficient way of alkylation.[3] Herein, we report a NiH catalysed regiodivergent and enantioselective hydroalkylation of sulfone. By using rationally designed ligands, high regioselectivity and enantioselectivity was achieved at the same time. This will open a new channel for drug discovery to study one various chiral sulfones.



[1] M. Feng, B. Tang, S. Liang, X. Jiang, *Curr. Top Med Chem*. **2016**, *16, 1200*.
[2] F. Velazquez; *et al. J. Med. Chem*. **2010**, *53,* 3075
[3] Z. Zhang, S. Bera, C. Fan *J. Am. Chem. Soc.* **2022**, *144*, 7015.
[4] K. Lim, T. Hayashi *J. Am. Chem. Soc.* **2015**, *137*, 3201.

Developing Molecular Tools for the Study and Detection of Calcium-Sensing Receptor

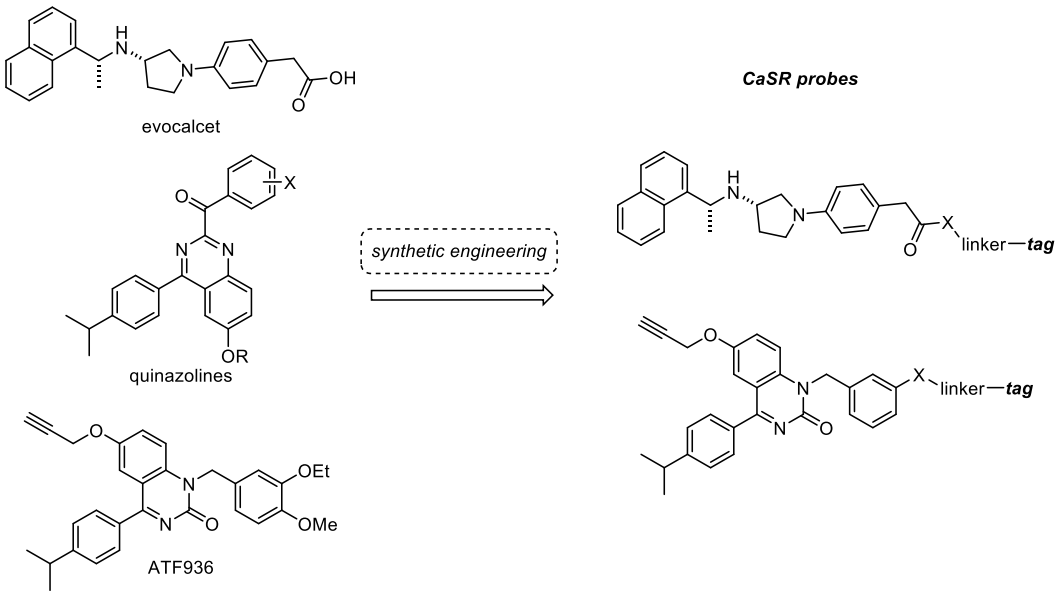
Jérôme Fischer[1], Dániel Batora[1], Luca Dick[1], Reto Kaderli[2], Jürg Gertsch[1], Martin Lochner[1]

[1]Institute of Biochemistry and Molecular Medicine, University of Bern, Bühlstrasse 28, 3012, Bern, Switzerland (jerome.fischer@unibe.ch). [2]Department of Visceral Surgery and Medicine, Inselspital, Bern University Hospital, Freiburgstrasse, 3010 Bern, Switzerland.

Background: The calcium-sensing receptor (CaSR) is a G protein-coupled receptor that plays a central role in the regulation of calcium homeostasis in humans.[1] It is highly expressed in parathyroid glands, pancreatic endocrine cells and kidneys. Impaired expression or function of CaSR causes several diseases and enlarged parathyroid glands, in particular, can lead to a pathological shift of calcium homeostasis and necessitate surgical removal in some cases.[2] Thus, the accurate pre- and intraoperative localisation of parathyroid glands is essential to avoid persistent complications that can significantly impair the patient's quality of life.[3] Molecular tools currently used in the clinic are not specific to the parathyroid glands and false-positive and false-negative readouts are common. Several small compounds and peptides have been developed to target and modulate CaSR as allosteric ligands, some of which are used in the clinic as so-called calcimimetic drugs to increase CaSR activity (e.g. cinacalcet, evocalcet and etelcalcetide).

Aim: To develop synthetic molecular probes for the study, modulation and localisation of the CaSR in cells and tissue.

Methods and Results: To this end, we have synthesised derivatives and conjugates of calcilytics (i.e. negative allosteric CaSR modulators), such as quinazolines and quinazolinones, and derivatives of evocalcet (positive allosteric modulator). In this context, we present our work on the synthesis of these probes and their preliminary biological assessment.



Bibliography

[1] F. M. Hannan, E. Kallay, W. Chang, M. L. Brandi, R. V. Thakker, *Nat. Rev. Endocrinol.* **2019**, *15*, 33–51.

[2] P. Riss, K. Kaczirek, G. Heinz, C. Bieglmayer, B. Niederle, *Surgery* **2007**, *142*, 398–404.

[3] J. Baj, R. Sitarz, M. Łokaj, A. Forma, M. Czeczelewski, A. Maani, G. Garruti, *Molecules* **2020**, *25*, 1724.

Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Difunctionalization of 1,3-dienes

Jan Forster

EPFL Lausanne
dan.forster@epfl.ch

Difunctionalization of 1,3 – dienes represent a very short access to highly functionalized building blocks. We present herein a three-component 1,2-amidoazidation and amidocyanation of 1,3-dienes. In the presence of fac-Ir(ppy)3 under blue LED irradiation, reaction of 1-aryl substituted 1,3-dienes with N-amidopyridinium salt and trimethylsilyl azide (TMSN3) affords exclusively the 1,2-amidoazidation products. The 1-alkyl substituted counterparts undergo the same reaction with moderate to high 1,2- vs 1,4-selectivity. Reduction of this mixture with PPh3 under dynamic kinetic conditions enriches significantly one of the two isomers thanks to the facile 1,3-azide shift allylic azides. The enantioselective cyanation can be achieved by adding copper along with a chiral ligand and TMSCN as cyanide source.

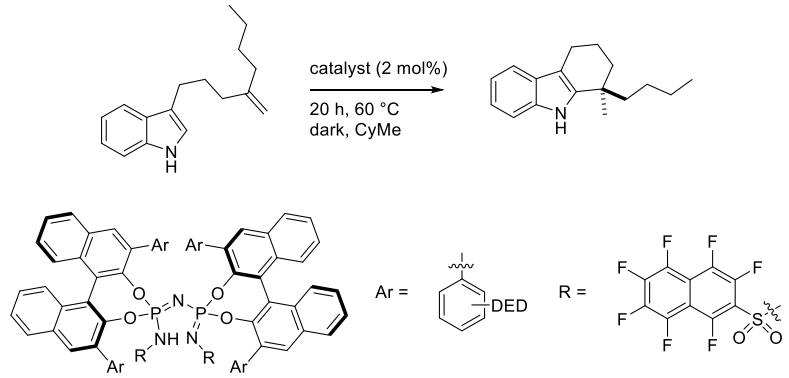
Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Investigation of London Dispersion Interactions in Imidodiphosphorimidate Catalysis

Michael Fuhrmann and Peter R. Schreiner*

Institute of Organic Chemistry, Justus Liebig University, Heinrich-Buff-Ring 17, 35392 Gießen, Germany

Understanding the fundamental interactions that govern enantiocontrol in asymmetric catalysis enables further improvement of catalyst design and development of new synthetic procedures. Elucidating the mechanism and key noncovalent interactions in catalytic reactions allows for implementation of moieties that predictably enhance beneficial interactions between catalyst and substrate.[1] Computational studies on the catalytic principle of imidodiphosphorimidates (IDPis) challenge the long established view on IDPi catalysis being mostly electrostatic in nature and highlights the importance of London dispersion interactions for the binding event.[2–5] Therefore, our goal is to investigate experimentally the role of London dispersion interactions in IDPi catalysis. For this purpose, we chose the IDPi catalyzed intramolecular hydroarylation of olefins with indoles developed by the List group as a suitable testing ground for these investigations.[6] Thus, the plan is to introduce dispersion energy donors (DEDs) to the phenyl moieties in 3,3'-position of the IDPis and examine their impact regarding reactivity and selectivity.



[1] J. P. Reid, *Comm. Chem.* **2021**, *4*, 1–4.
[2] T. Gatzenmeier, M. Turberg, D. Yepes, Y. Xie, F. Neese, G. Bistoni, B. List, *J. Am. Chem. Soc.* **2018**, *140*, 12671–12676.
[3] D. Yepes, F. Neese, B. List, G. Bistoni, *J. Am. Chem. Soc.* **2020**, *142*, 3613–3625.
[4] C. Eschmann, L. Song, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2021**, *60*, 4823–4832.
[5] J. P. Wagner, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12274–12296.
[6] P. Zhang, N. Tsuji, J. Ouyang, B. List, *J. Am. Chem. Soc.* **2021**, *143*, 675–680.

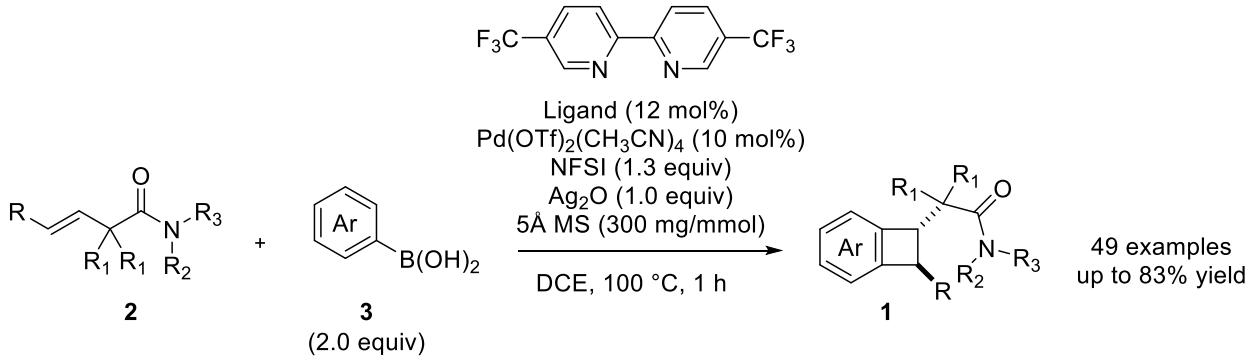
Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

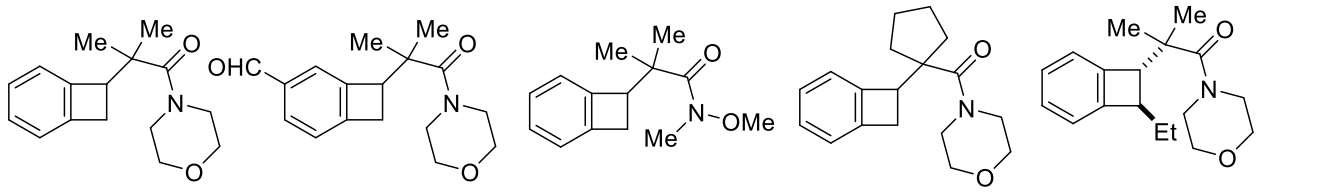
Oxidative [2+2] Annulation of Arylboronic acids and Alkenyl Amides Enabled by Pd(II)/(IV)-Redox Cycle

T.Fujii, S. Gallarati, C. Corminboeuf, Q. Wang, J. Zhu

EPFL-SB-ISIC-LSPN, 1015 Lausanne, Switzerland, takuji.fujii@epfl.ch

Benzocyclobutenes (BCBs) **1** are highly valuable synthetic targets because of their presence in natural products/medicinal drugs and the use as a reactive diene in [4+2] cycloaddition. However, the number of synthetical strategies are still limited.[1] We present herein a modular synthesis of BCBs **1** *via* a Pd(II)-catalyzed oxidative [2+2] annulation of alkenes bearing amide **2** with arylboronic acids **3**. Mechanistic studies indicate that the C(sp^2)–H bond activation involve the sigma-alkyl-Pd(IV) intermediate and that the rapid oxidation of sigma-alkyl-Pd(II) intermediate to its Pd(IV) counterpart is essential to avoid the formation of Heck adduct.[2]





The optimization of reaction conditions, the scope of alkenyl amides and functionalized arylboronic acids, the post-synthetic transformations, and mechanistic studies will be presented in this poster.

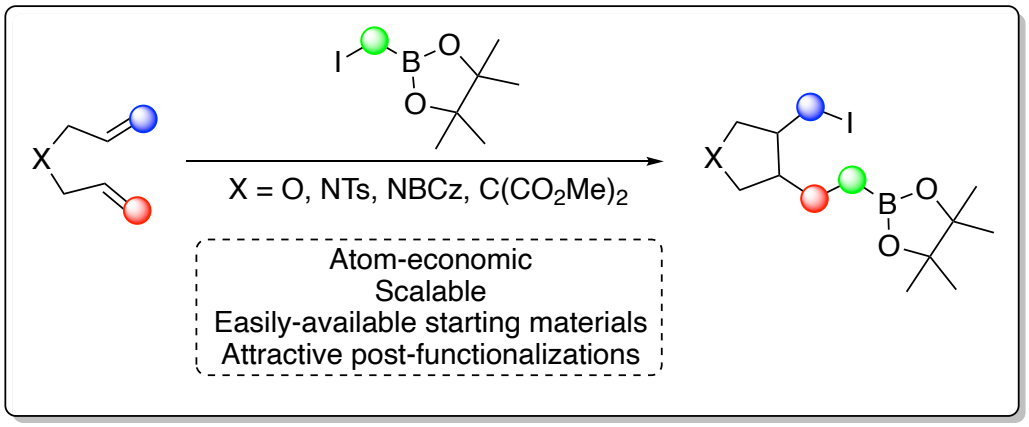
[1] S. Kotha, K. Lahiri, Y. Tangella, *Asian J. Org. Chem.* **2021**, *10*, 3166–3185.
[2] T. Fujii, S. Gallarati, C. Corminboeuf, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2022**, *144*, 8920–8926.

Iodine atom transfer mediated radical addition - cyclization processes using alpha-boryl radicals

Gaetano Geraci, Dr. Yanis Lazib, Dr. Fabrice Dénès, Leo Valentin Müller, Zoe Mäder, Prof. Philippe Renaud

Universität Bern (Department für Chemie, Biochemie und Pharmazie, Universität Bern, Freiestrasse 3, 3012 Bern, Switzerland)
gaetano.geraci@unibe.ch

Since the pioneering work of Suzuki[1] and his discovery of cross coupling reactions, boron has emerged as an important element for organic synthesis. Moreover, boron is as well contained in active compounds and, until 2022, 5 of them were approved by the FDA[2]. It is thus important to develop new organic reactions which help synthesizing new boron containing compounds. We exploited the unique features of alpha-boryl radicals and their addition to unsaturated systems[3][4] to develop an easy, scalable and efficient reaction to access 1,5-iodoboronic esters which possess a cyclopentane scaffold via 5-exo-*trig* cyclization. The optimization of the conditions and a scope of the reaction will be presented. The new products can be derivatized using further post-functionalization. Our new methodology could be used for the synthesis of small natural products, such as in the case of iridolactones.



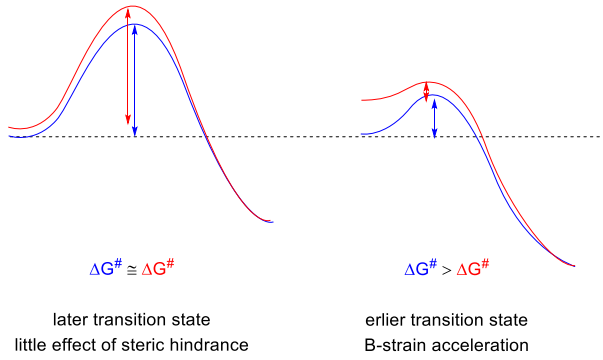
[1] N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Letters* **1979**, *20*, 3437–3440.
[2] K. Messner, B. Vuong, G. K. Tranmer, *Pharmaceuticals* **2022**, *15*, 264.
[3] Q. Huang, J. Michalland, S. Z. Zard, *Angewandte Chemie International Edition* **2019**, *58*, 16936–16942.
[4] N. D. C. Tappin, W. Michalska, S. Rohrbach, P. Renaud, *Angew. Chem. Int. Ed.* **2019**, *58*, 14240–14244.

Mechanistic studies on photochemical reactions: Can the Hammond postulate be applied to the *meta* effect?

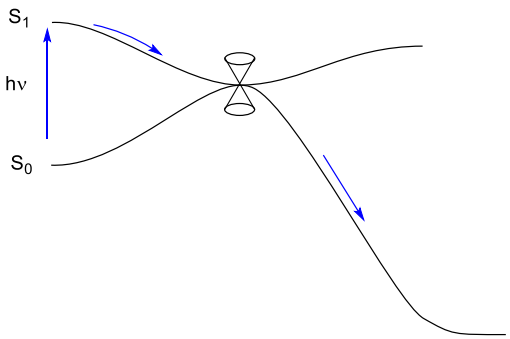
Gaël Jarjoura, Christian Bochet

Department of Chemistry, University of Fribourg, Chemin du Musée 9, Fribourg, Switzerland
gael.jarjoura@unifr.ch

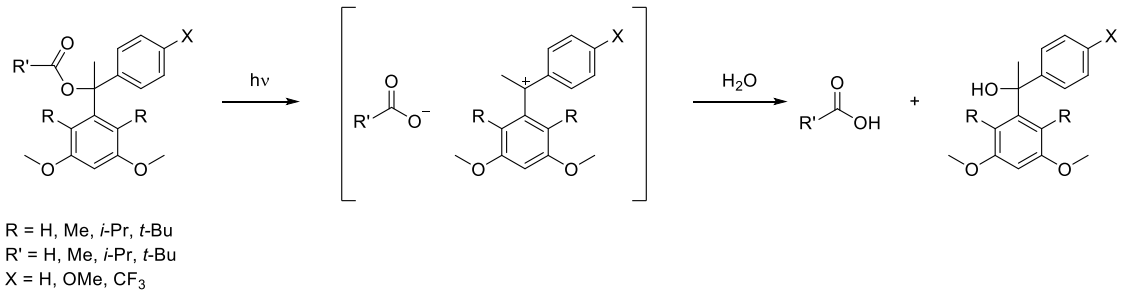
Previous work in our group explores whether the Hammond postulate can be applied on various photochemical reactions. In this work, the reaction studied is the *meta* effect. First described by Zimmerman in 1963[1], it is a photochemical phenomenon in which benzylic esters undergo an ionization at the excited state with electron donating substituents on *meta* positions of the aromatic ring. Thus, the bond dissociation must occur on the energy surface of the excited state. If the Hammond postulate is to be applied to such reactions, one can hypothesise that an early transition state will be more sensitive to steric effects than a late transition state. This would result in a change in kinetics when irradiating hindered and unhindered substrates, the rate difference being larger for early transition states (**Scheme 1**). A library of compounds with increasing steric hindrance and various electronic effects is to be synthesized (**Scheme 3**) and subjected to light irradiation. These reactions are to be monitored via HPLC and their rate measured in order to determine whether their transition states are early or late.



Scheme 1. Influence of the steric effect on the transition state



Scheme 2. Photochemical reaction in the singlet state



Scheme 3. Photochemical reaction to be performed

The spin state of these photochemical reactions is to be determined as well since a reaction in the singlet state would go through a conical intersection rather than a transition state (**Scheme 2**). This will be achieved through the use of triplet quenchers.

[1] H. E. Zimmerman, V. R. Sandel, *JACS*, **1963**, *85(7)*, 915-922.

Gold(I)-catalyzed Cascade Cyclizations as a Synthetic Tool towards Organic Materials

Justin Kahle, Christoph Hendrich, Robin Heckershoff and A. Stephen K. Hashmi

[a]Organisch-Chemisches Institut (OCI), Heidelberg University, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany.
[b]Chemistry Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia

j.kahle@stud.uni-heidelberg.de

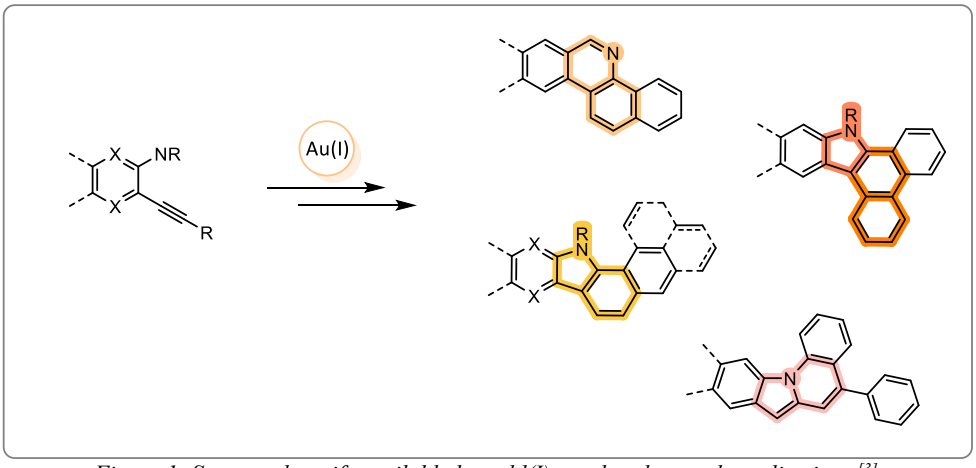


Figure 1: Structural motifs available by gold(I)-catalyzed cascade cyclizations.[3]

In both heterogeneous and homogeneous gold catalysis, the initial focus targeted methodology development. Mechanistic studies soon followed, and catalyst development became more apparent.[1] Later, these methods found application in total synthesis/pharmaceutical chemistry and in materials science.[1] The number of applications increased rapidly, expanding the circle of users of gold catalysis.[2] Homogeneous gold catalysts activate carbon-carbon multiple bonds through π-coordination, initiating a nucleophilic attack in a first step, followed by reactions with various electrophiles.[3] These inter- and intramolecular pathways lead to different reactivity patterns, providing short sequences and a modular approach for accessing different derivatives of a given product type.[3]

[1] C. M. Hendrich, K. Sekine, T. Koshikawa, K. Tanaka, A. S. K. Hashmi, *Chem. Rev.* **2021**, *121*, 9113.

[2] V. V. González, J. Kahle, C. Hüßler, R. Heckershoff, A. S. K. Hashmi, B. Birenheide, A. Hauser, J. Podlech, *Eur. J. Org. Chem.* **2023**, e202300545.

[3] a) J. Kahle, A. V. Mackenroth, C. Hüßler, P. D. Römgens, P. Schimanski, P. Krämer, M. Brückner, T. Oeser, F. Rominger, M. Rudolph, A. S. K. Hashmi, *manuscript in preparation* b) J. Kahle, A. V. Mackenroth, C. Hüßler, P. D. Römgens, P. Krämer, M. Brückner, F. Rominger, M. Rudolph, A. S. K. Hashmi, *manuscript in preparation* c) C. Hüßler, J. Kahle, M. C. Dietl, P. Krämer, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Org. Chem. Front.* **2023**, *DOI: 10.1039/d3qo00684k* d) R. Heckershoff, T. Schnitzer, T. Diederich, L. Eberle, P. Krämer, F. Rominger, M. Rudolph, A. S. K. Hashmi, *J. Am. Chem. Soc.* **2022**, *144*, 8306; e) R. Heckershoff, L. Eberle, G. May, P. Krämer, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Adv. Synth. Catal.* **2022**, *364*, 3559; f) C. M. Hendrich, S. Senn, L. Haas, M. T. Hoffmann, U. Zschieschang, L. C. Greiner, F. Rominger, M. Rudolph, H. Klauk, A. Dreuw, A. S. K. Hashmi, *Chem. Eur. J.* **2021**, *27*, 14778; g) C. M. Hendrich, V. D. Hannibal, L. Eberle, L. E. Hertwig, U. Zschieschang, F. Rominger, M. Rudolph, H. Klauk, A. S. K. Hashmi, *Adv. Synth. Catal.* **2021**, *363*, 1401; h) C. M. Hendrich, L. M. Bongartz, M. T. Hoffmann, U. Zschieschang, J. W. Borchert, D. Sauter, P. Krämer, F. Rominger, F. F. Mulks, M. Rudolph, A. S. K. Hashmi, *Adv. Synth. Catal.* **2021**, *363*, 549.

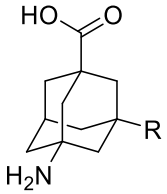
Swiss Summer School on Organic Synthesis 2023 August 27-31, 2023, Haute Nendaz

Towards an Asymmetric Synthesis of Adamantane-Based Amino Acids

Charlotte Lauter and Peter R. Schreiner*

Institute of Organic Chemistry, Justus Liebig University, Heinrich-Buff-Ring 17, 35392 Gießen, Germany

Over the last decades, the incorporation of nonproteinogenic amino acids into peptides, in particular, diamondoid based amino acids, has received considerable attention for pharmaceutical applications[1–2] as well as for catalysis.[3–4] Therefore, the asymmetric synthesis of chiral adamantane-based amino acids is a fundamental goal in organic chemistry. For this purpose, rhodium-catalyzed nitrenoid insertion has emerged as a convenient and effective way to introduce nitrogen functionality into organic molecules, offering high yields and good diastereoselectivities when using enantiopure sulfonimidamides as nitrenoid precursors.[5–7]



Currently, we are developing an enantioselective synthesis of adamantane-based amino acids via diastereoselective nitrenoid insertion on 1,3-substituted adamantane derivatives using sulfonimidamides as nitrenoid precursors. Subsequent post-functionalization enables the synthesis of diversly substituted adamantane-based amino acids. The versatility of this route provides possibilities for synthesizing drug derivatives, including chiral derivatives of Vildagliptin, a medication used for the treatment of type-2 diabetes.

[1] J. Müller, R. A. Kirschner, J. Berndt, T. Wulsdorf, A. Metz, R. Hrdina, P. R. Schreiner, A. Geyer, G. Klebe, *ChemMedChem* **2019**, *14*, 663–672.
[2] L. Wanka, K. Iqbal, P. R. Schreiner, *Chem. Rev.* **2013**, *5*, 3516–3604.
[3] C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 6180–6183.
[4] C. E. Müller, D. Zell, R. Hrdina, R. C. Wende, L. Wanka, S. M. M. Schuler, P. R. Schreiner, *J. Org. Chem.* **2013**, *78*, 8465–8484.
[5] C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343–350.
[6] F. Collet, C. Lescot, C. Liang, P. Dauban, *Dalton Trans.* **2010**, *39*, 10401–10413.
[7] P. Dauban, B. Darses, A. Jarvis, A.-K. Mafroud, G. Estenne-Bouhtou, G. Dargazanli, *Synthesis* **2013**, *45*, 2079–2087.