Organometallic Chemistry

The research in the Department of Organometallic Chemistry is focused on the development and understanding of organometallic catalysts, as well as on their application to advanced organic synthesis. Since Professor Fürstner was appointed Director in 1998, the Department has grown to its current size and has hosted several young scientists at the outset of their independent academic career (Professor Frank Glorius, 2001-2004; Professor Stefan Hecht, 2005-2006; Dr. Lisbet Kværnø, 2007-2008; Dr. Manuel Alcarazo, 2009-).

Dr. Lisbet Kværnø joined us in September 2007 as a "Max Planck Independent Research Group Leader" after she had finished her postdoc under the guidance of Professor D. A. Evans, Harvard University. For private reasons however, she decided not to pursue an academic career any further and left the Institute already in May 2008 to take up a position in industry. Her coworkers were integrated into the Fürstner group.

In December 2008, Dr. Manuel Alcarazo was appointed as a new junior research group leader. After a very successful postdoctoral stint with Professor Fürstner, with whom he had worked on the total synthesis of marine oxylipins as well as on the design of new ligands for homogeneous catalysis, Dr. Alcarazo won a prestigious "Ramon-y-Cajal" fellowship to start a research group in Spain. However, he accepted our offer to stay in Mülheim as an independent group leader. His research is currently focused on the coordination chemistry of main group elements in unusual oxidation states, the design of novel "frustrated Lewis pairs", and applications thereof to homogeneous catalysis and organic synthesis.

The major lines of Professor Fürstner's own research can be summarized as follows:

- The development of catalysts based on cheap, non-toxic, benign and readily available transition metals as substitutes for traditional noble metal complexes. Although not limited to, iron catalysis is prominently featured in this context. Particular attention is paid to the development of iron catalysts for cross coupling, cycloisomerization reactions, cycloadditions of unactivated substrates, and carbometalations of π-bonds. Considerable efforts are made to identify, isolate and characterize highly reactive organoiron intermediates to gain an understanding for the largely unknown mechanistic basis of such iron-catalyzed C-C bond-forming reactions.

- Catalysis based on the activation of π-systems with the aid of carbophilic Lewis acids such as Pt(2+) and Au(1+) has gained considerable momentum. Except for a few pioneering studies, this field was virtually inexistent until the late 1990's but is currently one of the most rapidly growing areas of homogeneous catalysis. As early as 1998, the Fürstner group proposed a unifying mechanism, which guided our investigations during the last decade. This hypothesis-driven approach led to the discovery of several new reactions, some of which have already been successfully applied to natural product synthesis. Moreover, we are dedicated to the characterization of pertinent reactive intermediates and the development of practical asymmetric variants.
- Significant efforts were made over the years to showcase the complementary logic of olefin metathesis and exploit its exceptional performance in advanced organic chemistry. We also wish to extend metathesis beyond its traditional scope. In this context, the group is committed to upgrade alkyne metathesis to a broadly applicable and user-friendly transformation, and to illustrate the remarkable scope of this reaction by applications to structurally complex and biologically relevant targets.
- The group is interested in developing concepts, which eventually allow one to replace notoriously stoichiometric reactions of proven versatility by catalytic processes (e.g. NHK reactions catalytic in chromium, carbonyl coupling catalytic in titanium etc.)
- An additional line of research implemented during the report period concerns the development of novel ligand architectures. Starting from conventional N-heterocyclic carbenes (NHC's), we proposed alternative design principles for (stable) singlet carbenes and also ventured into the coordination chemistry of formally zerovalent carbon. These investigations in the Fürstner laboratory are nicely complemented by the independent work of the Alcarazo group on nitrogen(+1)- or phosphorous(+1)-based ligands and novel frustrated Lewis pairs.

A significant part of our work is dedicated to the application of organometallic catalysis to the total synthesis of structurally complex natural products of biological significance; where indicated, we are also committed to prepare analogues by "diverted total synthesis" for further evaluation. From the chemical viewpoint, all projects intend to scrutinize the synthetic methods of interest to the Department. We wish to develop syntheses that are concise, convergent, productive and scalable; ideally, they should be largely catalysis-based and require a minimum of protecting group manipulations. With

regard to the targets, our choice is based on considerations of structural complexity, the biological activity, and the non-availability of meaningful amounts from the natural sources. Biological assessments of the compounds prepared in the laboratory are carried out in close collaboration with external academic and industrial partners. This includes contacts to the Chemical Genomics Center (CGC) of the MPG, of which Professor Fürstner is a founding member.

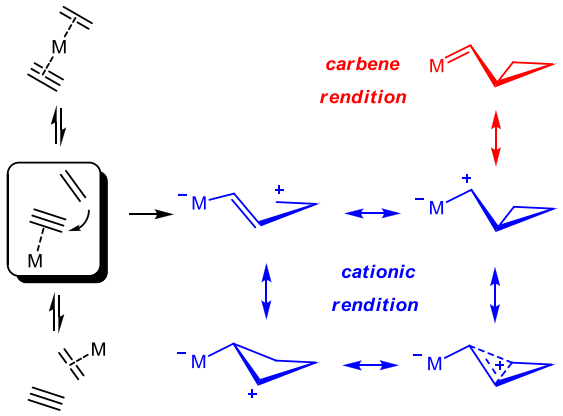
In many projects we enjoyed close collaborations with Professor Thiel and coworkers, who provided complementary insights into reactive intermediates, bonding modes and reaction mechanisms based on high-level computational methods. In certain cases, the Thiel group also helped with conformational analyses of complex macrocyclic target molecules. This mutually beneficial work has resulted in several joint publications during the reporting period.

Finally, it is emphasized that the research carried out in the Department would not be possible without the constant and excellent support by the analytical groups of the Institute. This invaluable input is reflected by the fact that various service group leaders and –members are coauthors of several published and forthcoming papers.

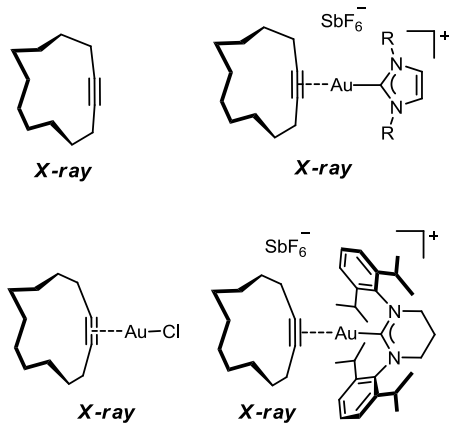
2.4.1 Research Area "π-Acid Catalysis" (A. Fürstner)

Involved: M. Alcarazo, S. Flügge, L. Morency, A. Schlecker, G. Seidel, T. Stork, H. Teller

Objective: During the last decade it became increasingly clear that the use of π-acids such as Pt(2+) or LAu(1+) provides tremendous opportunities for homogeneous catalysis and advanced organic synthesis. Guided by our own early mechanistic proposal, we continue to develop new Pt- or Au-catalyzed transformations and try to unravel the basis for the observed reactivity at the molecular level.

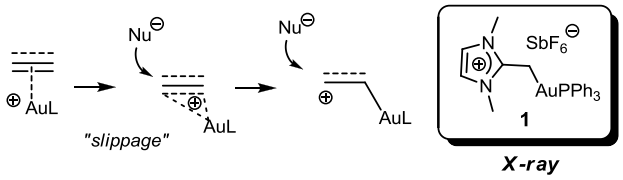


Results: In 1998, our group was the first to interpret skeletal rearrangements induced by carbophilic noble metal catalysts in terms of a unifying mechanism. It was proposed that activation of only one of the π-systems of the substrate(s) (here the alkyne) suffices to trigger the reaction, as the resulting complex is sufficiently deprived of electron density to experience attack by an appropriate nucleophile (here an alkene). The resulting net *trans*-addition product can formally be depicted as a non-classical cation in the coordination sphere of the metal or as an electrophilic metal carbenoid, if back-donation of electron density from the metal to the ligand plays a role. This proposal was speculative at the time but allowed many predictions to be made that could be experimentally probed. Although numerous calculations at different levels of theory published in the literature have addressed various aspects of this generic mechanism, the reactive intermediates themselves largely elapsed experimental characterization.

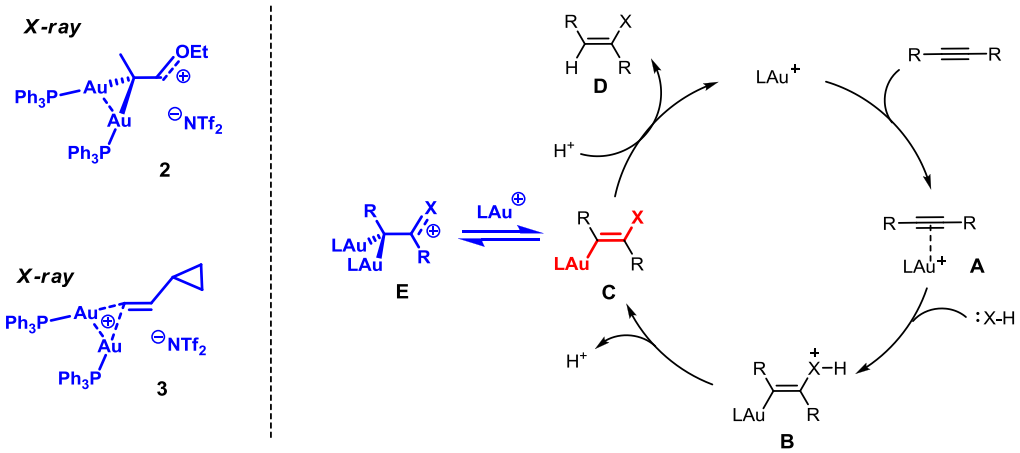


For example, only a very limited number of gold-alkyne complexes had been known at the outset of the project. During the report period, we managed to obtain a complete set of NMR- and crystallographic data for cyclododecyne as a prototype free ligand, the derived neutral [cyclododecyne·AuCl] complex, as well as for two

cationic [cyclododecyne·AuNHC]$^+$ complexes. These results allowed the changes to be studied in detail which different gold fragments impose onto the π-system. Comparisons with high-level DFT calculations carried out by the Thiel group led to valuable insights into the first step of a noble metal-catalyzed transformation.

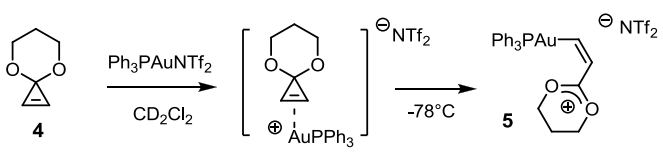


The second step of the generic mechanism consists of the attack of a nucleophile onto the π-complex. Literature reports had suggested that this process requires slippage of the metal along the ligand axis. We were able to provide experimental support for this notion; specifically, a series of gold complexes of diaminoalkenes was isolated, in which the reactivity of the nucleophile was trimmed down to that of a hardly coordinating counterion. X-ray crystallography revealed that the slippage process may even reach the extreme of an end-on coordination mode prior to reaction with the nucleophile. Although the heteroelement substituents in complex **1** are certainly non-innocent, this and related examples showed that the entire positive charge can be transferred from the catalyst to the π-system when functionalized substrates are used.

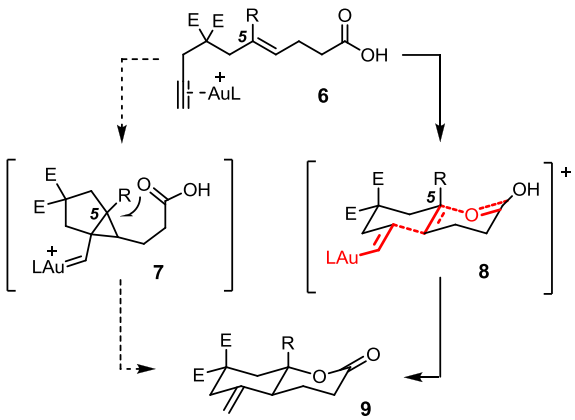


A remarkable result concerns the protodemetalation of the alkenylmetal species **B** formed upon net *trans*-addition of a protic nucleophile HX to an alkyne. It is generally assumed that simple loss of the proton followed by rapid protodeauration of **C** releases product **D** and regenerates the catalyst. By considering the isolobal relationship between H^+ and LAu^+ however, one may speculate that the catalyst itself could also (reversibly) incept **C** to give complexes of type **E**. Such a pathway might seriously compete with protodeauration given the affinity of the carbophilic transition metal to the π–bond. Although *gem*-diaurated species had previously been proposed in the literature, we were

the first to isolate and fully characterize two such complexes. At first sight, the structures of **2** and **3** in the solid state seem very similar; a closer inspection, however, revealed a surprisingly different bonding situation. In case of complex **2**, the C1-C2 bond is long whereas the C2-O bond is short, which implies net transfer of the charge from Au to the ligand; **2** is hence best described as consisting of an oxo-carbenium center flanked by a *gem*-diaurated site. In contrast, complex **3** contains a short olefinic C1-C2 bond and a regular C2-C3 single bond, suggesting that a non-classical three-center/two-electron bonding motif [Au_2C] must be present, which largely retains the positive charge. The ease with which complexes **2** and **3** could be made and their surprising stability insinuates that *gem*-diauration may play a much larger role in gold catalysis than previously recognized. We are currently investigating possible implications for catalyst optimization and asymmetric synthesis.

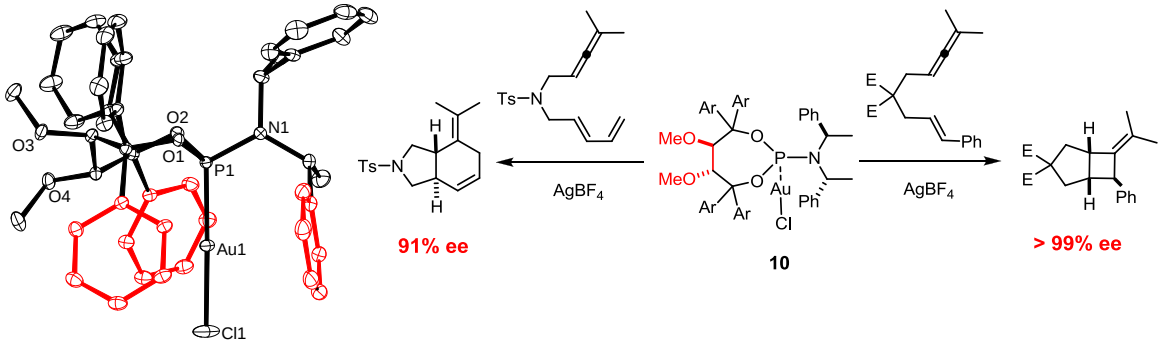


Our early mechanistic proposal had already pointed out that some reactive intermediates involved in platinum- or gold catalysis may be regarded as highly electrophilic metal "carbenoids" endowed with considerable "non classical" carbocation character. The argument was later simplified by others to the concept of "gold carbenes", which became invasive. Convinced that this description may not be fully adequate, experiments were devised to probe the character of the reactive intermediates in more detail. To this end, cyclopropenes such as **4** were reacted with LAu^+ fragments since the rearrangement of strained rings constitutes a well known entry into metal carbene complexes. In the case of gold, however, detailed NMR investigations showed that the resulting product **5** is a regular vinylgold species carrying the positive charge at a remote carbocationic site. In the ground state, the double bond character of the Au–C bond is marginal, with a rotational barrier as low as 30 $kJ \cdot mol^{-1}$ (which is less than the "double bond" character of the Ph–CHO bond in benzaldehyde and only one third of the double bond character of an amide bond). Although one may again argue that the substituents in **4** are not innocent, these data highlight the very strong bias for charge transfer from the metal to functionalized ligands.

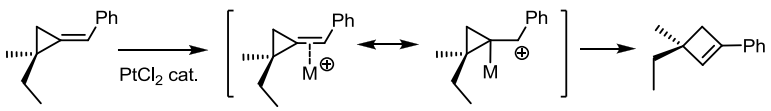


Additional information on the character of the reactive intermediates was deduced from reactivity data. Specifically, we could demonstrate that gold catalyzed

cycloisomerizations of enyne-carboxylic acid derivatives such as **6** are highly concerted processes, which follow the logic of the "Stork-Eschenmoser paradigm" of cationic polycyclizations. At least for substrates of this type, the outcome of the reaction is best explained by assuming highly delocalized charge density in the reactive intermediates (or transition states) rather than intervention of regular cyclopropyl gold carbenes.

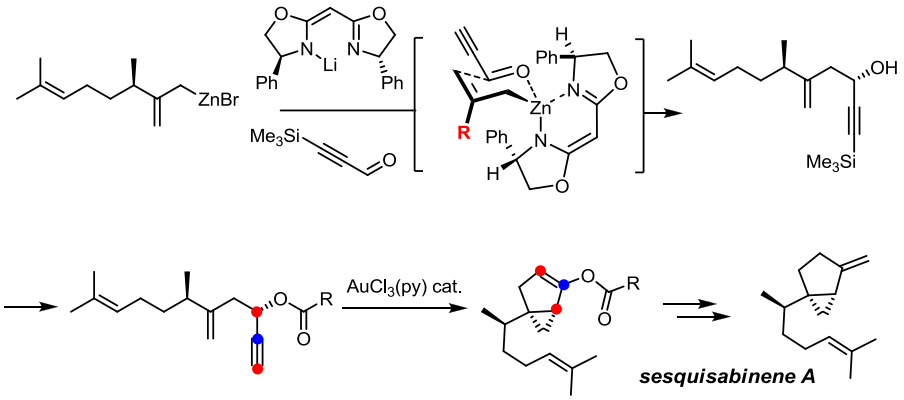


Asymmetric gold catalysis copes with the problem that the chiral ligand L* is located opposite to the substrate and is attached to the gold center via one-point binding. The rotational freedom of the L*–Au bond and the long distance render the effective transfer of stereochemical information highly challenging. Although several promising solutions were published in recent years using sophisticated ligands or chiral counterions, our group seeks to develop a less expensive alternative approach. It is based on the idea that free rotation about the L*–Au axis might be inconsequential if the crafted chiral environment is degenerate. In an attempt to reduce this design principle to practice, we developed a new type of TADDOL-based phosphoramidite with an open backbone. Despite an extensive literature, TADDOL's devoid of an acetal substructure have never been used in asymmetric catalysis before. X-ray diffraction studies showed that the derived phosphoramidites such as **10** craft a tight and highly C_3-symmetric chiral pocket about the coordinated gold center. Several applications to cycloaddition reactions led to high and, in part, unprecedented levels of chiral induction.



In parallel work, our group keeps exploring the preparative scope of noble metal catalysts. In collaboration with the group of Professor Marek at the Technion, Haifa, we were able to show that enantiomerically pure alkylidenecyclopropanes undergo ring expansion with retention of stereochemical integrity in the presence of catalytic $PtCl_2$. This method

allows cyclobutenes carrying quaternary chiral centers to be prepared in optically pure form, which are difficult to make otherwise.



We had previously proposed that propargyl esters, upon activation with π–acids, constitute stable synthetic equivalents of α–diazoketones. This notion was illustrated by a concise entry into cedrene, cedrol and no less than 10 terpenes of the sesquisabina- and sesquithuja families. Only the constitution of these latter compounds had been known at the outset; our stereochemically unambiguous synthesis allowed us to define the absolute and relative configurations of these olfactory natural products.
For additional studies on the control of gold catalyzed reactions with the aid of NHC ligands of different π–acceptor qualities, see Chapter 2.4.4.

Publications resulting from this research area: 29, 35, 36, 176, 178, 210, 258, 287, 398, 409

External funding: Fonds der Chemischen Industrie (stipends to S. Flügge and H. Teller); German-Israeli Project Cooperation (DIP); NSERC Canada (stipend to L. Morency); Spanish Ministerio de Educación y Ciencia (stipend to M. Alcarazo)

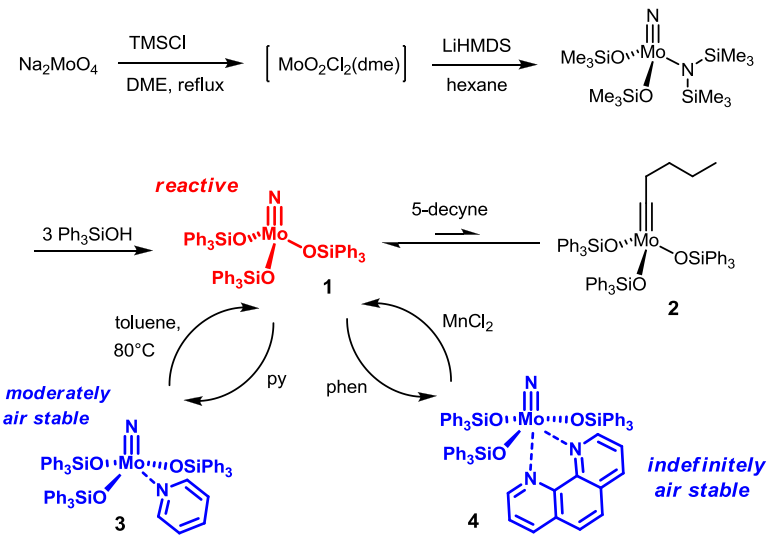
Cooperations: I. Marek (Haifa, IL); B. List, W. Thiel (Mülheim/Ruhr, DE)

2.4.2 Research Area "Metathesis" (A. Fürstner)

Involved: M. Alcarazo, M. Bindl, D. A. Clark, E. Heilmann, J. Heppekausen, V. Hickmann, A. Kondoh, K. Micoine, A. Picot, R. Stade

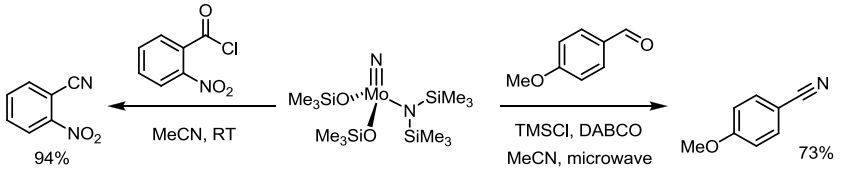
Objectives: Olefin metathesis has revolutionized organic synthesis during the last decade. While we continue to apply this transformation in our synthetic programs (see Chapter 2.4.5), our focus in metathesis research has shifted toward alkyne metathesis, for which we present user-friendly and exceptionally potent new catalysts.

Results: The first recorded examples of alkyne metathesis relied on the use of catalysts generated in situ from simple ingredients following empirically optimized recipes. Although these procedures are operationally simple, they require harsh conditions and are therefore of limited preparative value. It was only after the advent of defined high-valent metal alkylidyne complexes ("Schrock alkylidynes") that the full potential of this transformation could be exploited. Such complexes however, require careful handling under inert conditions; this may be one of the reasons why alkyne metathesis has not nearly become as popular as its alkene counterpart in the synthetic community. Our group is committed to change this situation by developing user-friendly catalysts and demonstrating their performance in synthesis.

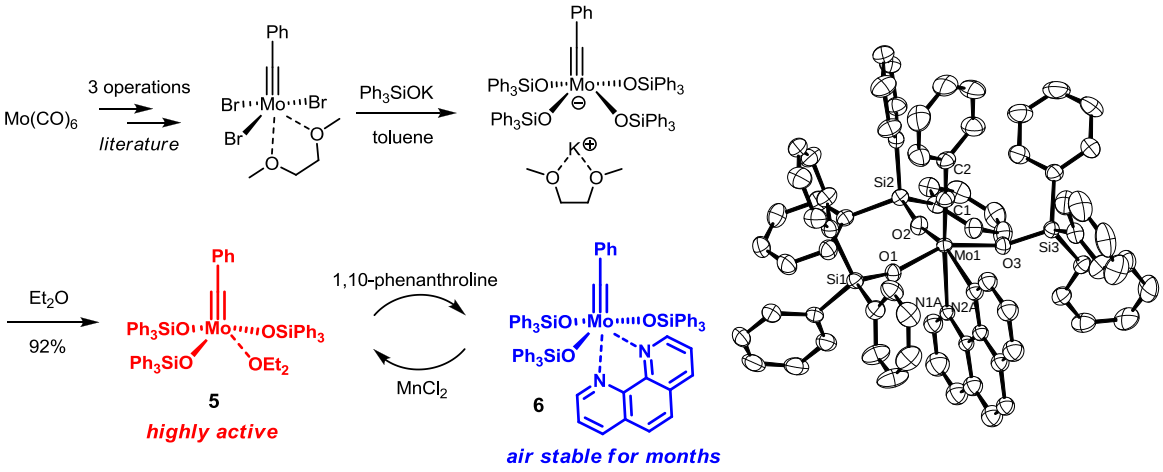


Inspiration was provided by a literature report, which showed that certain metal nitride complexes endowed with fluorinated alkoxide ligands, on treatment with sacrificial alkynes, equilibrate with the corresponding metal alkylidynes. However, the preparation of the required nitride precursor complexes was deemed unsatisfactory, not least because it involved potentially hazardous steps (azide chemistry). In a quest for more attractive alternatives, we were able to establish a much safer, quicker and scalable route to Mo-nitrides starting from inexpensive sodium molybdate. Moreover, we could show that triphenylsilanolate is a

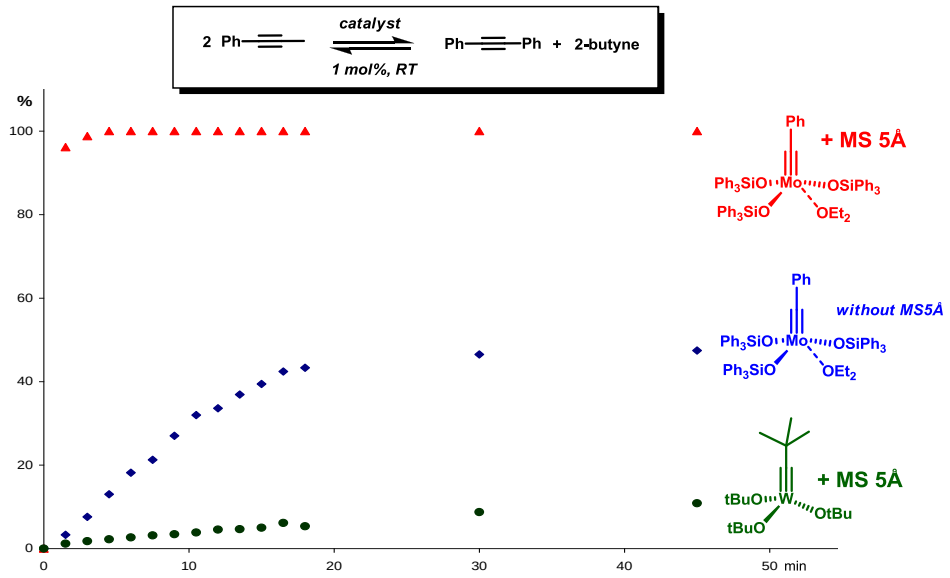
cheap and favorable substitute for the perfluorinated alkoxides previously used. The pyridine adduct **3** is sufficiently stable to be handled in air, yet reverts to the active species **1** at 80°C. The phenanthroline adduct **4** is indefinitely air stable. Although solutions of **4** themselves are inactive, addition of $MnCl_2$ engenders a ligand swap and thereby restores the catalytic performance. Mixtures of catalytic **4**/$MnCl_2$ (or other phenanthroline traps) gave excellent yields in alkyne metathesis reactions of all kinds and showed remarkable compatibility with a host of polar functional groups. So far, only acid chlorides and aldehydes were found to react with such molybdenum nitrides to give the corresponding nitriles (in the case of aldehydes by a mechanistically not yet fully understood redox process).



Despite the efficiency of **1** as precatalyst, the crucial equilibrium between **1** and the derived alkylidyne **2** clearly lies on the side of the nitride. This result suggested that the small amounts of **2** produced in situ must be superbly active. As a consequence, we prepared a series of previously unknown molybdenum alkylidynes of the general type $(Ph_3SiO)_3Mo{\equiv}CR$ (e.g. **5**) in pure form by adaptation of well established literature routes. These complexes were found to combine truly outstanding reactivity with a remarkable chemoselectivity profile; they clearly outperform all other alkyne metathesis catalysts previously tested in this laboratory. Equally rewarding is the fact that addition of 1,10-phenanthroline leads to an adduct of largely improved stability. Complex **6** can be stored in air for weeks without any signs of hydrolysis or degradation. Although solutions of **6** themselves do not induce metathesis, the highly active **5** is regenerated with $MnCl_2$ as a cheap, non-hygroscopic, hardly Lewis-acidic and benign additive.



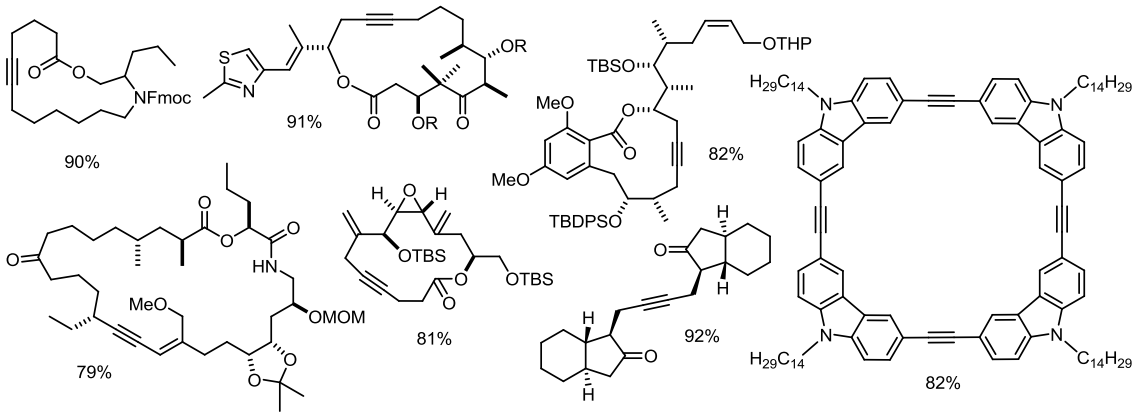
The distorted structure of **6** in the solid state explains the ease with which the phenanthroline ligand can be pulled off the Mo(6+) center. Likewise, the available data suggest that pending of the Mo–O–Si angles is facile. The resulting "flexible bulk" ensures the necessary space for substrate binding but protects the complex against bimolecular decomposition pathways. The only weakly donating Ph_3SiO-ligands impart a well-balanced level of Lewis acidity onto the d^0-molybdenum center, which ensures high activity and tolerance to polar substituents alike.



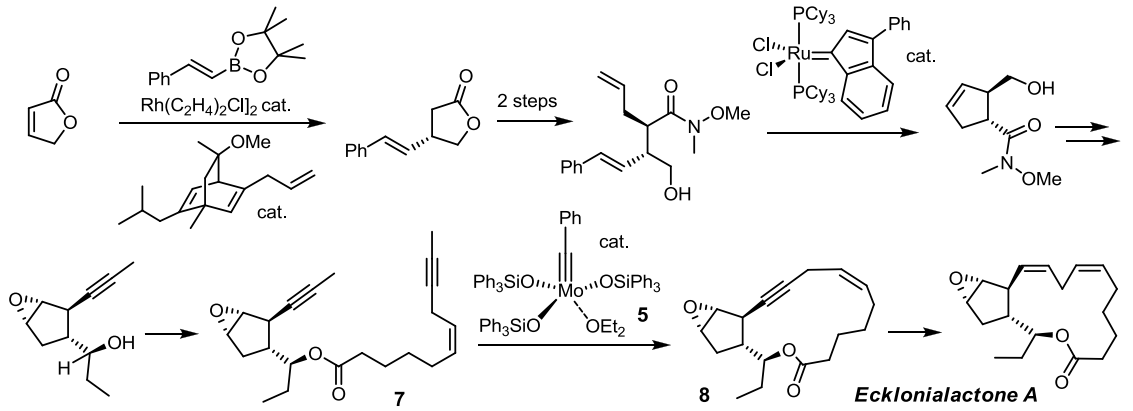
A priori, alkyne metathesis reactions of non-terminal alkynes lead to an equilibrium, which is traditionally shifted toward the products by driving the 2-butyne by-product out of the mixture at higher temperatures. Since complex **5**, however, effects the reaction at ambient temperature or even below, it was necessary to find another way to render the reaction productive in preparative terms. The addition of powdered MS 5 Å to the mixtures constitutes a simple and effective solution. In the presence of this additive, which traps the released butyne in its pores, alkyne metathesis reactions proceed with unprecedented rates under notably mild conditions. Although not yet fully optimized, 0.1 mol% of **5** were shown to ensure quantitative conversions at ambient temperature within short periods of time.

The compatibility of the new (pre)catalysts **3**, **4**, **5** or **6** with various functional groups is outstanding. Esters, ethers, various silyl ethers, thioethers, sulfonates, amides, carbamates, ketones, acetals, epoxides, nitro- and trifluoromethyl groups as well as various types of aromatic heterocycles (pyridine, thiophene, thiazole, carbazole) are well tolerated; nitriles are at least kinetically stable. Chiral centers next to an enolizable carbonyl group were not racemized, and elimination-prone primary tosylates as well as

acid- and base-sensitive aldol substructures remained intact. Although the orthogonal character of alkene- and alkyne metathesis had already previously been recognized, the rigorous distinction between the π-systems of alkynes and olefins is noteworthy: olefins are inert, independent of whether they are mono-, di- or trisubstuted, terminal, internal, or conjugated to a carbonyl group. A few representative products formed with the aid of these catalysts by inter- or intramolecular alkyne metatheses are shown below.

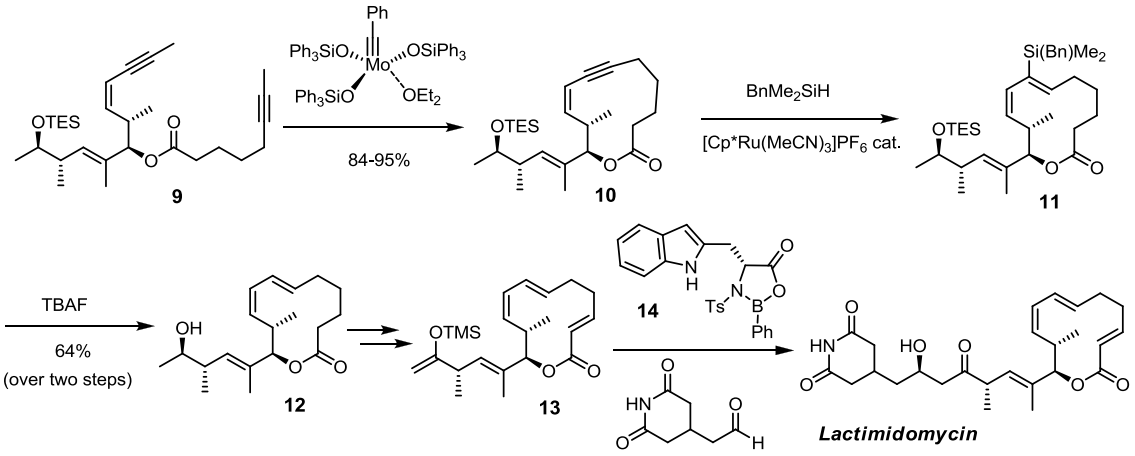


Our synthetic programs have already benefitted from these novel tools. Specifically, we developed a protecting group-free and catalysis-based total synthesis of the marine oxylipins of the **ecklonialactone** family. However, the projected RCAM of diyne **7** containing an unusually sensitive oxirane ring was unsuccessful when the traditional alkyne metathesis catalysts were used. Only complex **5** gave the desired cycloalkyne **8** in well reproducible 80% yield. This favorable outcome is ascribed to the tempered Lewis acidity of the catalyst as well as to the poor nucleophilicity of the peripheral silanolates. Semi-reduction of **8** then completed the total synthesis of ecklonialactone A.



A recent total synthesis of the potent cell migration inhibitor **lactimidomycin** features the stereocomplementary approach to *E*-alkenes via an alkyne metathesis/semi-

reduction sequence. The highly strained 12-membered 1,3-enyne **10** could be formed in excellent yield on a multigram scale with complex **5**. A subsequent ruthenium-catalyzed *trans*-hydrosilylation followed by protodesilylation of the resulting alkenylsilane **11** gave the 1,3-diene **12**. Its further elaboration to the target involved an oxidative enoate formation and a highly diastereoselective Mukaiyama aldol reaction as the key steps. Since lactimidomycin effectively reduces the motility of cancer cells, this compound holds considerable promise as a lead for the development of anti-metastatic drugs.



Other projects based on the use of alkyne metathesis completed during the report period concerned the preparation of all stereomers of the cytotoxic marine macrolide **amphidinolide V** as well as the total synthesis of the exceptionally potent F-ATPase inhibitor **cruentarin A** and a small collection of designer analogues. In both cases, the synthetic work was complemented by biological and biochemical evaluations of these natural products.

Publications resulting from this research area: 157, 158, 181, 319, 320, 362

External funding: Alexander von Humboldt Foundation (stipend to D. A. Clark)

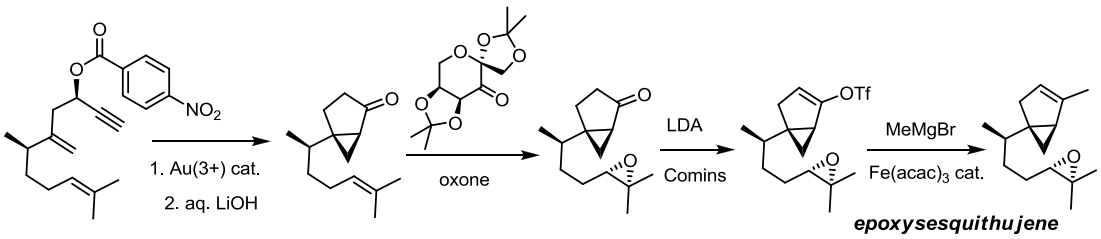
Cooperations: none

2.4.3 Research Area "Iron Catalysis" (A. Fürstner)

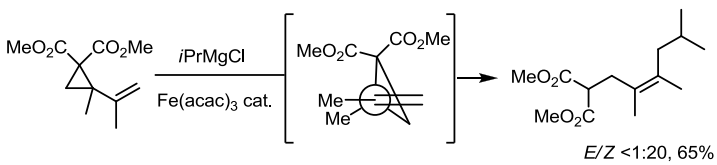
Involved: H. Krause, D. Laurich, A. Moyeux, A. Schlecker, B. D. Sherry, M. Sircoglou

Objective: The noble metals dominate a significant part of contemporary catalysis research despite of the high price, the need for expensive ligands, toxicity issues and environmental concerns. We are interested in emulating "noble" behavior by non-noble metals in a quest for more affordable and sustainable methodology.

Results: Inspired by pioneering studies of Kochi et al. published in the 1970's, our group has explored the preparative scope of iron catalyzed cross coupling reactions in some detail. Specifically, we showed that iron salts allow various types of (challenging) substrates to be activated under notably mild conditions (aryl chlorides, aryl tosylates, alkyl halides, alkynyl epoxides, enol triflates and –phosphates, acid chlorides, thiolesters etc.), yet is compatible with many functional groups. Such transformations are compliant with scale-up and have already been used with considerable success in other academic and industrial laboratories. An Account describing the current status of the field was published in the reporting period.

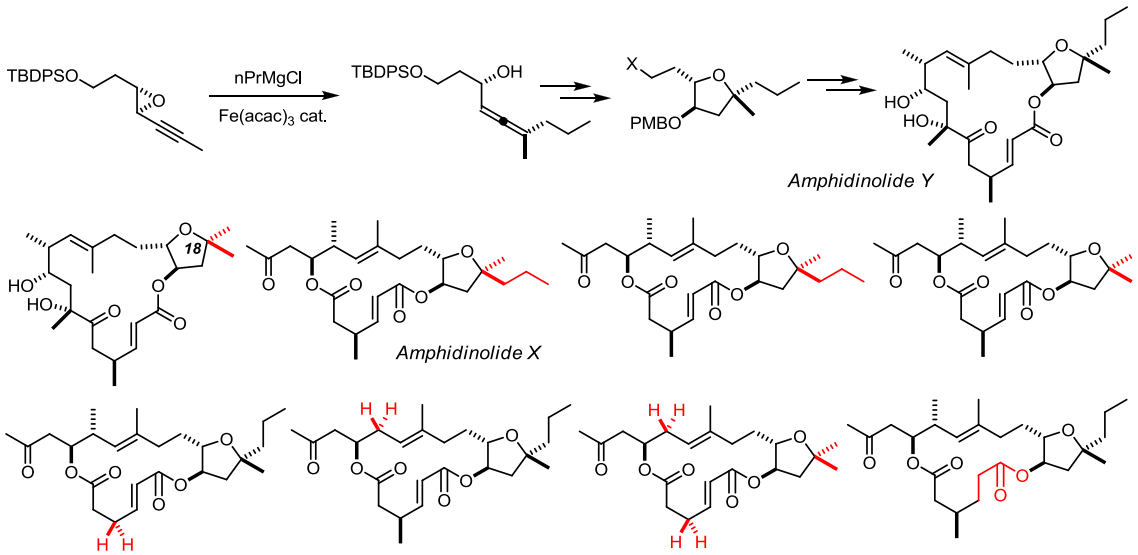


An illustrative example comes from our recent total synthesis of epoxysesquithujene, an ingredient of the essential oil of Asian *Valeriana* species. This application showed that the iron catalyzed coupling of an enol triflate leaves an adjacent cyclopropyl group as well as a reactive epoxide untouched. Based on this favorable outcome, all possible diastereomers could be formed without undue effort, which allowed us to assign the previously unknown stereostructure of this natural product as shown in the Scheme.



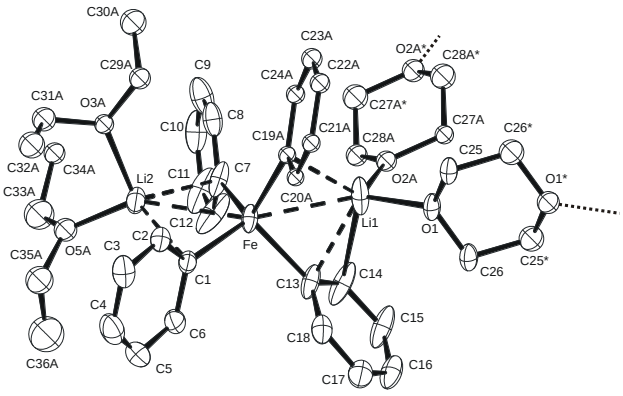
An unprecedented iron catalyzed transformation was found in the highly regioselective addition of

branched primary, secondary or even tertiary Grignard reagents to activated alkenylcyclopropanes. Compelling evidence for a direct addition mechanism as opposed to a single electron transfer- or an iron-allyl based process was obtained.



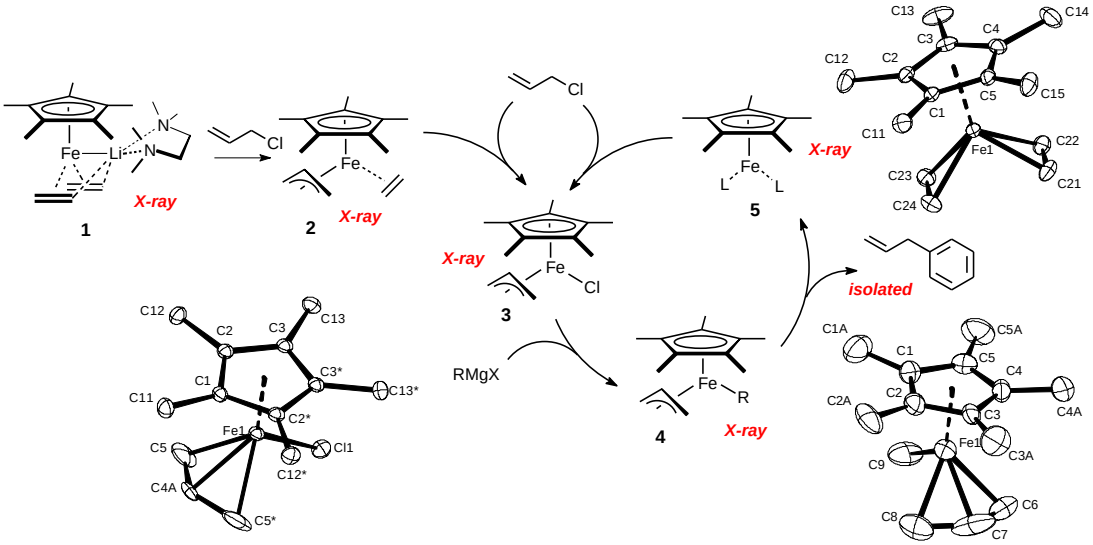
The iron catalyzed ring opening of propargyl epoxides with formation of allenes had previously served as a key step in our total synthesis of amphidinolide X and Y. In view of the promising cytotoxic activity of these extremely scarce macrolides, we now prepared a focused “library” of analogues for biological investigations, which were carried out in collaboration with a partner specialized in oncology. Ongoing projects intend to further illustrate the advantages of iron catalysis by practical and saleable syntheses of economically relevant compounds and by the preparation of structurally complex polycyclic natural products from the bis(bibenzyl) series.

In contrast to the mechanisms of traditional cross coupling reactions using palladium- or nickel catalysts, which have been extensively studied over the years, the understanding for iron catalysis is in its infancy. Therefore, our investigations into this largely void area of organometallic chemistry were extended during the report period. It becomes increasingly clear that iron catalyzed cross coupling reactions can follow at least two distinctly different mechanisms:

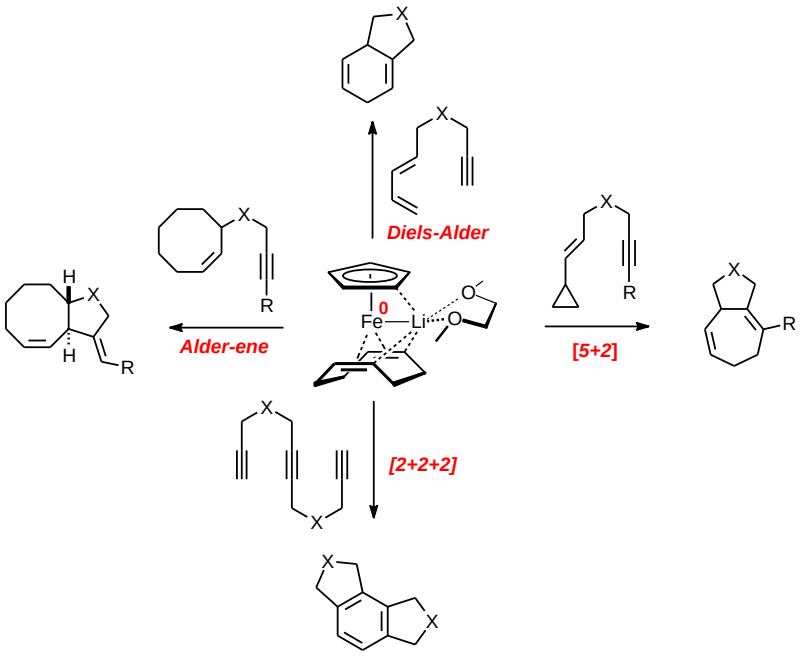


Iron catalyzed reactions of nucleophiles, which are unable to undergo β-hydride elimination,

most likely involve organoferrate complexes as the pertinent reactive intermediates. This notion had previously been supported by the isolation of the exceptionally sensitive and structurally unique "super ate" complex $[(Me_4Fe)(MeLi)][Li(OEt_2)]_2$. During the report period, we were able to gain further experimental evidence for the ferrate manifold by full characterization of $[Ph_4Fe][Li(Et_2O)_2][Li(1,4\text{-dioxane})]$, an equally pyrophoric species formed from $FeCl_2$ and PhLi. These structurally defined ate-complexes react with activated electrophiles such as acid chlorides, enol triflates or alkyl halides, but are unable to engage with aromatic substrates.



Iron catalyzed reactions of aryl chlorides and related electrophiles proceed via redox cycles. Since the active iron catalysts produced in situ from $Fe(acac)_3$ and RMgX themselves are ill defined and hardly amenable to mechanistic study, we used formally low-valent but well characterized iron complexes such as **1** for our mechanistic investigations. Control experiments made sure that **1** and related species themselves are catalytically competent. They react with prototype substrates such as chlorobenzene or allyl halides to give the regular insertion products. Surprisingly, however, excess substrate engenders a subsequent single electron oxidation (**2** → **3**); the resulting Fe(3+) species are amenable to transmetalation to give diorganoiron intermediates of type **4**, which, upon reductive elimination, release the product together with formally monovalent Fe-complexes such as **5**. As **5** is able to insert into the substrate, a basic catalytic cycle is closed. Despite their very high sensitivity, all intermediates of this scenario were unequivocally characterized by X-ray crystallography. Moreover, we started collaboration with Professor Wieghardt in an attempt to gain further insights by Mössbauer and/or EPR spectroscopy.



Our investigations into iron catalyzed cycloaddition and cycloisomerization reactions have also flourished during the report period. A host of preparative results showed that such transformations rival their noble metal catalyzed ancestors in terms of efficiency; the scope and the functional group tolerance are remarkable. Compelling evidence for the formation of metallacyclic intermediates was obtained by deuterium labeling studies as well as by the isolation and full characterization of pertinent organoiron intermediates. These studies are actively pursued since recent X-ray data indicate a very unusual bonding situation in 1,3-diene complexes of low valent iron.

Publications resulting from this research area: 33, 34, 36, 115, 177, 182, 261

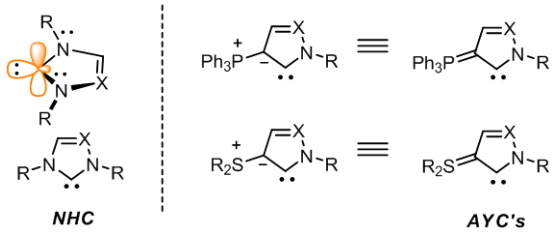
External funding: Fonds der Chemischen Industrie; Merck Research Council

Cooperations: W. Thiel, K. Wieghardt (Mülheim/Ruhr, DE)

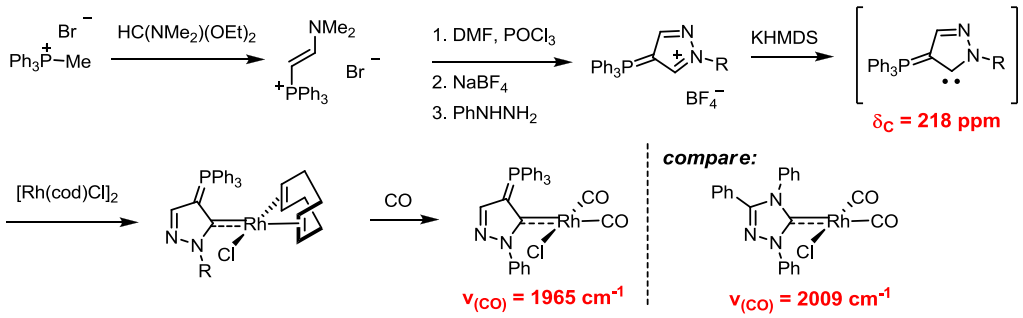
2.4.4 Research Area "Novel Donor Ligands" (A. Fürstner)

Involved: M. Alcarazo, K. Radkowski, T. Stork, R. M. Suárez

Objective: The tremendous success of NHC's as ancillary ligands for homogeneous catalysis has overshadowed the fact that alternative design may also lead to stable or metastable singlet carbenes. Likewise, carbon(0) compounds seem to promise interesting coordination chemistry.

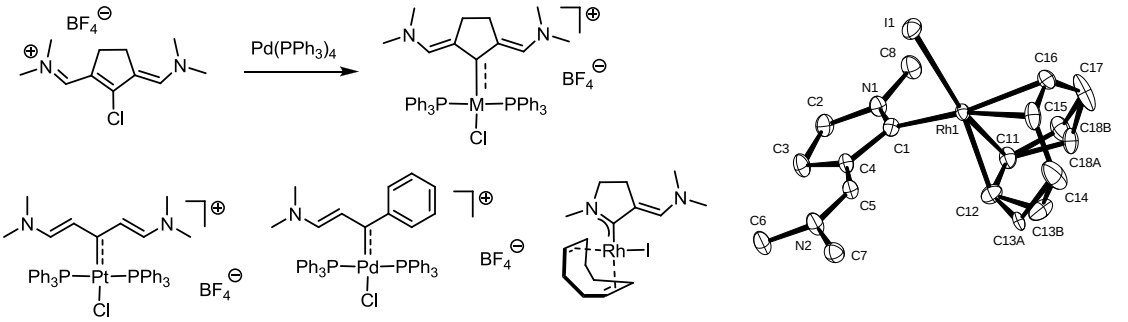


Results: All diaminocarbenes, including the classical N-heterocyclic carbenes (NHC's), largely owe their stability to the overlap of the lone pairs of the N-atoms with the empty p-orbital at the singlet carbene site; this interaction is much more important than steric shielding of the reactive center. Under this premise, it should be possible to obtain other types of (stable) singlet carbenes by formally replacing the N-atoms by other structural elements containing an electron pair in an orbital of appropriate symmetry.

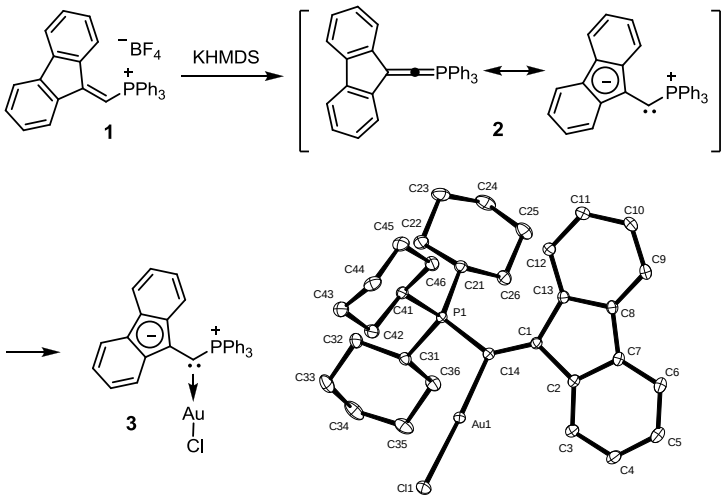


The polarized π-bond of a phosphorus-, sulfur-, or nitrogen ylide may represent an adequate structural element. Formal exchange of an endocyclic N-atom for an ylide leads to constructs termed "amino-ylide carbenes" (AYC's), which gain stability from the neighborhood of two very reactive sites. As the π-donating capacity of an ylide arguably exceeds that of an endocyclic N-atom whereas the inductive effect should be smaller, one might expect that AYCs exhibit pronounced electron releasing capacities. The required precursor salts are available in large quantities and in many structural variants by following well established synthesis routes. Deprotonation with a non-nucleophilic base generates the corresponding carbenes, which were trapped with appropriate metal salts to give air stable complexes of Rh(1+), Pd(2+) or Au(1+).

Along similar lines, the π-system of an enamine might qualify as a substitute for the N-atoms of traditional NHC's. We could demonstrate that stable metal complexes bearing singlet carbene ligands stabilized by lateral enamine moieties (vinylogous NHC's) are easily accessible by oxidative insertion of metals into chloro vinamidinium salts. Since the latter can be formed in great diversity and the resulting metal complexes are stable and rich in electrons, applications to homogeneous catalysis seem promising. The carbene character of the ligands is evident from spectroscopic and crystallographic data.

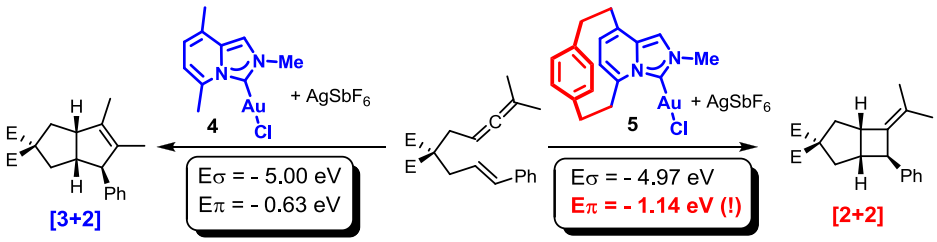


Yet another class of singlet carbene can be formed by deprotonation of alkenyl phosphonium salts such as **1**. The resulting product **2** can either be interpreted as a push-pull cumulene or as a singlet carbene. Whereas the observed ^{13}C NMR shift of the central C-atom at 198.8 ppm does not allow these resonance extremes to be distinguished, the exclusive binding of metals to the central position proves the availability of a lone pair at this site. Because of the excellent donor qualities of these new carbenes, the resulting complexes are rich in electron at the metal center yet air stable in many cases.

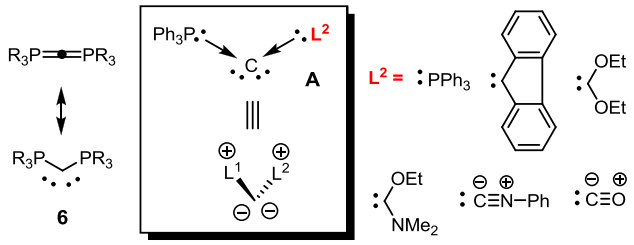


Whereas the σ-donor qualities of NHC's are undisputed and extensively used as an enabling feature for homogeneous catalysis, their π-acceptor properties are often considered weak or even negligible. In contrast to this perception, a study from this laboratory showed that the acceptor properties of NHCs can be up-regulated to the extent that they start dictating the observed reactivity. The comparison of the known imidazopyridin-ylidene ligand in **4** with its cyclophanic analogue contained in complex

5 is an instructive example. DFT calculations indicate that the σ-donor capacity of both NHCs (E_σ) is virtually identical, whereas the energies of their π-acceptor orbitals (E_π) are greatly different. This feature translates into the reaction behavior: exposure of an ene-allene to catalytic amounts of **4** triggered a [3+2]-cycloaddition, whereas complex **5** engendered exclusive formation of the corresponding [2+2] cycloadduct. The course of two additional, mechanistically unrelated transformations could similarly be affected by altering the π-acceptor property of the ancillary NHC, which is also considerably upregulated in triazol-ylidenes and the novel AYC's prepared in this laboratory. As it seems easier to tune the π-acidity of an NHC than to change the σ-donor properties, the general perception of this important class of ligands needs to be revised.

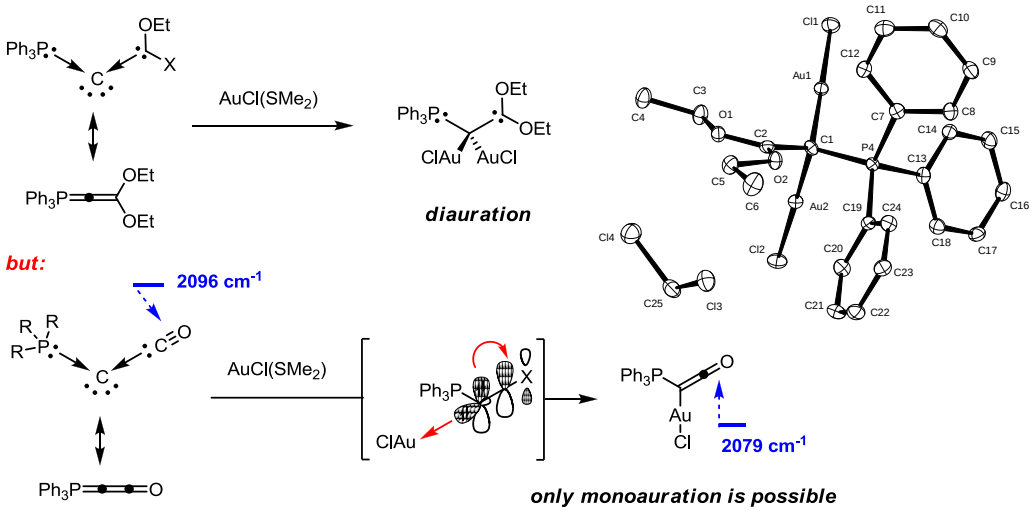


Organic compounds are commonly understood as substances based on carbon atoms which involve all four valence electrons in bonding. If two electrons form a lone-pair, as is the case in carbon monoxide, isonitriles or singlet-carbenes, one crosses the traditional borders to coordination chemistry and/or enters the realm of reactive intermediates. Compounds, wherein a carbon atom configures all four valence electrons in form of *two* lone-pairs may seem elusive at first sight. Following insightful early reports in the literature, however, recent computational studies led Frenking et al. propose that carbodiphosphoranes such as **6** actually consist of two phosphine "ligands" coordinated to a central, formally "zerovalent" carbon atom with two orthogonal lone pairs at disposition; one of them resides in an orbital of σ-symmetry (HOMO–1), whereas the other one occupies an orbital with largely π-character (HOMO).



We became interested in proving or disproving this provocative concept by experimental data. Moreover, we want to see if other (hetero)cumulenes endowed with electron releasing substituents should also be described as *complexes* of the general type $L^1 \rightarrow C \leftarrow L^2$ (**A**). Traditionally, capto-dative bonding modes are invoked only upon complexation of carbogenic compounds to a metal center, whereby the organic moiety always serves as

the "ligand". If the description $L^1 \rightarrow C \leftarrow L^2$ is physically meaningful, however, it implies that carbon itself can act as the "central atom" of a coordination compound, which differs fundamentally from the common understanding of organic chemistry.



To this end, we prepared a series of compounds of the conceived type $L^1 \rightarrow C \leftarrow L^2$, in which $L^1 = PPh_3$ was kept constant, whereas the donor capacity of the second internal "ligand" L^2 was gradually altered. By studying their coordination behavior, we could show that C(0)-compounds are present only if L^1 and L^2 are both strongly donating and, at the same time, meet rigorous geometrical requirements to prevent "back donation" of electron density from the central C-atom to the internal donor ligands L. This topological condition had not been recognized before; it explains why compounds with L^2 = CO, isonitriles or even certain carbenes cannot make two lone pairs available at the central C-atom they bind to. While our study has hence provided strong experimental support for the concept of carbon(0) as such, it also showed that C(0)-compounds are not as abundant as previously suggested solely on the basis of computations. The use of CO, isonitriles, or fluorenylidene as "ligands" L does not impart carbon(0) character onto a central C-atom, even though the resulting compounds are still best described in terms of σ-donation and π-back donation between neighboring carbon atoms. Therefore we conclude that the concept of "coordination chemistry *at* carbon" is by no means limited to seemingly exotic oxidation states but is much more general than previously anticipated. These investigations were carried out in close collaboration with Professor Thiel to back the experimental data up with high level computational results.

Publications resulting from this research area: 28, 29, 30, 149, 179, 286, 288

External funding: Fonds der Chemischen Industrie; Spanish Ministerio de Educación y Ciencia (stipend to M. Alcarazo)

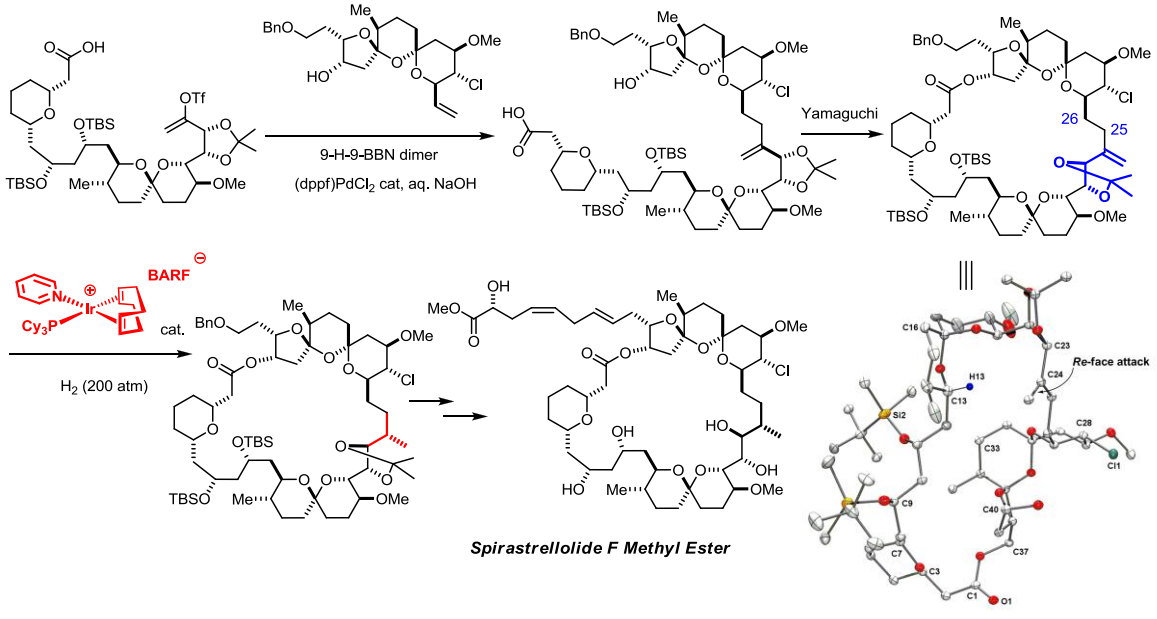
Cooperations: W. Thiel (Mülheim/Ruhr, DE)

2.4.5 Research Area "Catalysis-Based Syntheses and Evaluation of Bioactive Natural Products" (A. Fürstner)

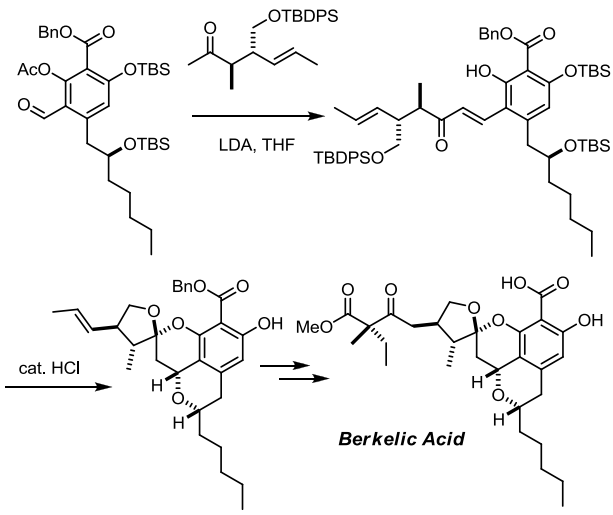
Involved: J. Ackerstaff, S. Benson, M. Bindl, L. C. Bouchez, P. Buchgraber, J. Ceccon, G. Chollet, M.-P. Collin, B. Fasching, J. Gagnepain, V. Hickmann, L. Jean, D. Laurich, K. Micoine, L. Morency, E. Moulin, G. O'Neil, J. Pospíšil, S. Schulthoff, T. N. Snaddon, M. Tamiya

Objectives: We pursue the synthesis of complex natural products by catalysis-based routes, evaluate their biochemical and biological properties in cooperation with external partners, and investigate structure/activity relationships by molecular editing.

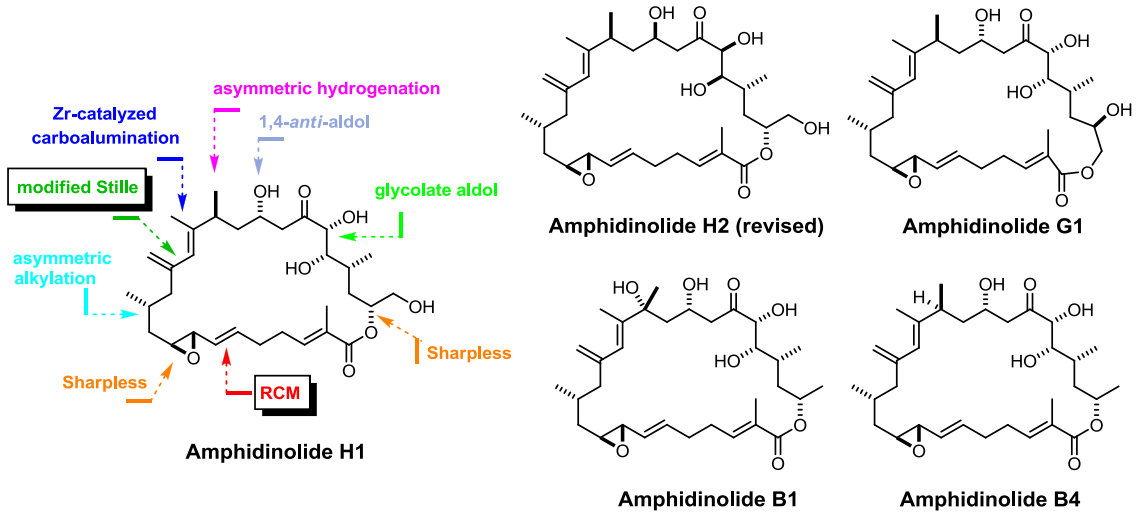
Results: The total synthesis of **spirastrellolide F**, a potent phosphatase inhibitor of marine origin, was successfully completed during the report period. At the outset of this project, neither the absolute nor the relative stereochemistry of this target containing no less than 21 chiral centers had been rigorously established. This situation forced us to devise particularly concise approaches to the required building blocks as well as a highly effective assembly process. After a first attempt to close the macrocyclic edifice by RCM at the non-stereogenic C25-C26 bond had failed (even a "relay strategy" was unsuccessful), we implemented an effective Suzuki reaction/macrolactonization strategy. This approach allowed the sensitive northern hemisphere to be combined with an elaborate enol triflate bearing a free carboxylic acid terminus.



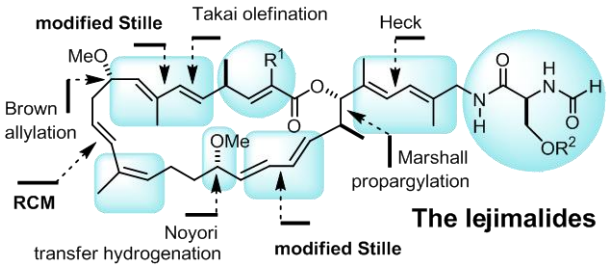
The course of the subsequent reduction of the *exo*-methylene group was rigorously controlled by imposing conformational constraints onto the macrocylic scaffold. To this end, an isopropylidene acetal on the adjacent diol unit was used to orient the olefin such that the *Si*-face was shielded by the BC-ring spiroacetal whereas the *Re*-face was open. Because of considerable transannular strain, however, only the use of a modified Crabtree catalyst escorted by a strictly non-coordinating BARF counterion was able to effect the hydrogenation. Since the reaction was exquisitely selective in our favor, a sound basis for the completion of the total synthesis was reached. A valuable spin-off of the project was the development of a new route to substituted pyrans via an alkyl-Suzuki-reaction/Michael addition cascade.



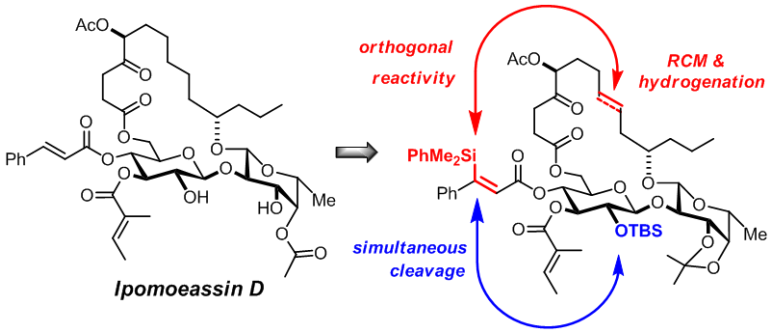
Another challenging project concerned the total synthesis of **berkelic acid**. Although less complex than the spirastrellolides, we noticed that the structure of this matrix metalloproteinase inhibitor derived from an extremophilic fungus had been misassigned by the isolation team. A newly devised one-pot triple-deprotection / 1,4-addition / spiroacetalization cascade brought all possible diastereomers into reach. The resulting comprehensive data set allowed us to determine the correct structure of the natural product.



The lability of more than one substructure embedded into the skeleton of **amphidinolide** H1 rendered the first total synthesis of this potently cytotoxic macrolide (IC_{50} in the picomolar range) exceptionally demanding. Key to success was the development of a modified Stille-Migita reaction protocol for the formation of the non-thermodynamic 1,3-diene unit of the target. This new protocol relies on the combined use of Pd(0), copper thiophene-2-carboxylate and tetrabutylammonium diphenyl-phosphinate as the promoter of choice and allowed this and a variety of other exigent cross coupling reactions to be performed under strictly neutral and fluoride-free conditions. The total synthesis of amphidinolide H1 also featured a ring closing metathesis reaction of a sensitive alkenyl epoxide derivative, which had hardly any precedent prior to this work. Once the route had been worked out and the fragment syntheses were optimized, the sister compounds amphidinolide B1, B4, G1 could also be obtained. In the case of amphidinolide H2, we noticed that the structure originally assigned to this product must be incorrect; a revision has been proposed.



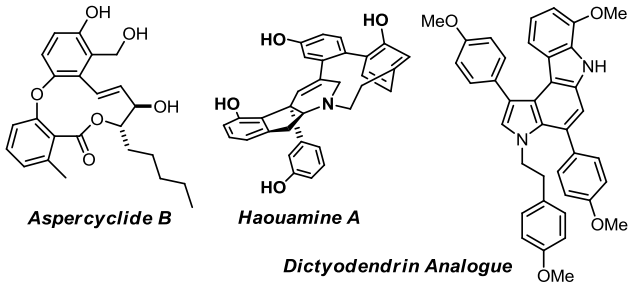
The modified Stille-Migita protocol is also instrumental for our still ongoing **iejimalide** project. To meet the demands of a serious preclinical evaluation of these promising cytotoxic agents, the total synthesis of iejimalide B has now been fully optimized to deliver one gram of this natural product in 16 steps (longest linear sequence, ca. 42 steps overall). In addition, more than 20 fully synthetic analogues were prepared and their antitumor properties evaluated by a company specialized in oncology using cell-based as well as tumor colony-based assays; in vivo studies are underway. Moreover, we prepared a hybrid structure, which combined the core of iejimalide with the tail region of the archazolids, a structurally related class of potent ATPase inhibitors.



Another promising class of anticancer agents are the **ipomoeassins**, a family of glycolipids isolated from a tropical morning glory plant. Our group completed the first total synthesis of all

members of this series, which required the development of a novel protecting group strategy (*C*-silylated cinnamate) to allow for the selective hydrogenation of the macrocycle formed by RCM without destroying the unsaturation in the esters attached to the carbohydrate rim. The acquired biological data show a striking correlation between the peripheral acylation pattern of the compounds and their cytotoxicity, which can be increased by two orders of magnitude by manipulation of a single acetyl group.

Another successful project concerned the **aspercyclides**, which posed considerable challenges due to the strain of their 11-membered ring containing seven sp^2-hybridized C-atoms. Only a Nozaki-Hiyama-Kishi reaction furnished the necessary thermodynamic driving force for the closure of this demanding ring system. Likewise, our synthesis of **haouamine A** is largely based on organometallic reactions and catalysts; the chosen approach intercepted a known intermediate of a previous total synthesis of this polycyclic alkaloid. Finally, a small collection of analogues modeled around the **dictyodendrin** alkaloids was prepared using a titanium-induced reductive coupling reaction previously developed by the group. This project revealed the peculiar reactivity of these highly electron rich heteroaromatic compounds, which were shown in our laboratory to efficiently cleave double stranded DNA in the presence of copper salts.



Publications resulting from this research area: 12, 27, 31, 32, 36, 37, 69, 155, 157, 164, 180, 181, 182, 218, 220, 231, 319, 344, 362, 363, 404

External funding: Chemical Genomics Center (MPG); Alexander von Humboldt Foundation (stipends to G. O'Neil and E. Moulin); Association pour la Recerche sur le Cancer, France (stipend to E. Moulin); Fonds der Chemischen Industrie (stipend to S. Benson); Natural Sciences and Engineering Research Council of Canada (stipend to L. Morency); Japan Society for the Promotion of Science (stipend to M. Tamiya); F. Hoffmann-La Roche

Cooperations: Chemical Genomics Center (Dortmund, DE); Oncotest GmbH (Freiburg, DE); R. Müller (Saarbrücken, DE); C. Nevado (Zurich, CH)