

## Research in the Department of Organometallic Chemistry

The Department of Organometallic Chemistry in its present form was created in 1998 when Prof. Fürstner was appointed as Director at the Institute. Its mission is the development of organometallic reagents and catalysts and their use as tools for advanced organic chemistry, notably the total synthesis of structurally complex and biologically relevant compounds. So far, the Department has hosted three junior groups in addition to Prof. Fürstner's own research team:

- Prof. Frank Glorius (2001-2004) started his independent career in Mülheim before he became Professor of Organic Chemistry at the University of Marburg (now Full Professor, University of Münster). His research focused on the development of new ligands (NHC's with flexible steric demands), the asymmetric hydrogenation of pyridines, and organocatalysis.
- Prof. Stefan Hecht (2005-2006) established a group working on organic materials chemistry. After completing his Habilitation (06/2006), he became Full Professor of Organic Chemistry at the Humboldt-University of Berlin.
- Dr. Lisbet Kvaerno joined the Institute only recently (09/2007). After finishing postdoctoral work under the guidance of Prof. D. A. Evans, Harvard University, Dr. Kvaerno managed to win an "Independent Junior Research Group" advertised by the Max-Planck-Society. Her projects deal with the development of new catalysts for asymmetric synthesis.

Prof. Fürstner's own research is dedicated to the development and understanding of organometallic reagents as enabling tools for advanced organic synthesis. By far the largest part of his agenda relates to homogeneous catalysis as one of the most important areas of contemporary chemistry research. Long term goals pursued in the Department comprise, inter alia:

- The development of catalysts based on cheap, non-toxic, benign and readily available transition metals, most notably iron, as substitutes for traditional noble metal complexes ("cheap metals for noble tasks")
- Attempts to unravel and exploit the complementary logic of olefin metathesis, and the extension of metathesis beyond its traditional scope (e. g. ring closing metathesis of alkynes, formal metathesis reactions catalyzed by noble metal salts etc.)

- The outline of novel concepts which eventually allow one to replace notoriously stoichiometric processes of proven versatility by catalytic regimens (eg. Nozaki-Kishi reactions catalytic in chromium, carbonyl coupling catalytic in titanium, Friedel-Crafts acylations catalytic in Lewis acid etc.)
- Benign catalysis by activation of  $\pi$ -systems with the aid of carbophilic Lewis acids
- Isolation and characterization of (short-lived) intermediates relevant for the catalytic cycles of interest.

A very significant part of our work is dedicated to the application of organometallic catalysts to the total synthesis of biologically active compounds, most notably complex natural products. This allows us to scrutinize – in a most stringent manner – the methodologies pursued in the Department, and, at the same time, provides meaningful amounts of highly valuable materials for testing. The targets are usually chosen according to the posed structural challenges, their biological significance, and non-availability from natural sources. Where appropriate, we are also committed to prepare collections of carefully designed structural variants for further evaluation by diverted total synthesis (“non-natural natural products”).

As a consequence, we entertain and foster collaborations with many experts outside the Institute to allow for proper testing of the natural products and analogues prepared by the group. One such collaboration enjoys even institutional support by central funds of the Max Planck Society: thus, Prof. Fürstner is a founding member of the Chemical Genomics Center (CGC) Initiative of the MPG (2005-).

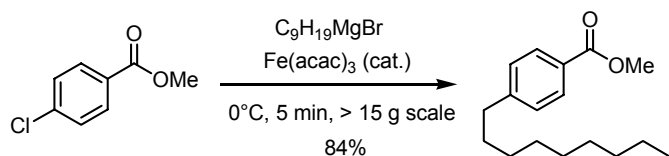
In addition, Prof. Fürstner’s team works closely together with several other groups at the Institute. Examples from the report period are: (i) an extended collaboration with Prof. Thiel concerning the understanding of the binding properties of macrolide antibiotics endowed with high affinity to the actin cytoskeleton, (ii) an ongoing collaboration with the Thiel group aiming at a better understanding of “through space” electronic communication within a newly designed planar chiral ligand scaffold, (iii) a fruitful exchange of information with Prof. Jonas in the field of organoiron chemistry. Last but certainly not least, the excellent contacts to the analytical groups of the Institute must be pointed out. Their support and expertise is an essential ingredient for much of the research carried out in this Department.

### 2.4.1. Research Area: “Cheap Metals for Noble Tasks” (A. Fürstner)

**Involved:** E. Kattnig, H. Krause, K. Majima, R. Martin, G. Seidel, C. Stimson

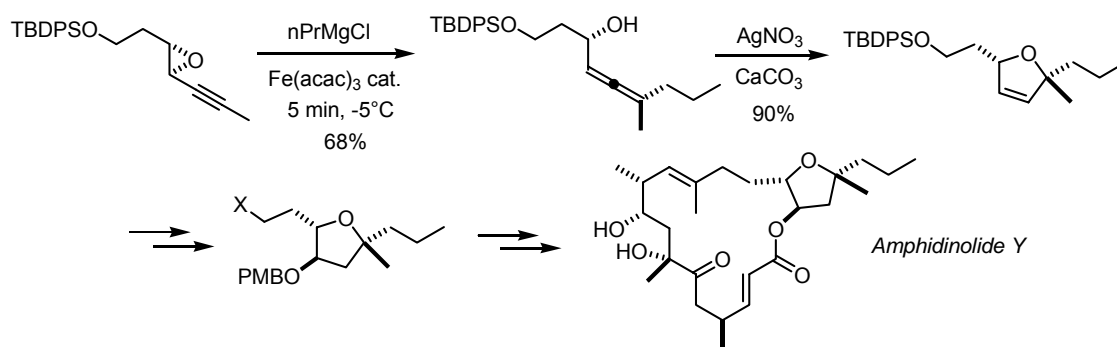
**Objective:** Late transition metals, and in particular the noble metals, dominate a significant part of contemporary catalysis research. Their use, however, is handicapped by the high price, the need for expensive ligands, toxicity issues and environmental concerns (nickel, cobalt). Therefore it is a worthwhile yet difficult endeavor to search for alternatives in a quest for more affordable and sustainable methodology.

**Results:** Pioneering studies published by Kochi et al. as early as 1971 had shown that simple iron salts qualify as precatalysts for certain cross coupling reactions of vinyl halides with Grignard reagents. Because of the overwhelming success of palladium- and nickel catalyzed cross coupling discovered shortly thereafter, Kochi’s result largely fell into oblivion for decades. Since 2001, our group has recapitalized on these lead findings (see previous report). Most notably, we were able to show that iron catalyzed cross coupling is much broader in scope than Kochi’s results may have suggested. It allows some of the most difficult types of substrates to be activated with ease (aryl chlorides, aryl tosylates, *alkyl* bromides, alkynyl epoxides, enol triflates and –phosphates, acid



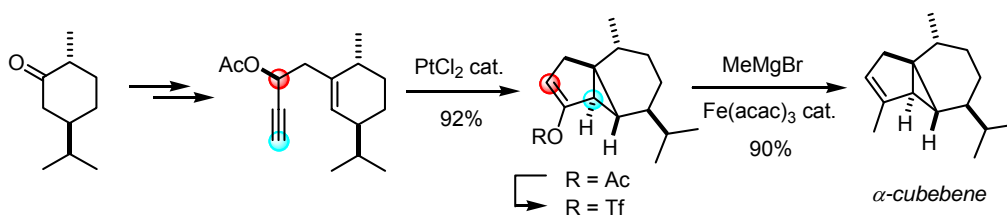
chlorides, thioesters etc.), yet is compatible with many functional groups due to the mild conditions and unprecedentedly fast reaction

rates. In most cases, cheap, non-toxic, air-stable, non-hygroscopic and environmentally benign  $\text{Fe}(\text{acac})_3$  qualifies as precatalyst. A representative example is the large scale preparation of 4-nonyl-benzoic acid (successfully checked by *Organic Synthesis*), a valuable component of high performance liquid crystalline materials.

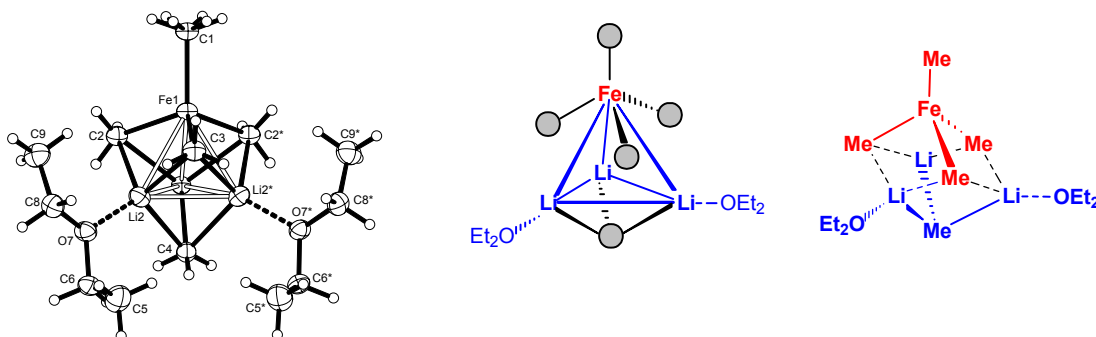


This methodology has also served as a key transformation in various natural product syntheses. A notable example from the 2005-2007 report period is the conquest of the

extremely scarce and highly cytotoxic marine macrolide **amphidinolide Y**, in which a *syn*-selective iron-catalyzed propargyl epoxide opening allowed us to conveniently install a quaternary center via a “relay” (central → axial → central) chirality transfer. The completion of the total synthesis of the sesquiterpene (–)- **$\alpha$ -cubebene** provides another illustration for the power of this methodology (this synthesis also features a PtCl<sub>2</sub>-catalyzed cycloisomerization developed in our group, cf. Chapter 2.4.2).

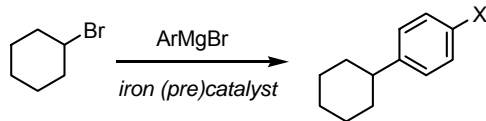


The biggest handicap of such Fe-catalyzed reactions, however, is the poor understanding of the mechanistic basis. The active species, generated in situ, is highly sensitive, short-lived, paramagnetic, non-stabilized and hence difficult to characterize. There is not even a consensus in the literature on its oxidation state. Therefore we launched a program aiming at the investigation of the underlying organoiron chemistry. In this context, we were able to show that iron-catalyzed C-C-bond formations may proceed along, at least, two distinctly different mechanistic pathways:



Specifically, iron catalyzed reactions of nucleophiles that cannot undergo  $\beta$ -hydride elimination (MeMgBr, MeLi, PhMgBr etc.) most likely involve organoferrate complexes as reactive intermediates. We were able to fully characterize such a compound – despite its *exceptional* sensitivity – which has truly remarkable structural attributes. Thus, reaction of FeCl<sub>3</sub> and MeLi affords the “super-ate” complex [(Me<sub>4</sub>Fe)(MeLi)][Li(OEt<sub>2</sub>)<sub>2</sub>], which not only comprises a homoleptic ferrate moiety, but also incorporates an extra equivalent of MeLi to complete a tetrahedral metallic frame end-capped by a methyl ligand devoid of any direct contact to the iron center. Unstabilized compounds of this type were previously unknown but show the exact reaction behavior characteristic for iron-catalyzed processes involving methyl donors.

In contrast, organomagnesium compounds with two or more C-atoms reduce the  $\text{FeX}_3$

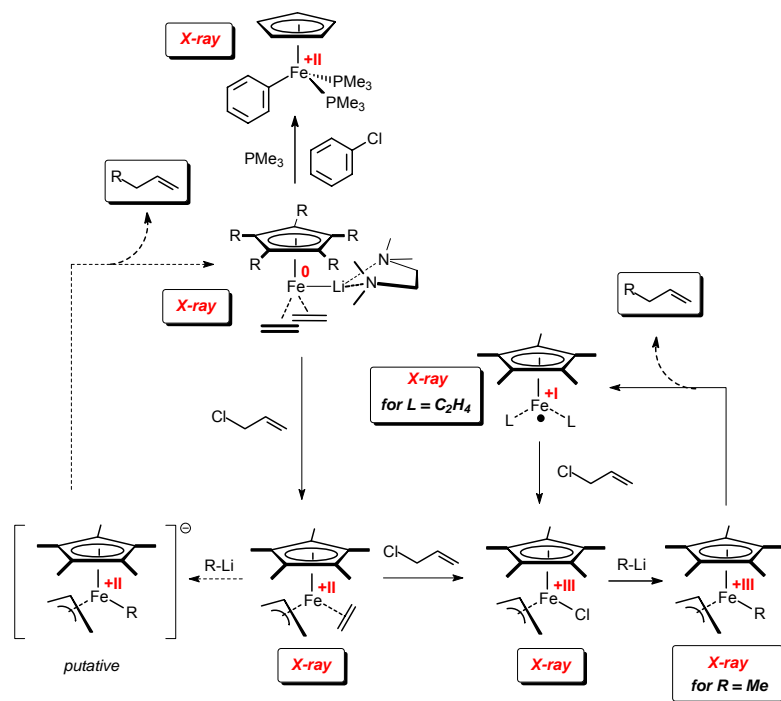


$\text{Fe}(\text{acac})_3$	69% (X = Me)
$\text{Li}_2[\text{Fe}(\text{C}_2\text{H}_4)_4]$	94% (X = H)
$\text{Li}[\text{CpFe}(\text{C}_2\text{H}_4)_2]$	81% (X = H)

precatalyst to low valent clusters of the formal composition  $[\text{XFe}(\text{MgX})]_n$  and  $[\text{Fe}(\text{MgX})_2]_n$ . The behavior of such intermetallic species can be mimicked with the aid of the structurally well defined lithium ferrate complexes  $\text{Li}[\text{CpFe}(\text{C}_2\text{H}_4)_2]$  and  $\text{Li}_2[\text{Fe}(\text{C}_2\text{H}_4)_4]$  pioneered

by Jonas et al., which carry kinetically labile olefin ligands and hence exhibit a “bare” metal center of the formal oxidation states 0 and –II, respectively. Such complexes are exceedingly useful catalysts even for the most difficult cross coupling of *alkyl* halides.

Once the functional relationship between the “in situ” catalysts and the Jonas-type

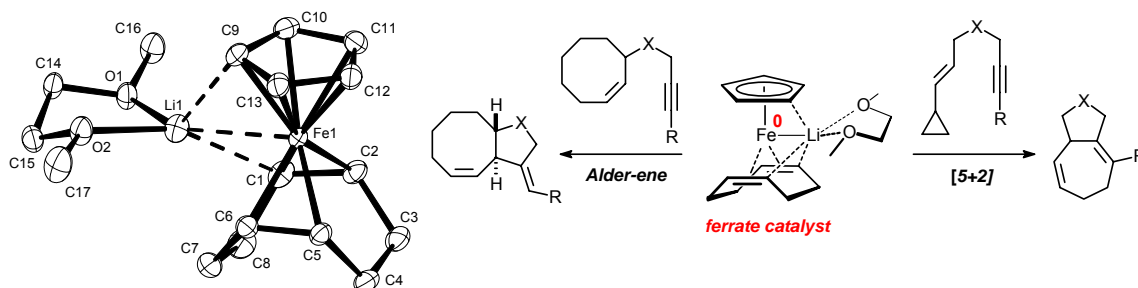


ferrate complexes had been established, the latter were used to investigate the structure of putative reactive intermediates. We were able to show that they undergo not only regular oxidative insertion reactions but also single electron transfer processes on reaction with aryl-, alkyl- or allyl halides. Most of the resulting intermediates could be characterized

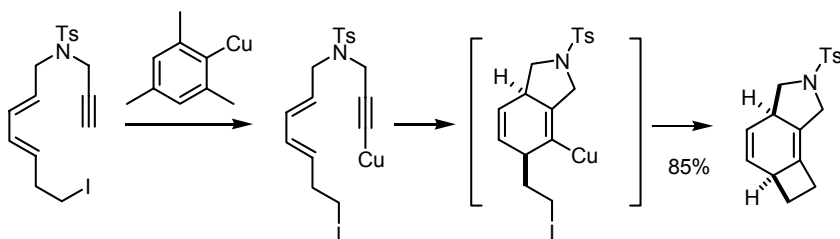
by X-ray crystallography, despite their high sensitivity. On this basis, it was possible for the very first time to provide experimental evidence for the elementary steps of the catalytic cycle(s) responsible for iron-catalyzed cross coupling.

The kinetic lability of the olefins in such low-valent ferrate complexes provides additional opportunities. Specifically, they effect a variety of cycloaddition and cycloisomerization reactions of the Alder-ene, [4+2], [5+2] and [2+2+2] type. These reactions are thought to proceed via initial ligand exchange followed by oxidative cyclization of e. g. an enyne substrate. During the report period, such skeletal rearrangements have been extensively studied and compelling evidence for the proposed

metallacyclic intermediates has been obtained. Although Alder-ene and higher order cycloadditions have previously been the domain of palladium-, rhodium- and ruthenium catalysts, this investigation emphasizes that very cheap and benign iron complexes also hold considerable promise.



In addition to the iron catalyzed skeletal reorganizations, we developed a new copper-based method that allows [4+2] cycloadditions to be combined with a subsequent alkylation (acylation) step into a reaction tandem. This unprecedented cascade proceeds via copper acetylide/vinyl copper intermediates, delivers tricyclic products in high yield and excellent diastereoselectivity, and therefore opens new vistas for the venerable Diels-Alder reaction.



**Future directions:** Deepen the mechanistic understanding of iron catalyzed C-C-bond forming reactions as the basis for further explorations into their scope. Scrutinize the utility of iron- as well as copper-based cycloadditions by applications to target oriented synthesis.

**Publications resulting from this research area:** 53, 54, 55, 270, 272, 452

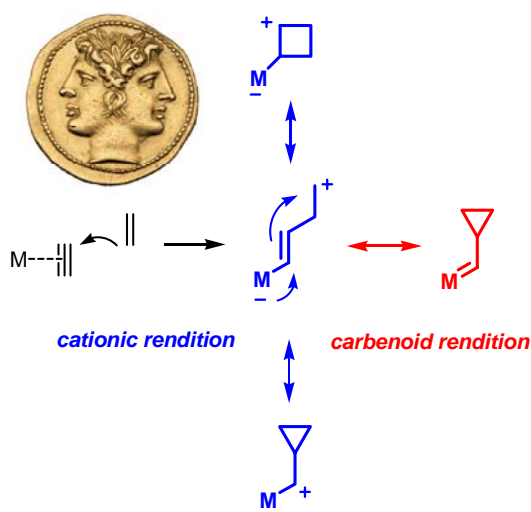
**External funding:** Alexander-von-Humboldt Foundation (stipend to R. M.), Pfizer Inc. (stipend to K. M.), Deutsch-Israelische Projektkooperation (DIP)

**Cooperations:** K. Jonas (Mülheim/Ruhr, DE)

### 2.4.2. Research Area “Novel Concepts for Catalysis” (A. Fürstner)

**Involved:** C. Aïssa, M. Alcarazo, V. César, T. Gress, P. Hannen, E. Heilmann, J. Kennedy, D. Kremzow, P. Davies, G. Seidel, A. Schlecker

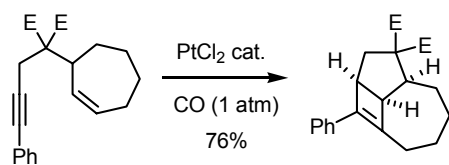
**Objective:** We aim at developing conceptually novel catalytic cycles and try to explore complementary access routes to catalysts of proven utility. The activities in this field during the report period mainly concerned the use of noble metal salts (e. g.  $\text{PtCl}_2$ ,  $\text{LAuCl}$ ,  $\text{CpRu}^+$ ) as user-friendly yet highly efficient  $\pi$ -acids, and the preparation and use of unconventional N-heterocyclic carbene ligands.



**Results:** In 1998, our group was the first to interpret skeletal rearrangements catalyzed by  $\text{PtCl}_2$  and related noble metal templates (e. g.  $\text{LAu}^+$ ) in terms of electrophilic metal cyclopropyl “carbenoids” endowed with considerable “non classical” carbocation character. Since then, this field of research has gained considerable momentum and is presently one of the most rapidly growing areas of homogeneous catalysis research. It is rewarding to see that our original mechanistic hypothesis has been able to account for a host

of diverse transformation by extension of the underlying principles. Therefore we have compiled a comprehensive review, which summarizes the many preparative advances in the field and provides the first in depth discussion of the structural basis responsible for the capacity of platinum- and gold catalysts to activate  $\pi$ -bonds.

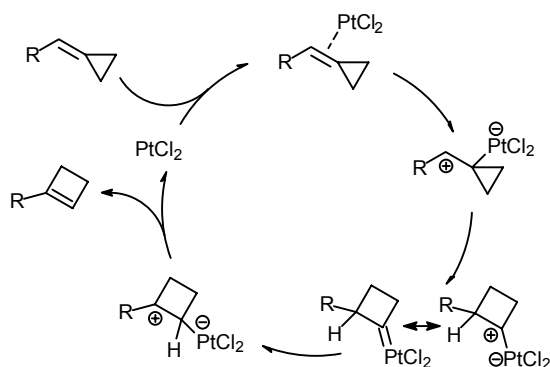
This mechanistic insight also powers a hypothesis-driven program directed toward the exploration of new reaction modes. Specifically, we were able to show that enynes bearing an arene group on their alkyne terminus readily convert into highly strained cyclobutene derivatives that are very difficult to prepare otherwise. Such previously unknown reactions are substantially accelerated when performed under an atmosphere of CO; this simple trick has already found widespread use in the community. Cyclobutenes are also accessible via  $\text{PtCl}_2$ -catalyzed rearrangements of alkylidene cyclopropanes through a



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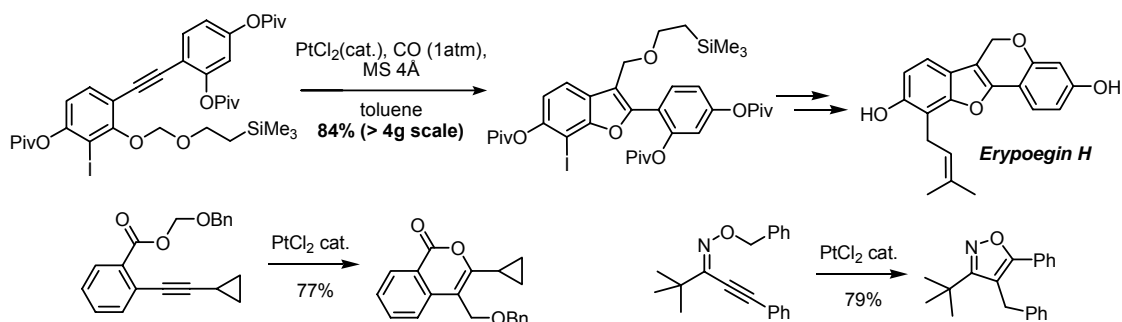
catalytic cycle that nicely illustrates the dual character of the putative intermediates. Because of the strain inherent to such products, this rearrangement can be combined



with further transformations such as ring-opening/ring closing metathesis into productive catalysis cascades, if suitable olefinic tethers are placed in vicinity to the incipient cyclobutene ring.

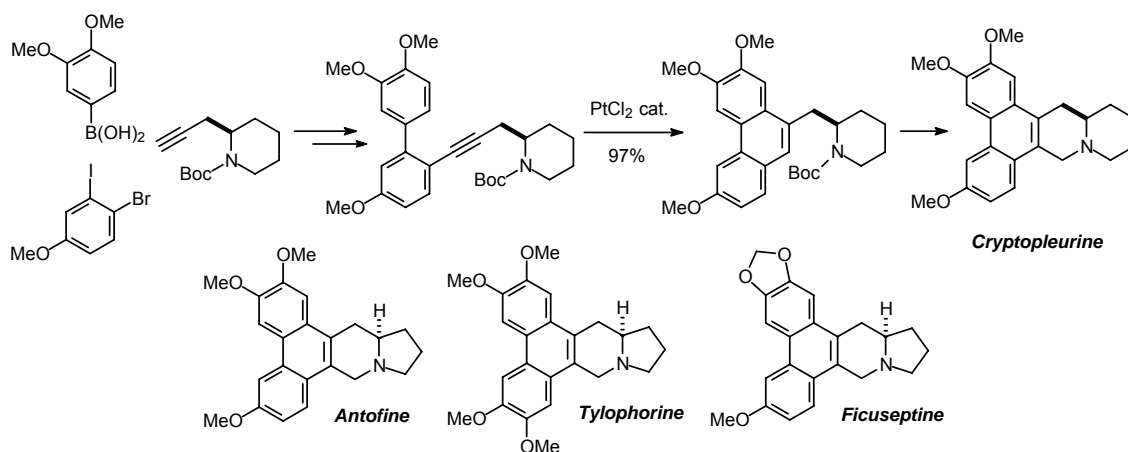
Noble metal catalyzed cycloisomerizations have been extensively used for the preparation of heterocycles. Particular mention deserves an efficient, scalable and

low-tech transformation of O-allylated, -benzylated or alkoxy-methylated 2-alkynyl phenol derivatives into the corresponding benzofurans. Thereby, the substituent readily migrates from oxygen to the C-3 position of the heterarene scaffold in a formal carboalkoxylation process. This methodology paved the way for a concise total synthesis of the antibiotic erypoegin H and cognates, which exhibit promising activity against a panel of methicillin- and vancomycin-resistant bacterial strains. The compatibility of the C-I bond shows that the behavior of Pt(2+) is orthogonal to that of conventional late transitions metal catalysts in that it does not open the usual redox manifolds. Furthermore, the underlying concept is by no means limited to benzofurans but can also be used for the synthesis to other important types of heterocycles (indoles, benzothiophenes, isoxazoles, isocoumarins etc.)

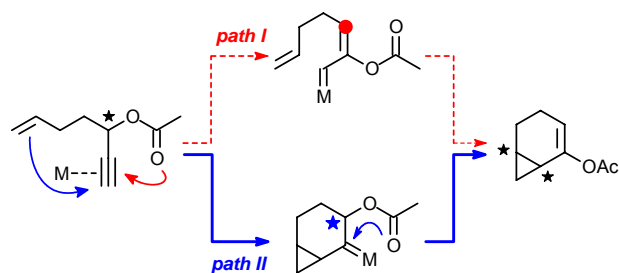


A Pt-catalyzed rearrangement also opened a straightforward entry into the phenanthroindolizidine alkaloid series. Because of the modularity of this approach, we were able to prepare a collection of such anti-tumor compounds that enabled our partners at the Yale University School of Medicine to conduct detailed SAR studies concerning cytotoxicity and NF- $\kappa$ B signaling. This study led to the remarkable finding that structurally very closely related compounds may nevertheless not be functional analogs.



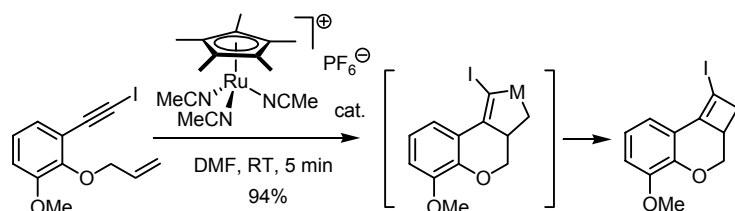


An important chemical insight was gained during the total synthesis of cubebene based on a  $\text{PtCl}_2$ -catalyzed cycloisomerization (see also Chapter 2.4.1). Thus, it was shown for



the first time that the configuration of the center carrying the propargyl acetate translates into the product stereostructure. It is hence impossible that this center is planarized before the new cyclopropane has formed; this finding, in turn, advocates the

notion that the reaction path involves cyclopropyl metal carbenes rather than vinyl carbenes as key intermediates.

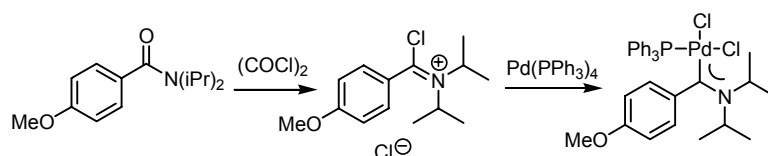
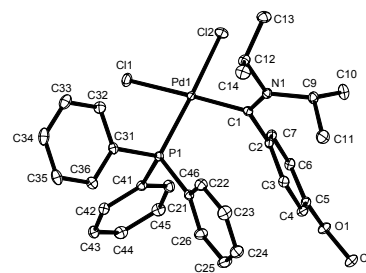


Further studies in the cycloisomerization arena concerned the surprisingly facile ruthenium catalyzed transformation of enynes bearing halide substituents at their alkyne terminus into strained halo-cyclobutene derivatives, although a redox cycle is believed to be operative in this case.

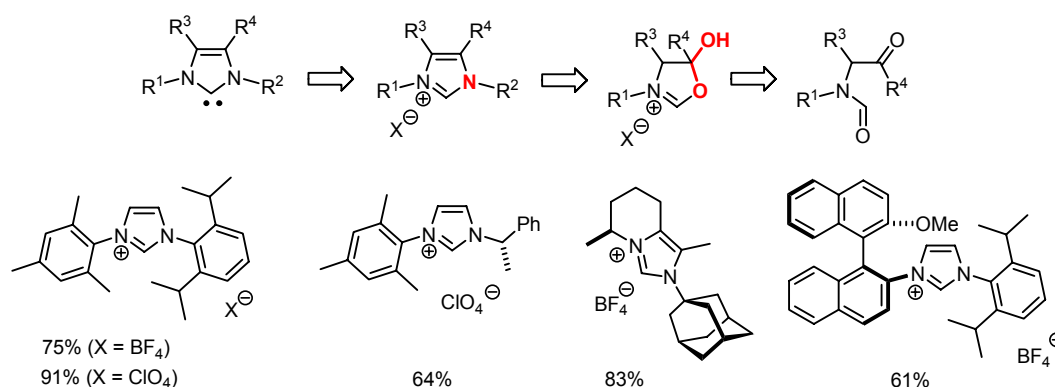
Another important topic are N-heterocyclic carbenes (NHC's) and metal complexes thereof. The following contributions have been made during the report period:

- (1) We had previously shown that metal-NHC complexes can be obtained by oxidative insertion of a low-valent metal into 2-chloro-1,3-disubstituted imidazolium salts. This method is complementary to the commonly used route

based on ligand exchange and allows to prepare complexes that are difficult to form otherwise, including Fischer-type carbene complexes of palladium and nickel. The scope of this new method has been extensively studied and the resulting complexes were used as catalysts for various C-C- and C-N-bond forming reactions.

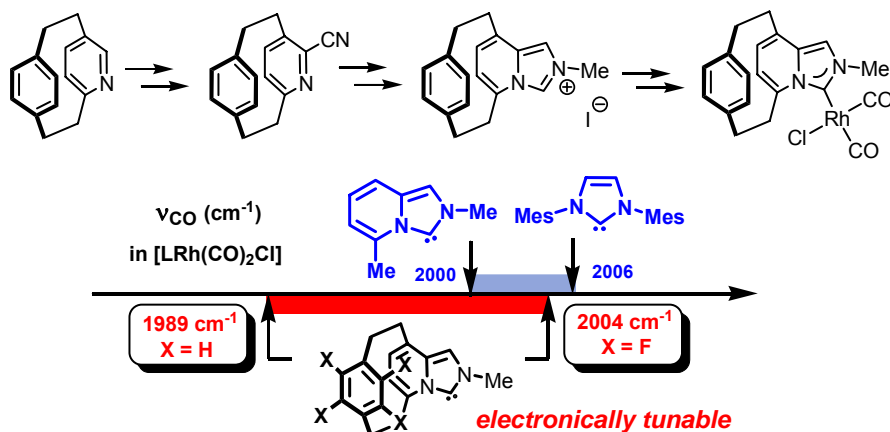


- (2) Despite the huge number of NHC's known in the literature, several obvious and seemingly trivial substitution patterns remain largely unexplored. This includes NHC's with two different aryl groups on the N-atoms; likewise non-symmetrical imidazolium salts (as NHC precursors) with one N-aryl and one N-alkyl group are rare and essentially limited to those having primary N-alkyl substituents. These gaps in the structural landscape reflect the limitations of the established syntheses routes. We were able to devise a user-friendly, scaleable and highly flexible new entry based on a heterocycle interconversion strategy which allows one to obtain such elusive substitution patterns with ease. We are now exploring the potential of such imidazolium salts and NHC's derived thereof in catalysis.

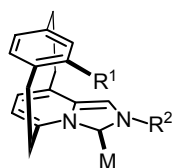


- (3) An unprecedented type of *planar chiral* NHC has been designed which holds considerable promise for the following reasons: The parent compound of this series is the strongest donor amongst all diamino-stabilized five-membered NHC's known to date. Importantly, however, substitution of the lid of the cyclophane with four fluorine atoms allows to down-regulate the donor capacity

to a previously unknown degree by “through space communication” with the carbene center underneath, while maintaining the steric demand of the ligand virtually unchanged.



Moreover, the novel ligand set is not only planar chiral, but also allows one to precisely position a suitable substituent  $\text{R}^1$  on top of the bound metal center, such that the chiral binding pocket is clearly defined. Ongoing work in this laboratory is trying to exploit these favorable structural attributes.



**Future directions:** Expand the scope of noble metal catalyzed processes and improve the understanding for the underlying mechanisms; develop asymmetric versions where appropriate, and try to characterize the relevant reaction intermediates. Exploit the favorable characteristics of planar chiral NHC's, improve the synthesis route, and develop other tunable ligands of this type.

**Publications resulting from this research area:** 48, 49, 98, 263, 265, 269, 271, 273, 407, 442, 445, 452

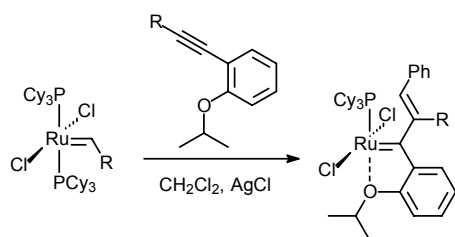
**External funding:** Alexander-von-Humboldt-Foundation (stipend to V. César), Spanish Ministerio de Educación y Ciencia (stipend to M. Alcarazo), Canadian NSERC (fellowship for J. Kennedy), Fonds der Chemischen Industrie, Deutsch-Israelische Projektkooperation (DIP).

**Cooperations:** W. Gao, Y.-C. Cheng (Yale University School of Medicine, USA).

### 2.4.3. Research Area “Metathesis” (A. Fürstner)

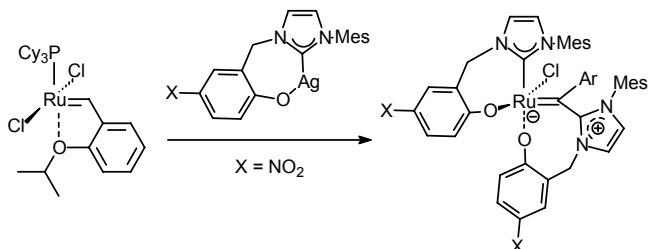
**Involved:** M. Bindl, J. Blank, M. Bonnekessel, P. Davies, B. Fasching, S. Flügge, L. Jean, A. Korte, O. Larionov, C. Müller, C. Nevado, T. Nagano, G. O’Neil, L. Turet

**Objectives:** Olefin metathesis has revolutionized organic synthesis during the last decade. While we continue to apply this transformation, our major focus has shifted toward alkyne metathesis, which, we believe, qualifies as a similarly enabling tool.



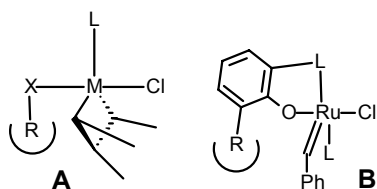
**Results:** Exposure of terminal alkynes to suitable metal carbene complexes usually results in “living” polymerization with formation of polyacetylene derivatives by stepwise insertion of the monomer into the catalytically active  $M=CR_2$

bond terminating the growing chain. We showed that this process can be interrupted after the first insertion step with an alkyne that carries a chelating substituent. Phenylacetylene derivatives bearing an *ortho*-isopropoxy group are particularly effective, which cleanly deliver vinylcarbene complexes of the Hoveyda-type by a versatile and general new route.



We have also found evidence that N-heterocyclic carbenes, which serve as ancillary ligands in some of the most powerful alkene metathesis catalysts known to date, may not be as innocent as usually

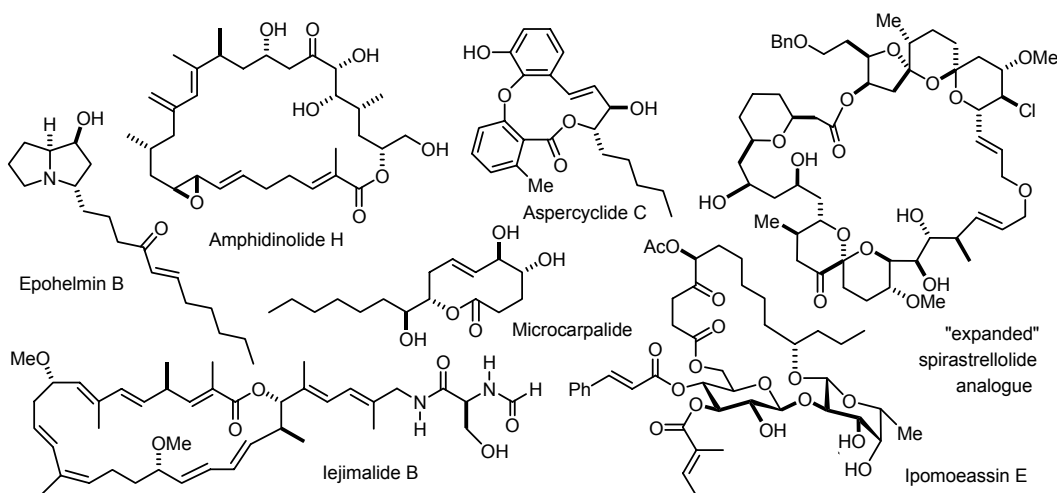
assumed. Upon trans-metallation of a Ag-NHC complex with a standard metathesis catalyst, a respectable amount of a new ruthenium species (with some zwitterionic character) has been isolated and characterized by X-ray crystallography, in which an NHC unit has attacked the alkyldiene moiety. This observation has implications for the stability and degradation pathways of the commonly used olefin metathesis catalysts.



Arguably the biggest challenge for alkene metathesis is

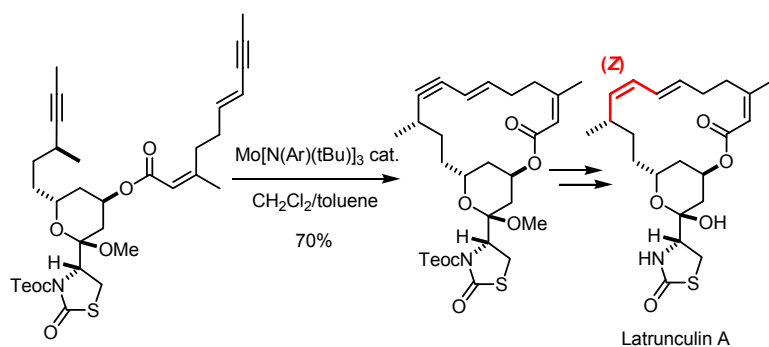
the development of stereoselective catalysts. Despite the fact that computational studies (including those from the Thiel group) provide a fairly detailed picture of the elementary steps on the reaction coordinate, no such system is presently available and our own efforts in this area also met with only limited success. It is assumed that a Z-

selective catalyst must be able to block one side of the incipient metallacyclobutane intermediate **A**, which we intend to accomplish with the aid of complexes of the general type **B**. After several attempts, we have very recently learned how to graft prototype alkylidenes of this type, which now undergo testing in the laboratory.



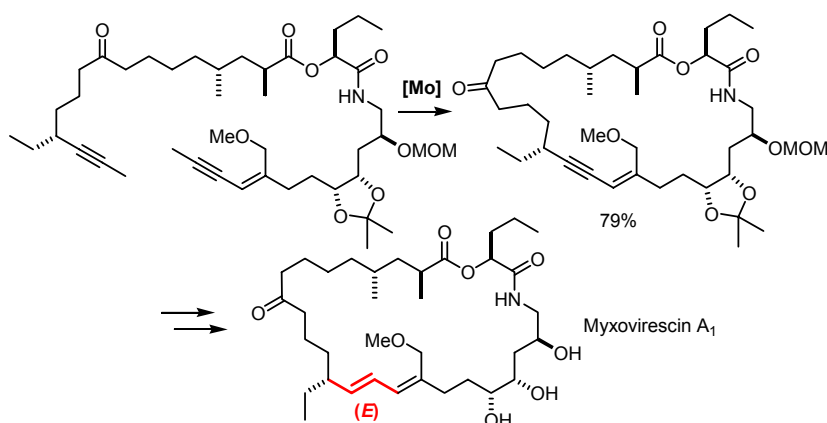
Apart from these daunting issues, alkene metathesis keeps serving our synthetic purposes exceedingly well. Several complex natural products were obtained during the report period using RCM and CM as key transformations. Since most of the targets had been chosen for their biological significance, some projects will be discussed in more detail in Chapter 2.4.4 (“Catalysis Based Syntheses and Evaluation of Bioactive Natural Products”). All of them, however, explore the very limits of contemporary metathesis chemistry. Specifically, the cyclization of *aspercyclide C* posed considerable challenges due to the very high strain inherent to its polyunsaturated frame (seven  $sp^2$  hybridized C-atoms in an 11-membered ring!). The first total synthesis of the highly cytotoxicity macrolide *amphidinolide H* features an exceptionally rare example of productive metathesis of a vinyl epoxide, whereas the synthesis of *ipomoeassin* required the development of a novel protecting group strategy ( $\underline{C}$ -silylated cinnamate) to allow for the selective hydrogenation of the macrocycle formed by RCM without destroying the unsaturated esters in the periphery. Our first attempt to prepare the phosphatase inhibitor *spirastrellolide* revealed a present limitation of RCM, as the densely functionalized macrocycle would not form, even though a “relay metathesis” was envisaged to assist ring closure; only a ring expanded product could be obtained, forcing us to revise our original synthesis plan. The arguably most impressive example, however, is the successful preparation of *iejimalide B* by selective activation of two out of no less than 10 (!) double bonds in the cyclization precursor. This result must also be seen in the light of an attempted formation of this potent anticancer agent by a lactonization strategy, which – in sharp contrast to RCM – had failed miserably.

Whereas RCM is now widely embraced by the synthetic community, the ring closing metathesis of alkynes (RCAM) still lags behind. This transformation was first described by our group in 1998 using a Schrock tungsten alkylidyne catalyst; shortly thereafter, we introduced an alternative system based on molybdenum trisamido complexes activated in situ. Although both types of catalysts are air- and moisture sensitive, their remarkable application profile makes us believe that RCAM qualifies as a truly enabling tool for organic synthesis. We are committed to demonstrate its outstanding performance and very wide scope by applications to increasingly complex cases.



A representative example is the total synthesis of the actin-binding marine natural product **latrunculin A**. The catalyst generated in situ from  $\text{Mo}[\text{N}(\text{Ar})(t\text{Bu})_3]_3$  and  $\text{CH}_2\text{Cl}_2$  allows to

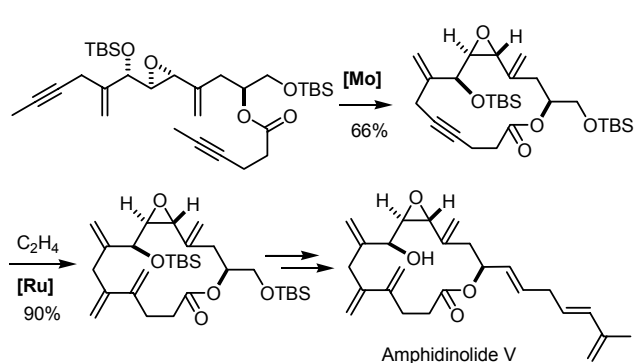
forge a highly strained 16-membered ring, and rigorously distinguishes between the triple- and the double bonds of the polyfunctionalized substrate. Lindlar reduction of the RCAM-product to the *Z*-alkene resulted in a stereoselective synthesis of latrunculin A, which is presently inconceivable with the aid of regular alkene metathesis.



The orthogonal character of alkyne- and alkene metathesis was equally instrumental for a largely catalysis-based approach to the antibiotic **myxovirescin A**. In this particular case, the cycloalkyne

was transformed via *trans*-hydrosilylation/desilylation into the corresponding *E*-alkene, thus showing that RCAM opens stereoselective entry into either olefinic series.

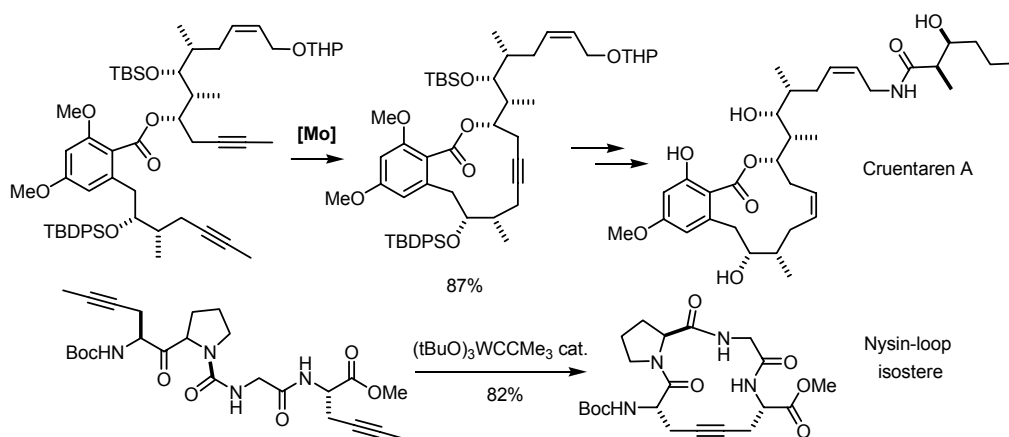
An entirely different use of RCAM is illustrated by our approach to **amphidinolide V**. Gratifyingly, the molybdenum catalyst turned out to be compatible with the very fragile vinyl epoxide as well as the allylic alcohol group of the substrate. The resulting cycloalkyne was then subjected to an enyne cross metathesis with ethylene gas to build the characteristic vicinal *exo*-methylene branches of the target. Due to the flexibility of



the chosen approach, it was possible to prepare all conceivable stereoisomers without undue efforts, which allowed us to establish the previously unsecured stereostructure of this natural product.

Similarly instructive examples are the successful use of RCAM for the

stereoselective synthesis of *cruentaren A*, a potent anticancer agent and selective F-ATPase inhibitor, as well as the preparation of an alkynylogous isostere of the peptidic lantibiotic *nysin Z*. Overall, we believe that these examples provide compelling evidence that alkyne metathesis applies to highly functionalized targets at the forefront of organic synthesis, just as RCM does. We take this as an encouragement to further expand its scope and improve the arsenal of catalyst, e. g. in terms of stability.



**Future directions:** Translate the growing understanding for the stereodetermining step in RCM into catalyst design; improve the stability of the available RCAM catalysts; extend metathesis to other  $\pi$ -systems; keep exploring these remarkable transformations by applications to advanced organic synthesis.

**Publications resulting from this research area:** 46, 47, 50, 56, 58, 60, 121, 274, 437, 443, 444, 446, 447, 448, 449, 450, 489

**External funding:** Alexander-von-Humboldt Foundation (stipend to J. Blank, G. O'Neil, C. Nevado), Fonds der Chemischen Industrie (stipends to A. Korte, M. Bonnekessel, S. Flügge, C. Müller)

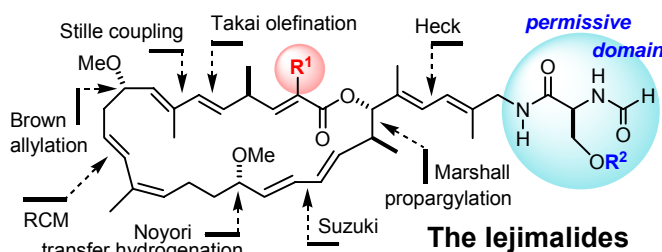
**Cooperations:** V. Jensen (University of Bergen, NO); R. M. J. Liskamp (University of Utrecht, NL); M. R. Buchmeiser (University of Innsbruck, AT, now Leipzig)

#### 2.4.4 Research Area “Catalysis Based Syntheses and Evaluation of Bioactive Natural Products” (A. Fürstner)

**Involved:** C. Aïssa, P. Buchgraber, J. Cecon, C. Chevrier, M. Domostoj, B. Fasching, M. Fenster, J. Gagnepain, C. Godbout, E. Kattinig, E. Moulin, C. Müller, T. Nagano, G. O’Neil, C. Nevado, K. Radkowski, F. Téply, M. Tremblay, L. Turet, M. Waser, M. Wuchrer

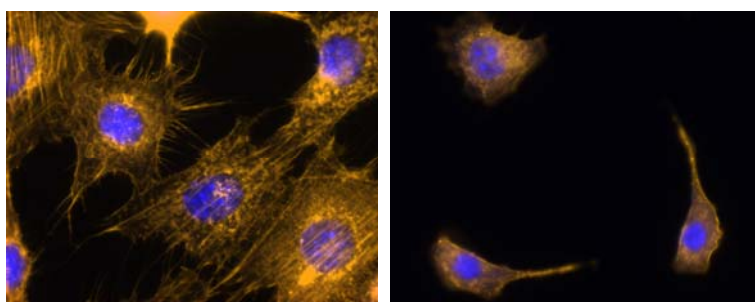
**Objectives:** We pursue the synthesis of complex natural products by largely catalysis-based routes, evaluate their biochemical and biological properties, and investigate possible structure/activity relationships by systematic editing.

**Results:** A concise total synthesis of the highly cytotoxic marine natural products **iejimalide A-D** was developed based on an effective ring closing metathesis (RCM) reaction of a cyclization

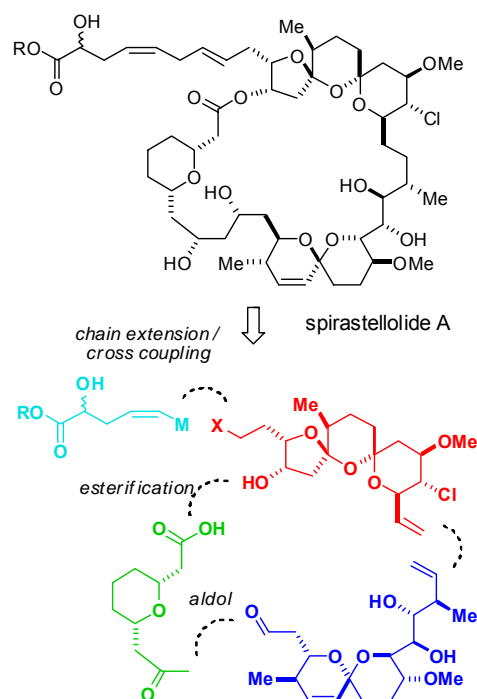


precursor containing no less than 10 double bonds. Because of the exceptional sensitivity of this polyunsaturated intermediate and its immediate precursors toward acid, base and even gentle warming, the assembly process hinged upon the judicious choice of protecting groups and the careful optimization of all individual transformations. As a consequence, particularly mild protocols for Stille as well as Suzuki reactions of elaborate coupling partners have been developed that hold considerable promise for applications in other complex settings. Moreover, a series of non-natural “iejimalide-like” compounds was prepared, in which the entire framework of the natural lead has been systematically edited. With the aid of these compounds it was possible to uncover the previously unknown effect of iejimalide and analogues on the actin cytoskeleton, and their equally unknown capacity to up-regulate caspase-3, a key enzyme of the signal transduction cascade leading to apoptosis. Moreover, our sample collection allowed us to demonstrate the exceptional cytotoxicity of such macrolides against a panel of 36 human cancer cell lines, with the lowest  $IC_{70}$  values reaching the picomolar / low nanomolar range. Since these data suggest that the iejimalides might qualify as lead structures for the development of novel anticancer agents, we actively pursue our investigations of this very demanding class of polyene macrolides.





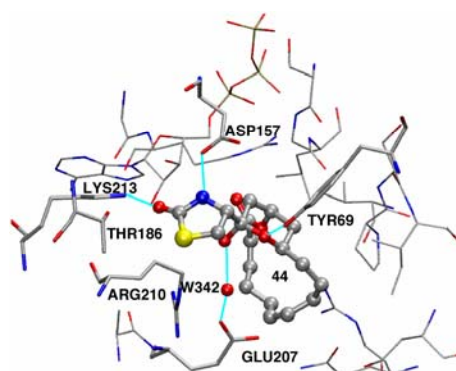
Fluorescence micrographs (250 $\times$ ) of NIH3T3 fibroblasts before (left) and after incubation with iejimalide B (right), showing the actin depolymerization capacity of the macrolide.

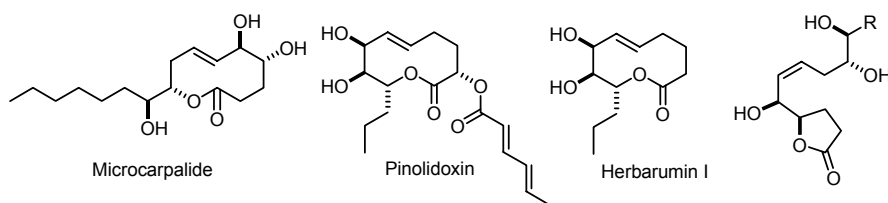


Our studies directed toward **spirastrellolide A** are also quite advanced, although the total synthesis of this protein phosphatase 2A inhibitor of unheard selectivity remains to be completed. This project had to cope with the fact that the stereostructure of the target – containing no less than 21 chiral centers in a 38-membered ring – was yet unknown at the outset of our studies. We managed to develop scaleable and reliable routes to all necessary subunits and have commenced to investigate their assembly. As mentioned in Chapter 2.4.3, however, the envisaged macrocyclization via RCM failed even if the “relay concept” was applied. Therefore we are presently revising the

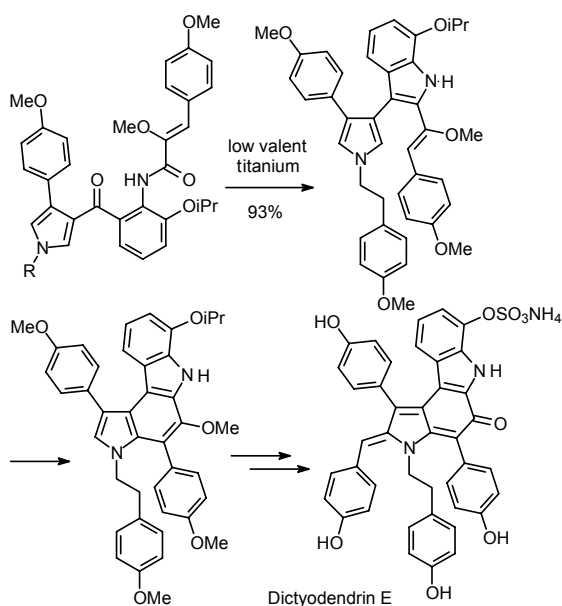
end game based on the intelligence gathered in the exploratory studies.

A particularly fruitful project, that came to an end during the report period, was the targeted pursuit and biochemical evaluation of the **latrunculins** (see also previous report). Alkyne metathesis opened a very satisfactory entry into this product class, which allowed us to prepare a sizeable number of latrunculin-like macrolides with deep-seated structural modifications. Importantly, some of these synthetic analogues turned out to be significantly more active than the natural products themselves in their capacity to depolymerize actin protein filaments in fibroblast cells. With the help of extensive QM/MM calculations performed by the Thiel group have we now been able to provide a rationale for this highly rewarding result.



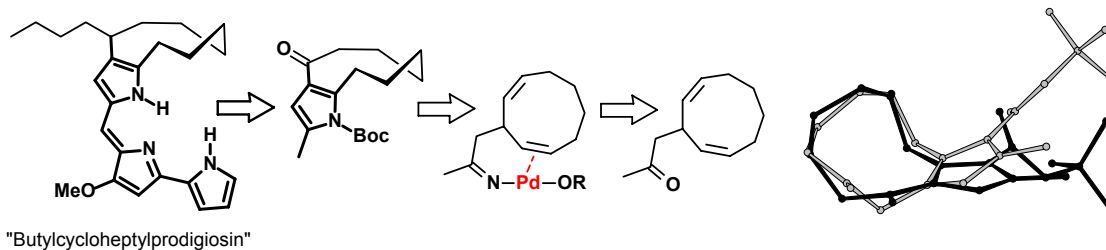


**Microcarpalide** also constitutes a valuable lead in the quest for selective actin binders. Therefore we have developed the most productive synthesis of this nonenolide known to date, and have also demonstrated that related 10-membered lactones and even much simpler butanolides exhibit similar levels of microfilament disrupting activity. Even though somewhat less potent than the best latrunculins, such compounds have the distinct advantage of being much less toxic and may hence be useful entry points for more focused programs in the realm of medicinal chemistry or crop protection.



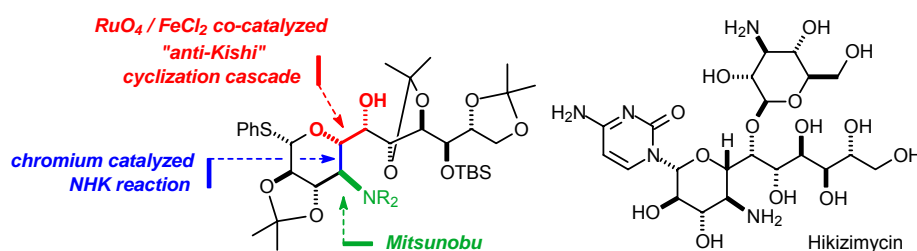
Entirely different challenges were posed by the **dictyodendrins**. These intriguing pyrrolo-carbazole alkaloids are the first telomerase inhibitors isolated from a marine source. Since telomerase is overexpressed in ca. 90% of all malignant tumors, small molecule inhibitors of this key regulatory enzyme are on high demand. With the aid of a titanium-induced reductive indole synthesis, previously developed by our group, followed by an efficient  $6\pi$ -electrocyclization event as the key steps has it

been possible to prepare substantial amounts of three naturally occurring dictyodendrins and a host of synthetic analogues. While the evaluation of their telomerase inhibitory activity is still pending, the pronounced but previously unrecognized capacity of such alkaloids to cleave double stranded DNA was firmly established.



“**Butylcycloheptylprodigiosin**” constitutes another demanding heterocyclic target that came into reach during the report period. Its highly strained *ortho*-pyrrolophane scaffold was accessed by a palladium catalyzed reaction of an oxime ester with a suitably located

olefin in vicinity (Narasaka-Heck reaction) followed by a site-selective isomerization. Many conformational peculiarities of nine-membered cycloalkenes surfaced during this project, an area surprisingly void of secured information prior to this investigation. A small collection of analogues has also been prepared which allowed us to demonstrate that the nuclease-like activity of such alkaloids is innately linked to the presence of an intact tripyrrolic backbone. Furthermore, it was shown that prodigiosins exhibit promising inhibitory activity against various phosphatases, including *Mycobacterium tuberculosis* protein tyrosine phosphatase A, an enzyme believed to be responsible for a complex biochemical mechanism enabling survival of this pathogen in host organisms.



Finally, an unprecedentedly short approach to the 'higher-sugar' core of the complex anthelmintic nucleoside antibiotic **hikizimycin** was developed. Key to success were a chromium-catalyzed Nozaki-Hiyama-Kishi reaction following a protocol previously developed in this laboratory, as well as a dihydroxylation/cyclization cascade co-catalyzed by RuO<sub>4</sub> and FeCl<sub>2</sub>, which seemingly violates established stereochemical rules and outperforms conventional dihydroxylation protocols.

**Future directions:** Identify, synthesize and evaluate (hopefully) relevant targets; prepare functional analogues by structural editing via largely catalysis based routes. Expand the panel of biological assays available to us. It should be emphasized that these projects are particularly labor intense and invariably need long time frames.

**Publications resulting from this research area:** 1, 15, 51, 52, 57, 58, 118, 264, 266, 267, 268, 270, 271, 274, 275, 443, 444, 445, 446, 447, 448, 449, 450, 451

**External funding:** Chemical Genomics Center (MPG), AvH (stipends to M. Domostoj, M. Fenster, G. O'Neil, C. Nevado), Association pour la Recherche sur le Cancer, France (stipend to E. Moulin), Fonds der Chemischen Industrie (stipend to C. Müller), Fonds de Recherche sur la Nature et les Technologies, Quebec (stipend to C. Godbout), NSERC Canada (stipend to M. Tremblay), FWF Austria (stipend to M. Waser), Deutsch-Israelische Projektkooperation (DIP), Merck Research Council

**Cooperations:** H. Waldmann, O. Müller (MPI Dortmund, DE), Oncotest GmbH (Freiburg, DE), W. Gao, Y.-C. Cheng (Yale University School of Medicine, USA)

### 2.4.5 Research Area “Functional (Macro)molecular Architectures“ (S. Hecht)

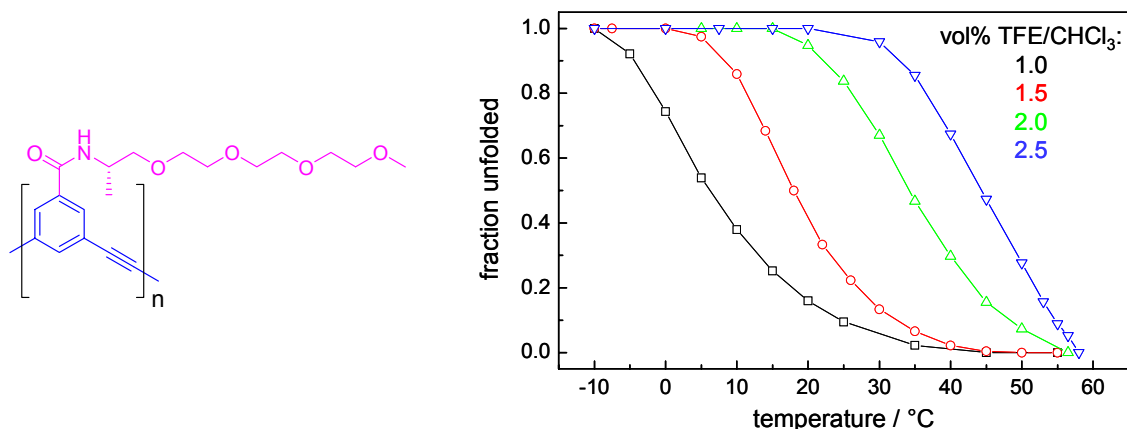
**Involved:** M. A. Balbo-Block, A. Khan, R. M. Meudtner, M. V. Peters, R. S. Stoll, R. Goddard

**Objective:** Our research program aims at developing new chemical approaches to the emerging nanosciences by designing (macro)molecular entities of defined size and shape with desired implemented functionality and external adressability.

#### 1. Tubular and Responsive Foldamers

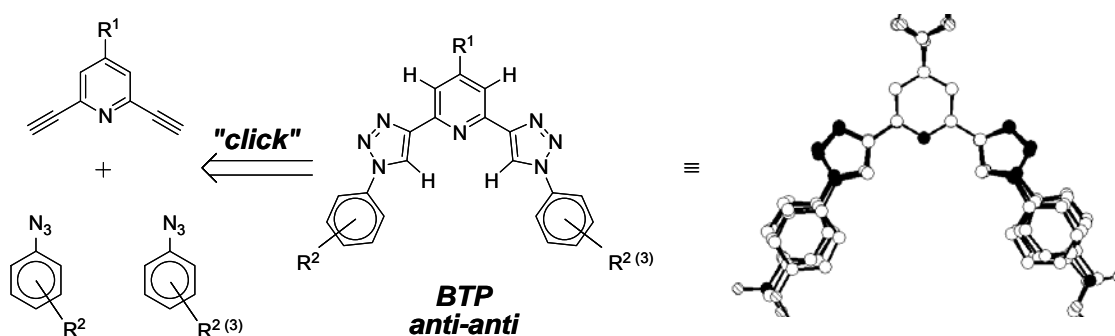
The design of artificial oligomeric and polymeric strands capable of adopting well-defined secondary – and to a certain degree – higher order structures has gained considerable attention in recent years due to the many potential applications of such compounds in both the bio and materials sciences. Our major focus has been on various phenylene ethynylene oligomers and polymers as well as extended heteroaromatic backbones aiming at the design of adressable and regioselectively functionalized organic nanotubes and responsive dynamic systems.

Among the many backbones – so called “foldamers“ – amphiphilic oligo(*meta*-phenylene ethynylene)s offer the important advantage of a void interior, which can be exploited for the design of tubular structures. The advantage over self-assembled structures relies in control over the tube dimensions (inner/outer width as well as length) and their adressability. We have recently developed a novel synthetic route to access lengthy and defect-free poly(*meta*-phenylene ethynylene)s (PmPEs) via an *in-situ* deprotection and Pd-catalyzed Sonogashira-Hagihara polycondensation protocol. After folding the polymeric strand into the corresponding hollow helix, covalent bonds were used to lock the fragile folded equilibrium structure by means of dimeric crosslinks introduced by photodimerization of cinnamates. To overcome the structural perturbation associated with covalent linkage, we have more recently developed non-covalently stabilized nanotubes based on PmPEs with hydrogen-bonding amide based side chains. The polymers form extremely stable helices in various media and show a remarkable thermal renaturation behavior, i.e. “inverse melting behavior“ (Scheme 1), contrasting typical biopolymers such as polypeptides and DNA. The polymers could be prepared with a high degree of polymerization, especially considering the employed step-growth polycondensation methodology, and display a significant persistence length. Furthermore,  $\pi$ -conjugated *ortho*-linked as well as alternating *ortho-para*-linked phenylene ethynylene oligomers and polymers were successfully synthesized.



Scheme 1. PmPE with alanine-derived side chains and unusual thermal renaturation behavior.

To improve the photochemical stability of the foldamer backbone, important for photoswitchable systems (see below), and to introduce responsiveness to chemical stimuli such as changes in pH or metal ion concentration we have engaged in the design of a new family of foldamers based on alternating triazole-pyridine scaffolds. The so called “clickamers“ were readily obtained using modern Cu-catalyzed 1,3-dipolar cycloaddition reactions. Initially, a variety of symmetrical 2,6-bis(1-phenyltriazol-4-yl)pyridines (BTPs) carrying electron-withdrawing and –donating groups at both the terminal phenyl as well as the central pyridine moieties were synthesized. Non-symmetrical derivatives could also be prepared via a repetitive synthesis, which most recently enabled preparation of discrete oligomers up to the pentaicosamer (25mer). Both in solution and in the solid state, the backbone adopts a kinked horseshoe-like *anti-anti* conformation (Scheme 2).



Scheme 2. Retrosynthesis of various BTP derivatives and overlay of single crystal X-ray structural analyses (side chains partially omitted for clarity).

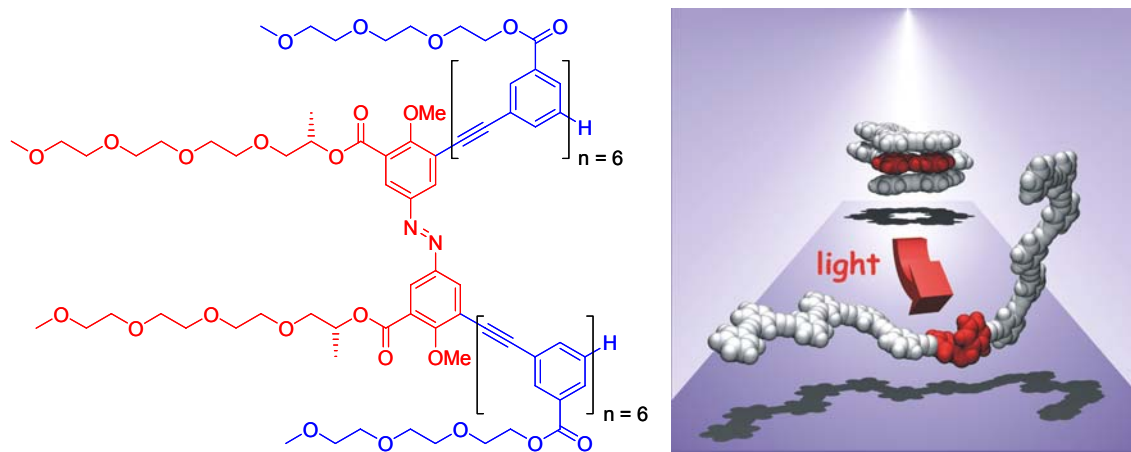
The conformational preference is based on the destabilization of the *syn-syn* conformation due to electrostatic repulsion of the adjacent heterocyclic nitrogen atoms’ lone pairs and steric repulsion of the neighboring *ortho*-hydrogen atoms. The longer oligomers adopt a helical secondary structure in solution and show an unexpected

response, i.e. helix reversal, to pH changes and/or metal ions. The BTP scaffold represents furthermore a new and promising ligand platform as shown by the interesting spin and luminescence behavior of the corresponding iron and europium complexes, respectively.

## 2. Photoswitchable Transporters and Catalysts

The realization of molecular-scale devices is inevitably tied to the design of molecular entities capable of carrying out a desired function ideally under external control. As light represents perhaps the most attractive external stimulus since it is non-invasive and allows for both spatial and temporal resolution, we have engaged in the design of photoresponsive and more precisely photoswitchable systems, offering the advantage of truly reversible behavior. Major focus has been on the design of photoswitchable foldamer hosts and nucleophiles/bases as “smart“ transporters and organocatalysts, respectively. In addition various photoswitches have been investigated on the single molecular and ensemble level on surfaces.

Photoisomerizable azobenzene units were incorporated into the central backbone of a *meta*-phenylene ethynylene oligomer. Due to the attachment of both oligomeric foldamer substrands to the *meta*-positions of the central photochromic azobenzene unit the resulting oligomer adopts a folded conformation in the *trans* form, i.e. “dark state“. Irradiation lead to helix denaturation due to the large structural changes associated with the photochemical *trans*→*cis* isomerization (Scheme 3). This transition is readily reversed by using light of the appropriate wavelength or simply heat.

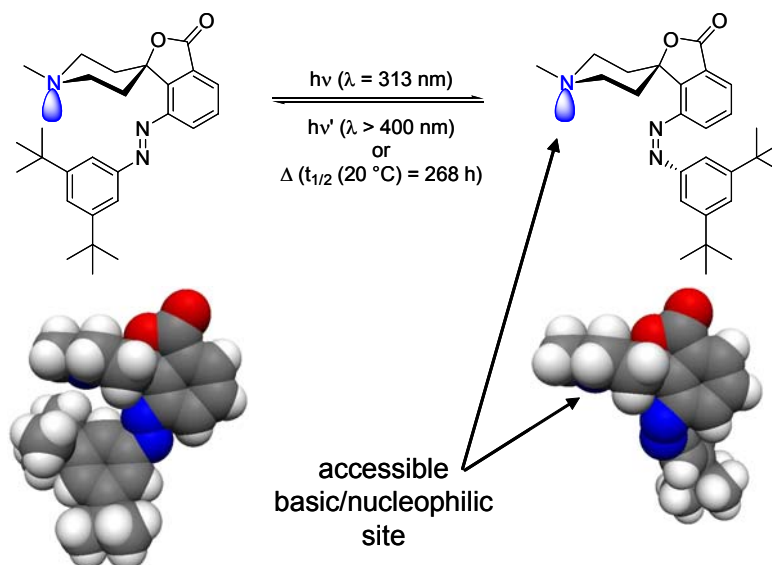


Scheme 3. Structure and illustration of a prototypical photoswitchable foldamer (transporter).

More importantly, we could show that hydrophobic guest molecules can efficiently be encapsulated into the interior of the foldamers host, allowing for the controlled transport of chemical species. Currently, the efficiency and loading capacity of the transporter is

being improved by increasing the azobenzene content – in fact a foldamer family composed entirely of azobenzene units is being synthesized – and extending to a polymeric system.

Photoisomerizable azobenzene units have also been utilized to reversibly shield a reactive site, therefore enabling the design of photoswitchable catalysts. While initial attempts to design photoswitchable metalloporphyrins failed due to detrimental energy transfer from the azobenzene to the metalloporphyrin inhibiting photoisomerization, a first successful example is based on a spiro-fused N-alkylated piperidine (Scheme 4). In the *trans*-isomer the sterically bulky azobenzene efficiently shields the axial lone-pair of the piperidine nitrogen atom. Irradiation leads to a large structural reorganization and enables access to the basic/nucleophilic site in the *cis*-isomer. Indeed, in the nitroaldol reaction (Henry reaction) of 2-nitroethane and 4-nitrobenzaldehyde the irradiated catalyst showed an approximately 10-fold increased activity. While this catalyst potentially allows for temporal and spatial control over catalysis – in particular interesting in the context of polymerization catalysis – the system is currently being improved by varying the substitution pattern on the azobenzene fragment, the piperidine nitrogen atom, and the lactone moiety.



Scheme 4. Photoswitchable organocatalyst (single crystal X-ray structural analysis for the *trans*-isomer and DFT model for the *cis*-isomer) employed in a nitroaldol, i.e. Henry reaction.

**Publications resulting from this research area:** 8, 9, 71, 72, 86, 87, 209, 218, 299, 300, 301, 302, 339, 340, 481, 532, 541

**External funding:** DFG

**Cooperations:** M. Bühl (Mülheim/Ruhr, DE), L. Grill (FU Berlin, DE), J. P. Rabe (HU Berlin, DE)