Research in the Department of Organometallic Chemistry

The "Department of Organometallic Chemistry" in its present form exists since 1998 when Prof. Fürstner was appointed as Director at the Institute. Since then, the Department has undergone a phase of rapid growth, leading to its present size of ca. 40 coworkers. This number includes the group of Dr. Frank Glorius, who has joined the Institute in August 2001 (Liebig fellowship, Fonds der Chemischen Industrie). Dr. Glorius has rapidly assembled a sizeable team, allowing him to pursue his own scientific interests which fit excellently into the overall mission of the Department. Prior to finishing his "Habilitation", Dr. Glorius was offered a C3 professorship at the University of Marburg (effective December 2004). It is planned to replace him by a new group leader in 2005.

Prof. Fürstner's scientific interests focus on the use of organometallic reagents as tools for advanced organic synthesis. Thereby, special emphasis is given to catalysis in general as one of the most important and most rapidly growing areas amongst the chemical sciences. In this context, our long standing interest in alkene and alkyne metathesis deserves particular mentioning. Another long term project deals with "novel concepts" for catalysis, with the intention

(i) to replace established stoichiometric reactions by catalytic processes of equal or even higher efficiency
(ii) to increase the scope of existing methods by improved (ligand) design
(iii) to explore conceptually novel catalytic scenarios of potential relevance for organic synthesis.

As will be outlined in detail below, our investigations into cross coupling reactions (iron- rather than palladium-catalyzed; novel heterocyclic carbenes and carbene complexes etc.), platinum-catalyzed skeletal rearrangements, (*E*)-selective semi-reductions of alkynes, as well as the asymmetric hydrogenation of heterocycles (Glorius) fall into the realm of this research topic.

In parallel work, the organometallic reagents and catalysts studied and developed in Mülheim are put under scrutiny by applications to the total synthesis of bioactive natural products. The target molecules are chosen according to their structural complexity and biological significance. This line of research is pursued in the belief that the reach of synthesis to the *practical* construction of elaborate products lags far behind the seeming maturity of the discipline. Therefore it is important to find new reactions which have an impact on the fundamental logic of retrosynthetic planning. Further

priority issues are (i) the "economy of steps" of the overall sequences, (ii) a significant increase in molecular complexity per step, (iii) a maximum mass transfer from the substrate to the products ("atom economy"), (iv) the valorization of bulk chemicals, and (v) the use of as many catalytic processes within a given sequence as possible. In this context it is worth mentioning that two total syntheses have been completed during the report period that are (almost) entirely catalysis based and employ almost exclusively methodology developed in our Department.

During the report period, our collaborations with biochemistry and biology experts outside the Institute have been significantly expanded and strengthened. This allows us to screen and evaluate all relevant products formed during our total synthesis campaigns in various enzymatic and cellular assays. Additional in vitro tests (e.g. DNA cleavage) are carried out in house. Particularly notable is the close collaboration with the Max-Planck-Institut für Molekulare Physiologie in Dortmund (Prof. Waldmann) which will become part of the "Chemical Genetics Center" of the Max-Planck-Society to be launched in 2005.

Finally, the significant overlap with research activities of other groups at the Institute should be pointed out. Pertinent examples are (i) the close collaboration with Dr. Glorius which led to the first implementation of the asymmetric pyridine-hydrogenation technology into an advanced total synthesis, (ii) a project with Prof. Thiel concerning the analysis of the stereochemical course of alkene metathesis reactions, and (iii) a fruitful exchange of information with Prof. Jonas in the new field of iron-catalyzed cross-coupling. Finally it should be mentioned that close ties to all analytical groups exist which are essential for success in the timely field of applied organometallic chemistry and catalysis research as carried out in this Department.

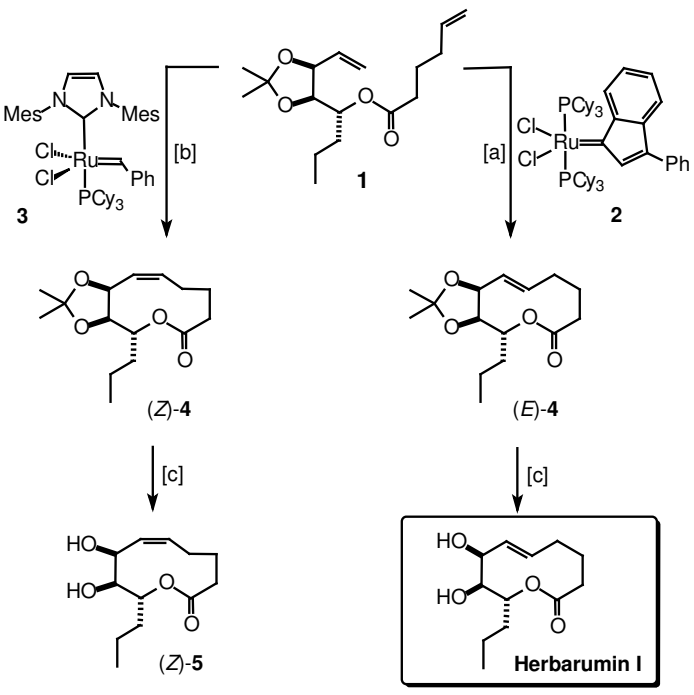
2.4.1 Research Area "Metathesis of Alkenes and Alkynes" (A. Fürstner)

Involved: C. Aissa, G. Blond, A.-S. Castanet, P. Davies, D. De Souza, F. Jeanjean, F. Lacombe, A. Leitner, L. Parra, S. Prühs, K. Radkowski, J. Ragot, P. Razon, R. Riveiros, B. Scheiper, F. Stelzer, M. Schlede, D. Song

Objective: Metathesis has revolutionized organic synthesis during the last decade. Our work in this highly competitive area intends (i) to demonstrate the strategic advantages associated with the use of this reaction by prototype applications to target oriented synthesis, (ii) to develop catalysts with even better performance, (iii) to control the stereochemical outcome of the reaction, and (iv) to improve its industrial application profile.

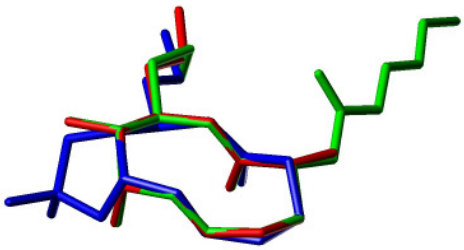
Results: As outlined in the last report, our work on ring closing alkene metathesis (RCM) started in 1995 when we were able to show that this reaction allows to form medium-sized and macrocyclic rings with exceptional efficiency, although such products were previously believed to be beyond its reach. Investigations into novel catalyst design (ruthenium allenylidenes, -indenylidenes, ruthenium-NHC complexes) as well as the first metathesis reactions in supercritical media followed shortly thereafter.

A major shortcoming of RCM as well as cross metathesis (CM), however, is the lack of control over the configuration of the newly formed double bond. A significant part of the work carried out during the report period has been dealing with this important problem. Thereby, several lines of investigations have been pursued:

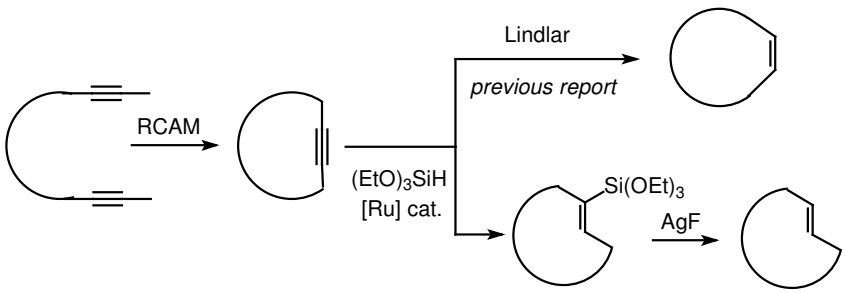


First, we have shown how to deal with this stereochemical issue by exerting thermodynamic versus kinetic control. This concept was implemented into the first total synthesis of the herbicidal lactone **herbarumin**.

Specifically, semiempirical calculations for the corresponding isopropylidene acetal indicated that the (*Z*)-olefin (*Z*)-**4** is ca. 3.5 kcal mol^{-1} more stable than (*E*)-**4** due to the rigid bicyclic skeleton. This enthalpic difference translates into good stereoselectivity during ring closure. In fact, RCM of diene **1** using the 'second generation' ruthenium complex **3** resulted in the exclusive formation of the (*Z*)-alkene, likely because the chosen catalyst is able to equilibrate the products initially formed under the reaction conditions; this outcome is therefore deemed to reflect thermodynamic control. In contrast, the use of our indenylidene catalyst **2** bearing two phosphine ligands allowed to trap the kinetic (*E*)-isomer in excellent yield and purity. To the best of our knowledge, these transformations are the first example for the deliberate formation of either possible isomer of a given cycloalkene by stereocontrolled RCM. This concept was also successfully applied to the total syntheses of the marine natural product **ascidiatrienolide** and the herbicide **pinolidoxin**.

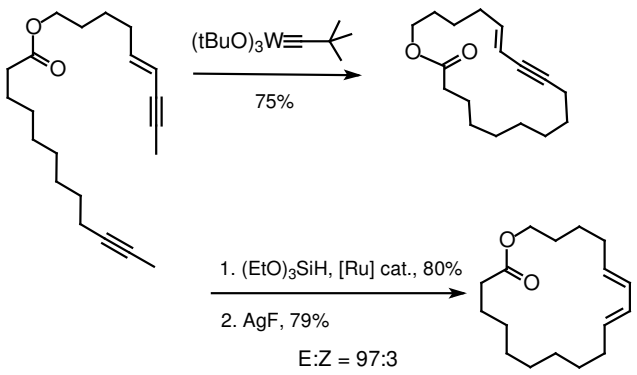


Overlap of the X-ray structures of **herbarumin** (red), **herbarumin** isopropylidene acetal (blue), and **pinolidoxin** (green) revealing the highly conserved conformation of their ten-membered lactone cores.

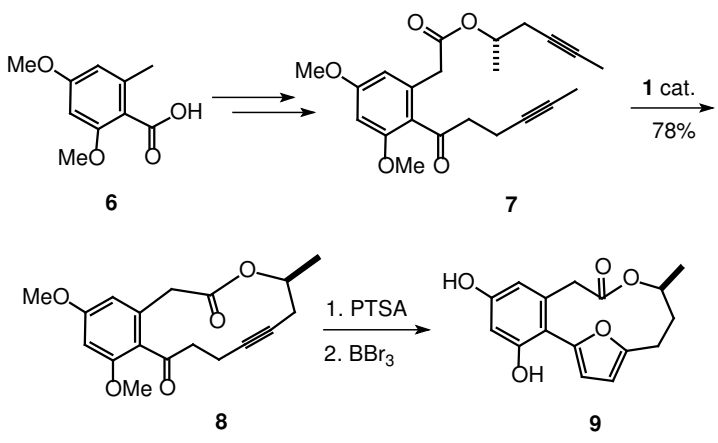


The third and so far most successful way to exert rigorous stereocontrol takes recourse to alkyne metathesis followed by semi-reduction. It had already been shown during the last report period that ring closing alkyne metathesis (RCAM) followed by Lindlar hydrogenation opens a reliable entry into macrocyclic (*Z*)-alkenes. Since the complementary methods for the conversion of alkynes to (*E*)-alkenes are limited in scope and rather unattractive, the full potential of RCAM could not be exploited. To fill this gap, a sequence of *trans*-selective hydrosilylation of the (cyclo)alkyne substrates followed by a protodesilylation of the resulting vinylsilanes was developed which opens an effective, mild and highly stereoselective entry into (*E*)-(cyclo)alkenes. $[Cp^*Ru(MeCN)_3]PF_6$ turned out to be the

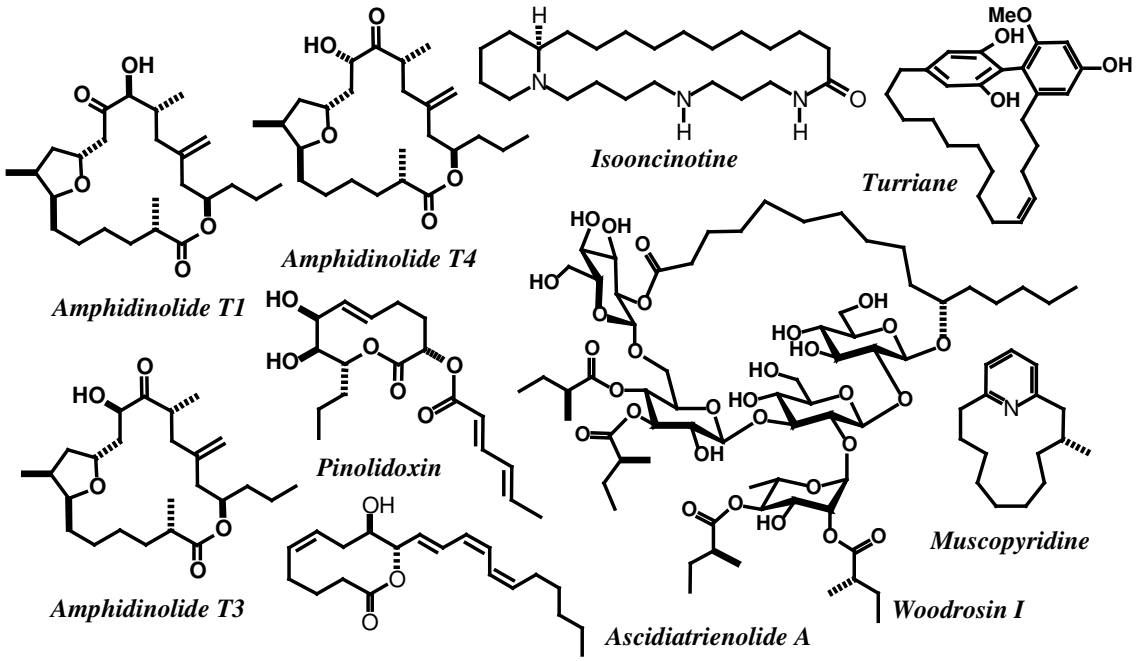
catalyst of choice for the *trans*-hydrosilylation, while the protodesilylation is best achieved with either AgF or a combination of AgF cat./TBAF in aq. MeOH/THF.



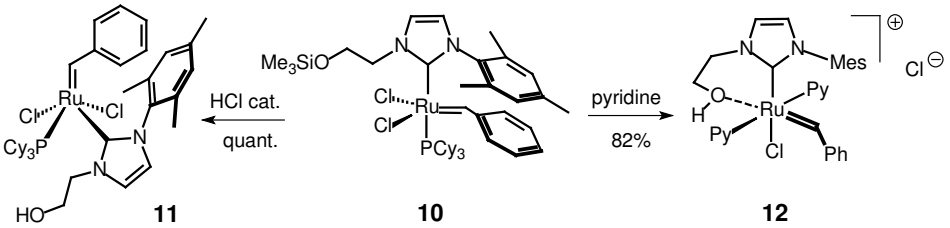
This concept was then extended to the preparation of stereodefined 1,3-dienes. Specifically, treatment of a suitable enyne-yne substrate with an alkyne metathesis catalyst engenders a high yielding formation of a cyclic enyne. *trans*-Selective hydrosilylation followed by protolytic cleavage of the C-Si bond affords the desired (*E,E*)-cycloalka-1,3-diene in good yield and excellent isomeric purity. This results is remarkable as it illustrates the fully chemoselective course of the alkyne metathesis as well as of the hydrosilylation reaction, both of which occur exclusively at the triple bond without affecting the adjacent alkene. It should be pointed out that conjugated dienes are most difficult to prepare by conventional alkene metathesis, because the established catalysts attack both double bonds with similar ease and therefore usually afford complex mixtures of various stereoisomers and ring-contracted products.



A conceptually different use of alkyne metathesis is featured in our synthesis of the tubulin binding compound **citreofuran (9)**. The heterocyclic ring embedded into the macrocyclic skeleton of this compound was encoded by cycloalkyne **8** which derived from a high yielding RCAM reaction of the readily available diyne **7**. Treatment with acid renders the alkyne entity in **8** susceptible to nucleophilic attack by the adjacent ketone, thus forming the furan ring. RCAM can therefore serve heterocyclic chemistry as well.

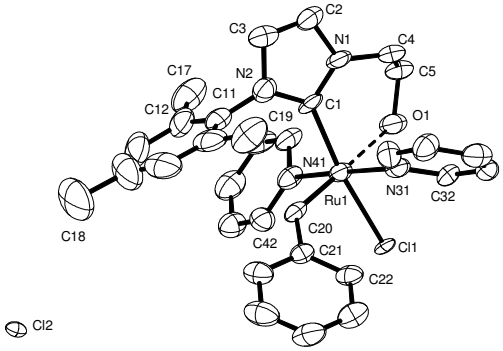


The scope of RCM and RCAM has been further illustrated by a host of applications to the total synthesis of various natural products. The most advanced examples are the complex glycolipid **woodrosin I**, and the entire family of the potent cytotoxic but very scarce marine macrolides of the **amphidinolide T** series. The **turrianes** were prepared both by an alkene- and by an alkyne metathesis route, thus allowing for a direct comparison of these methods. While the standard ruthenium catalysts for alkene metathesis are easy to use, it is only the alkyne metathesis approach which enables a fully stereoselective and hence practical synthesis. Although structurally less complex, the spermidine alkaloid **isooncinotine** and the olfactory alkaloid **muscopyridine** also deserve mentioning, because their syntheses rely (almost) exclusively on metal catalyzed reactions developed in our laboratory (see below).



Finally, two unusual and unprecedented rearrangements of Grubbs-type ruthenium carbene complexes have been discovered during our work on the immobilization of functionalized derivatives such as **10**. Cleavage of the lateral silyl group with ethereal HCl spontaneously affords complex **11** in which the NHC- and the phosphine ligand are *cis*- rather than *trans*-disposed. Even more strikingly, treatment of the same complex with pyridine engenders an ionization by loss of one of the chlorides with formation of the octahedral complex **12**. It is particularly surprising that the hydroxyl group on the

alkyl side chain in **12** merely serves as a Lewis base rather than as an alkoxide ligand to the Ru center. The structure of this very unusual complex has been secured by X-ray analysis.



Publications resulting from this research area: 36, 38, 44, 45, 46, 48, 49, 95, 148, 198, 201, 202, 204, 205, 206, 282, 374, 396, 415

External funding: DFG (Leibniz program); Fonds der Chemischen Industrie; Merck Research Council; Boehringer-Ingelheim

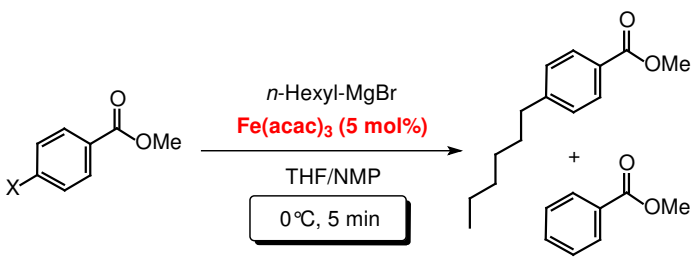
Cooperation: W. Thiel (Mülheim/Ruhr, DE)

2.4.2 Research Area "Iron Catalyzed Cross Coupling Reactions" (A. Fürstner)

Involved: M. Bonnekessel, E. Kattnig, H. Krause, D. Laurich, A. Leitner, O. Lepage, R. Martin, M. Méndez, B. Scheiper, G. Seidel

Objective: Cross coupling reactions using palladium (or nickel) catalysts constitute one of the most important developments in preparative chemistry during the last 40 years; they are widely practiced in academia as well as in industry. We intend to explore conceptually novel alternatives to these classical C-C-bond forming reactions, employing catalysts that are cheap, efficient, benign and non-toxic.

Results: Reminiscent of a pioneering study of Kochi et al. published as early as 1971 on the use of iron salts for the cross coupling of *vinyl* halides with organometallic reagents (a reaction which found surprisingly few applications during the following decades), a program was launched with the aim to investigate the potential of iron catalysis in more detail. Thereby our investigations were guided by the mechanistic hypothesis that the reaction of iron salts with e.g. Grignard reagents might lead to highly reduced clusters containing iron centers of the formal oxidation state –II (as suggested by previous studies of Prof. Bogdanović) as the catalytically competent species. Based on this, we were able to show that cheap, non-toxic, air-stable, non-hygroscopic, and environmentally benign $Fe(acac)_3$ and related pre-catalysts effect the cross coupling of *alkyl*magnesium halides with (hetero)aryl halides and –sulfonates with truly remarkable efficiency. The most notable features of this process can be summarized as follows:



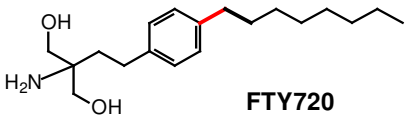
X	Coupling	Reduction
I	27%	46%
Br	38%	50%
Cl	> 95%	
OTf	> 95%	
OTs	> 95%	

(i) Aryl chlorides, -triflates and even –tosylates are better substrates than the corresponding aryl bromides or –iodides which prevail in palladium-catalyzed reactions. In view of the lower price and better availability of aryl chlorides, this reactivity profile constitutes a major advantage in practical terms.

(ii) The reactions proceed with unprecedented rates at or even below ambient temperature, reflecting the exceptional capacity of the iron catalyst formed in situ for C-Cl bond activation.

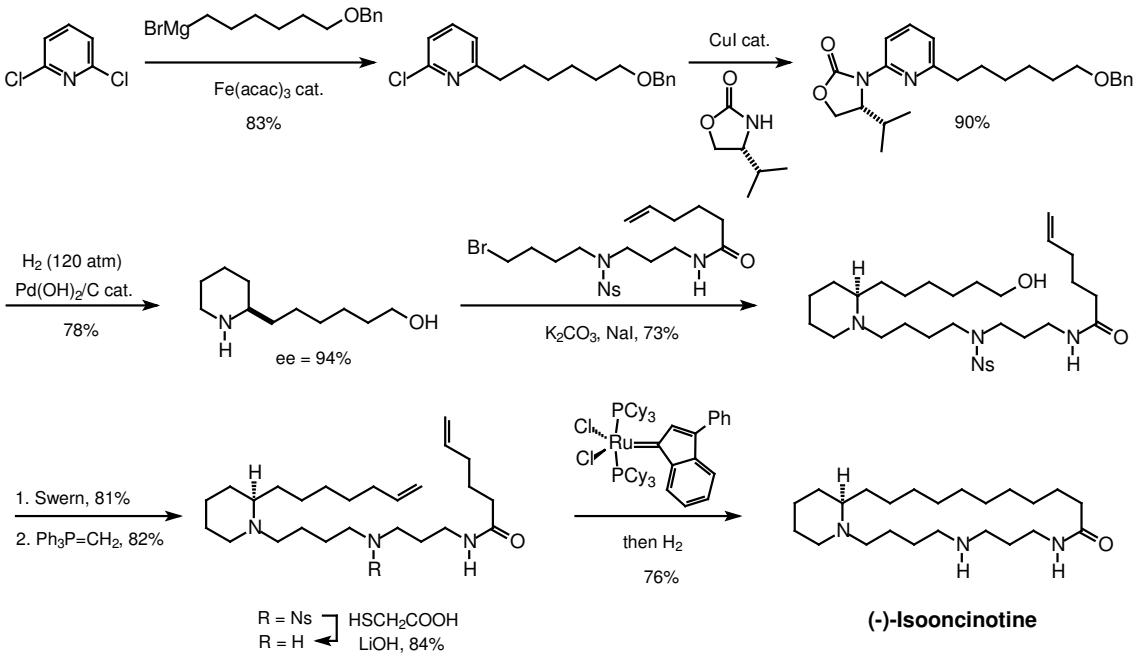
(iii) This remarkable rate of cross coupling translates into an attractive chemoselectivity profile, tolerating functional groups that usually react with Grignard reagents (esters, nitriles, sulfonates etc.)

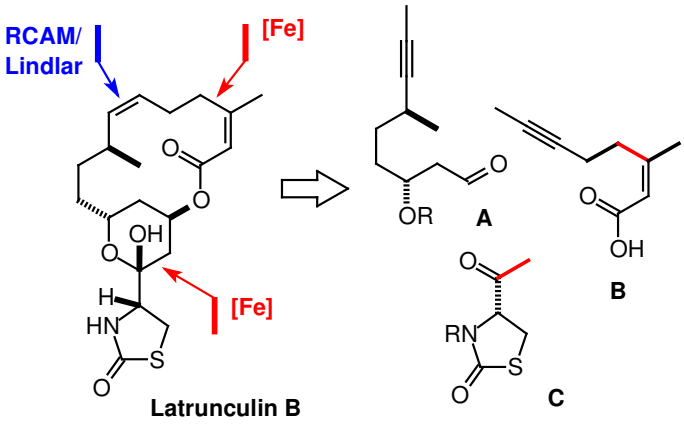
(iv) The reactions can be easily performed on multigram scale, as shown by the synthesis of **FTY720**, a promising immunomodulatory drug candidate presently in clinical phase III studies.



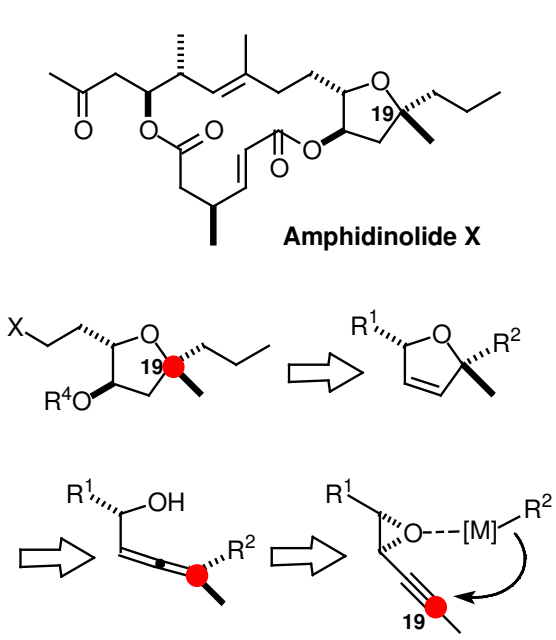
FTY720

(v) The method also allows for consecutive cross coupling reactions in one pot, as exemplified by a highly integrated synthesis of the musk-odored alkaloid **muscopyridine**. This synthesis is entirely catalysis based and employs only procedures developed in our laboratory. Similarly, the iron-catalyzed method constitutes a key transformation en route to the spermidine alkaloid **isooncinotine**, which also features the power of the asymmetric pyridine hydrogenation technology developed by Dr. Glorius, as well as the ease of macrocyclization via RCM employing our ruthenium indenylidene catalyst.

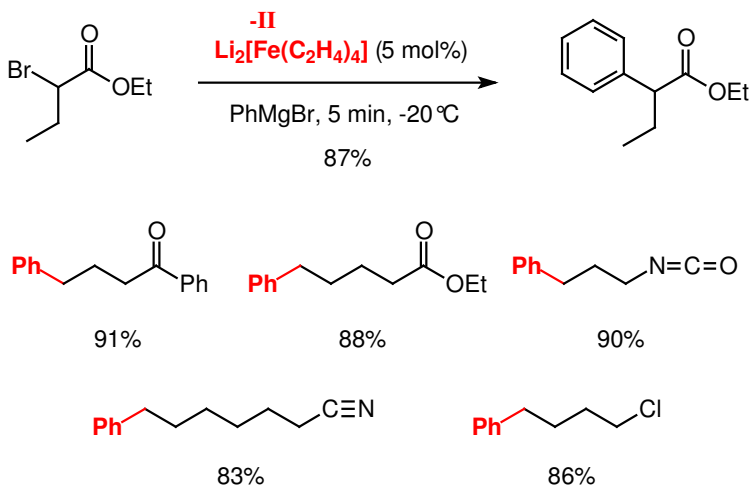




In addition to (hetero)aryl chlorides and –sulfonates, iron catalysis also applies to alkenyl triflates as well as to acid chlorides as the electrophiles. Since various functional groups are again tolerated, this method provides access to e.g. functionalized ketones that are difficult to prepare otherwise. The formation of the building blocks **B** and **C** required for the total synthesis of the highly potent actin-binding macrolide **latrunculin B** illustrate this aspect. Taking recourse to the alkyne metathesis/Lindlar strategy for the construction of macrocyclic (*Z*)-alkenes, we were able to accomplish a concise and highly flexible total synthesis of this bioactive target as well as of a library of analogues (cf. Chapter "Catalysis Based Syntheses and Evaluation of Bioactive Natural Products").



Propargyl epoxides represent yet another class of electrophiles that were found to react with Grignard reagents in the presence of catalytic amounts of $Fe(acac)_3$. Under these conditions, they convert into allene derivatives with complete transfer of the central chirality of the epoxide to the axial chirality of the emerging product. Since the major allene isomer formed is *syn*- rather than *anti*-configured, this new iron-catalyzed method nicely complements the (mainly stoichiometric) copper-based procedures previously described in the literature. This stereochemical outcome is tentatively explained by a directed delivery of the nucleophile. This novel transformation served as a key step of the first total synthesis of the cytotoxic marine natural product **amphidinolide X** recently completed in our laboratory. In our approach, the quarternary center C-19 is relayed to a readily available propargyl epoxide via a chiral allene intermediate.



Low-valent iron catalysts induce an even more unusual transformation. While palladium- and nickel catalyzed cross coupling reactions of *alkyl* halides are notoriously difficult and have been possible only recently using rather sophisticated and highly optimized ligand systems, we found that bare iron centers effect such reactions with exceptional ease and efficiency. Although "in situ" systems can be used for this purpose, best results were obtained with the well defined complex $[(tmeda)Li]_2[Fe(C_2H_4)_4]$ originally developed by Prof. Jonas. Under these conditions, chemoselective cross coupling reactions of secondary bromides, primary iodides and all kinds of allylic halides with *aryl*-Grignard reagents can be accomplished even in the presence of other electrophilic sites such as ketones, esters, nitriles, or isocyanates. The fact that the Jonas ate-complex containing an Fe(−II) center leads to an exceptionally active catalyst system supports the notion that highly reduced metal centers may play a decisive role in such catalytic processes. Mechanistic investigations aiming at a better understanding of this aspect are presently underway.

Publications resulting from this research area: 40, 41, 202, 206, 208, 375, 391, 414, 425

External funding: DFG (Leibniz program); Fonds der Chemischen Industrie (Kékule stipends for B. Scheiper and M. Bonnekessel); Alexander von-Humboldt-Foundation (stipends for O. Lepage, R. Martin, and M. Méndez); Deutsch-Israelische Projekt-kooperation (DIP)

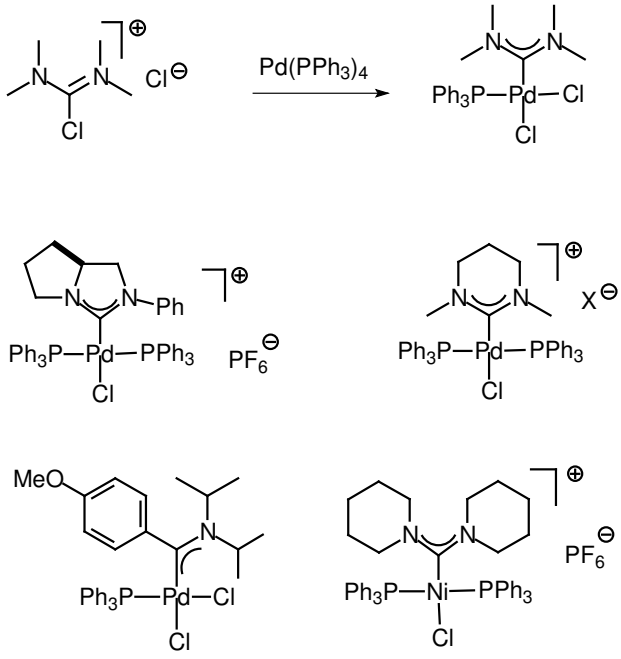
Cooperations: K. Jonas (Mülheim/Ruhr, DE); F. Glorius (Mülheim/Ruhr, DE)

2.4.3 Research Area "Novel Concepts for Catalysis" (A. Fürstner)

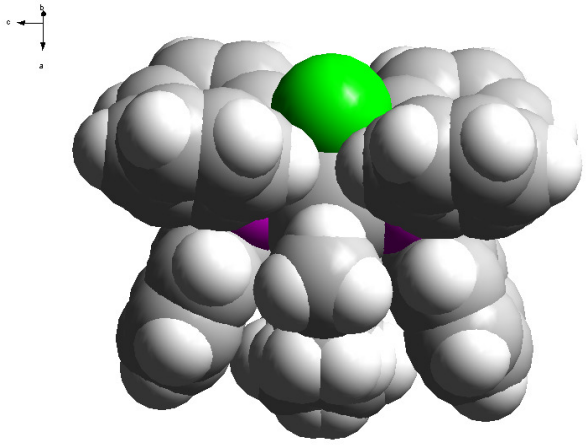
Involved: T. Gress, P. Hannen, H. Krause, D. Kremzow, V. Mamane, G. Seidel

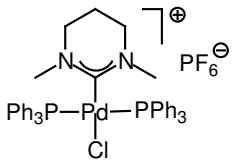
Objectives: A long term goal consists in the development of novel catalytic scenarios for advanced organic synthesis. Particular emphasis is given to transformations that result in a significant increase in molecular complexity. Moreover, we intend to develop alternative routes to established catalyst- and ligand systems of proven relevance.

Results: Transition metal complexes with N-heterocyclic carbene (NHC) ligands show considerable potential as catalysts for organic synthesis and fine chemical production. They are usually prepared by ligand exchange or salt metathesis on treatment of a suitable metal precursor with the appropriate carbene formed as a discrete or a transient species. In none of these established procedures does the metal template change its oxidation state. As part of our program aiming at the design of novel metal-NHC catalysts and their applications to advanced organic synthesis, we considered that oxidative insertion of a low-valent metal into a 2-chloro-1,3-disubstituted imidazolinium salt may open an alternative entry into this important class of compounds. In fact, reaction of either $Pd(PPh_3)_4$ or $[Ni(cod)_2]/PPh_3$ with various 2-chloroimidazolinium- or –amidinium salts affords metal-diaminocarbene complexes in good to excellent yields. This procedure allows to incorporate (acyclic or ring expanded) carbene fragments that are very difficult to access otherwise. Moreover, a variety of enantiomerically pure, chiral metal-NHC complexes have been prepared by this novel route. Furthermore it was shown that oxidative insertion also paves a way to prototype Fischer carbenes of Pd(II). Since the required starting materials are readily available from urea- or thiourea derivatives, this approach allows for substantial structural variations of the ligand backbone. The catalytic performance of the resulting library of nickel- and palladium-carbene complexes has been evaluated by applications to



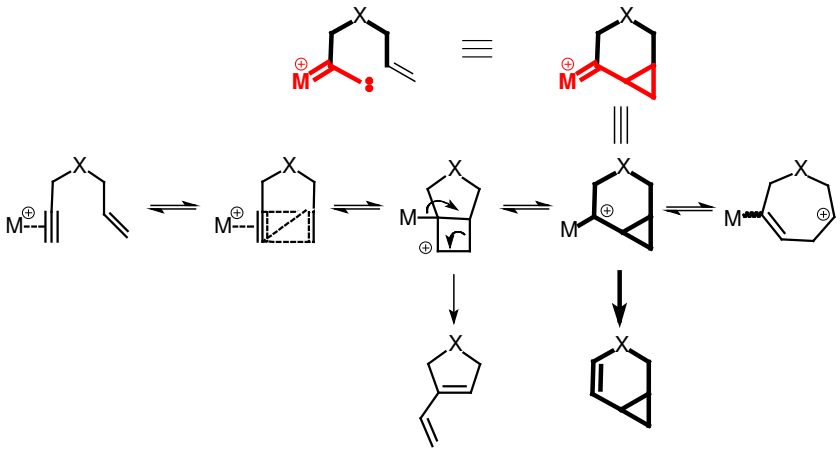
prototype Suzuki-, Heck-, and Kumada-Corriu cross coupling reactions as well as Buchwald-Hartwig aminations. It was found that even Fischer carbenes show appreciable catalytic activity. Moreover, representative examples of all types of neutral and cationic metal carbene complexes formed in this study were characterized by X-ray crystallography.

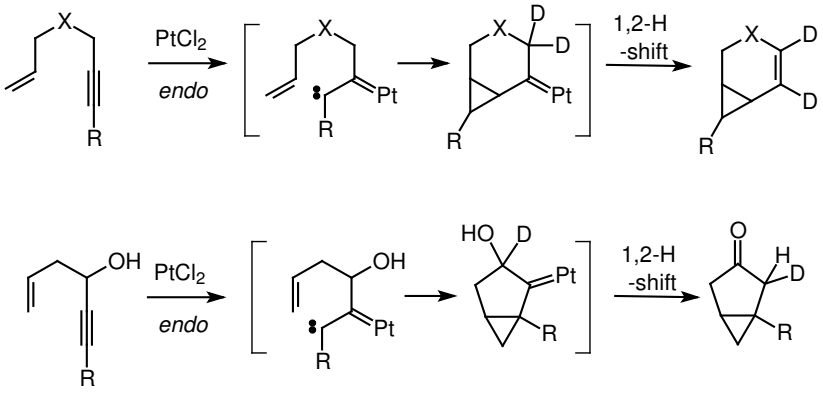




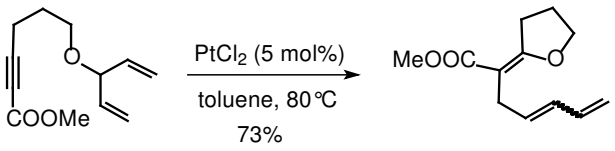
Space filling representation of the cationic carbene complex shown in the insert. The 1,3-dimethyl-3,4,5,6-tetra-hydropyrimidin-2-ylidene ligand is sandwiched between two phenyl rings. The chlorine (green) in *trans* position to the carbene is readily accessible.

Another major line of research is dealing with skeletal rearrangements effected by catalysts with high affinity to π-systems. In previous work we had suggested that alkynes coordinated to suitable π-acids are susceptible to attack by tethered nucleophiles, engendering a host of cycloisomerization reactions. Depending on the nature of the chosen catalyst, the reactive intermediates are best viewed as "non-classical" carbo-cations (M^+ = proton) or as a cyclopropylcarbene species (M^+ = Pt, Au, In etc.). Since the cyclopropyl ring of the latter itself formally derives from attack of a carbene onto the double bond of the substrate, the original alkyne complex represents a *vic*-dicarbene synthon; such species are elusive in conventional chemistry. We have been able to demonstrate the "carbenoid" character of the reactive intermediates by labeling experiments and have exploited these complexity inducing reactions for various preparative purposes.

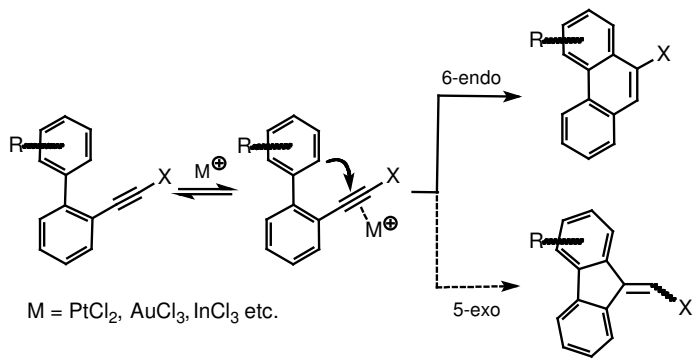




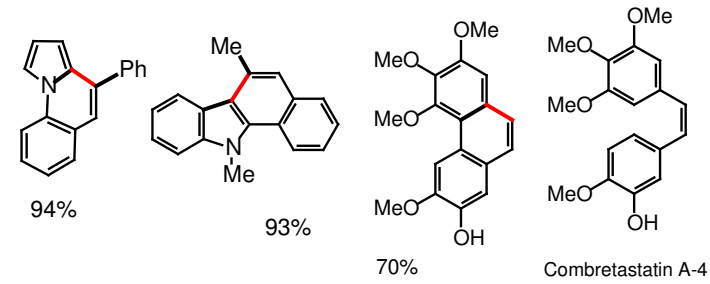
Specifically, they allow to form bicyclo[3.1.0]-hexane skeletons from readily accessible homoallylic alcohols. A concise total synthesis of the terpene derivatives sabinol and sabinone illustrates this aspect. If the homoallylic alcohols used as the substrates are enantiomerically pure, excellent levels of chirality transfer can be secured.

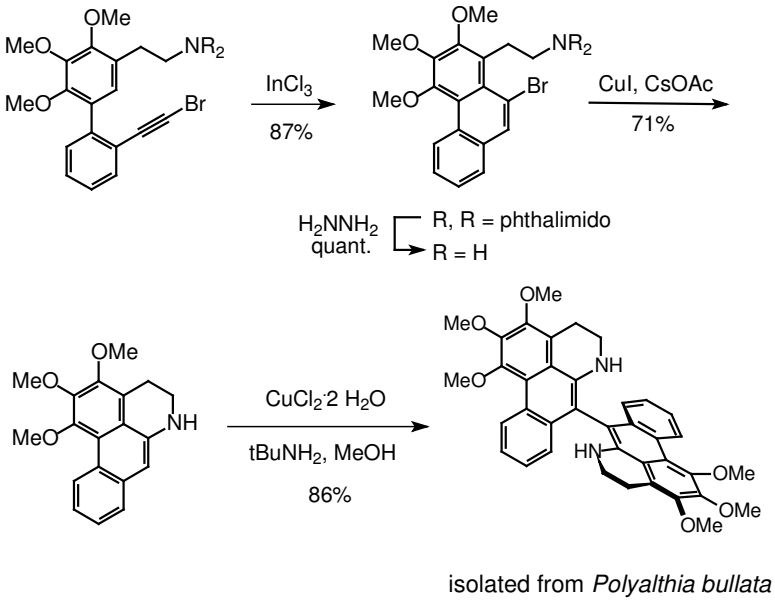


Furthermore, it was possible to extend this concept beyond alkenes as the tethered nucleophilic reaction partners. Thus, the use of allyl ethers results in an unprecedented O→C allyl transfer process which also takes a highly stereoselective course. Even more useful in preparative terms are closely related skeletal reorganizations of alkynes attached to suitable biaryl residues. They open access to phenanthrenes as well as to various types of polycyclic heteroarenes. The mild reaction conditions and the compatibility of the late transition metal catalysts with various functional groups enabled the first total synthesis of an **aporphine alkaloid** derived from *Polyalthia bullata* as well as the total synthesis of a series of naturally occurring phenanthrenes that are closely related to the cytotoxic agent **combretastatin A4** which is presently undergoing phase II clinical studies for the treatment of solid tumors.



analogously:





Publications resulting from this research area: 42, 47, 207, 209, 254, 346, 388, 389

External funding: DFG (Leibniz program); Fonds der Chemischen Industrie; Merck Research Council; Deutsch-Israelische Projektkooperation (DIP)

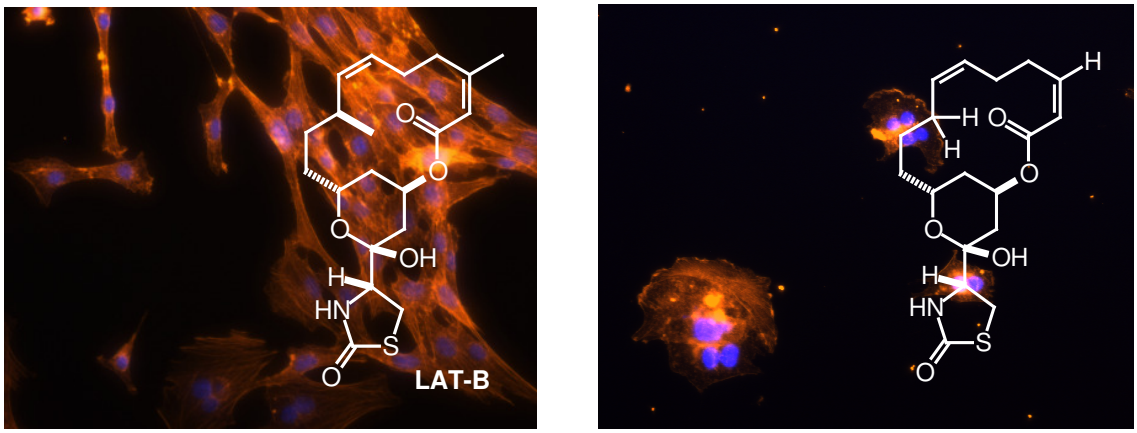
Cooperation: none

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

Involved: M. Albert, M. Fenster, F. Feyen, H. Krause, D. Kirk, M. Matheu, J. Mlynarski, H. Peters, K. Radkowski, J. Ruiz-Caro, F. Stelzer, D. De Souza, L. Turet

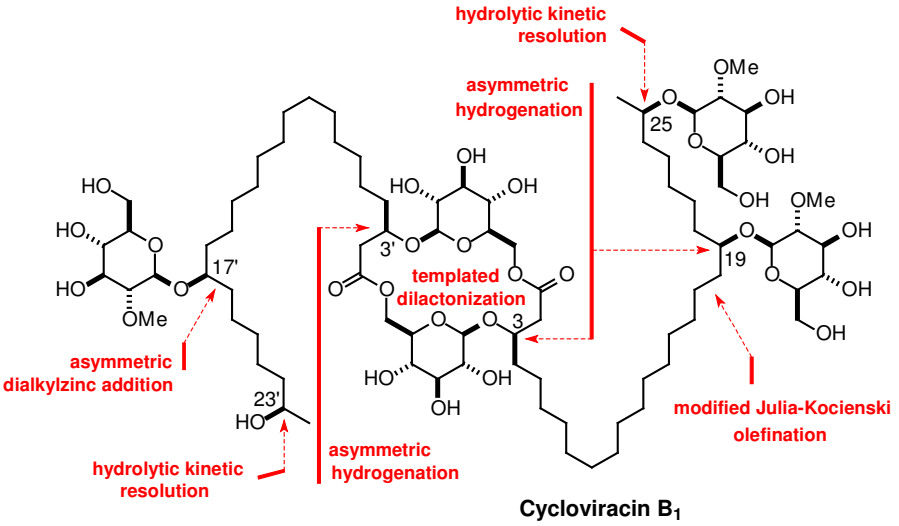
Objectives: We intend to prepare complex natural products, preferably those which are hardly available from their natural sources, and to validate their biochemical and biological properties. Special emphasis is given to the design of synthesis routes that are largely catalysis based, economic in the overall number of steps, and highly flexible. Where appropriate, focused libraries of analogues are prepared for structure/activity relationship studies.

Results: Actin as one of the two major components of the cytoskeleton determines the shape and mechanical properties of eukaryotic cells and is responsible for cell motility processes as fundamental as exo- and endocytosis. Our present knowledge about the many biological roles of actin derives to a large extent from a "chemical genetics" approach using probe molecules able to dissect this highly sophisticated and inherently dynamic microfilament structure. Among them, the **latrunculins** gained particular importance because of their striking selectivity and the rapid onset of action. They form 1:1 complexes with actin monomers which are incapable of polymerizing to the intact protein filament network. Surprisingly though, very little is known about the structural elements responsible for actin binding.



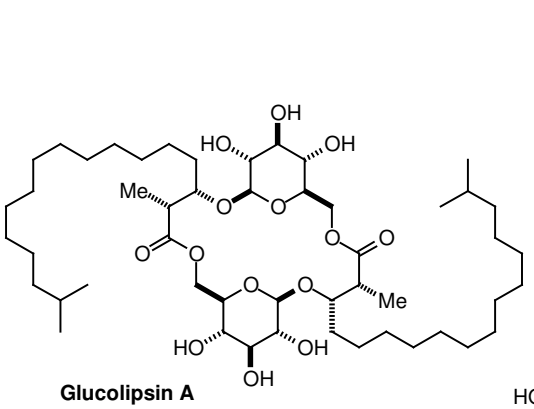
Stained cell line incubated with latrunculin B (left) or a structurally simplified latrunculin B analogue (right) which turned out to be significantly more potent.

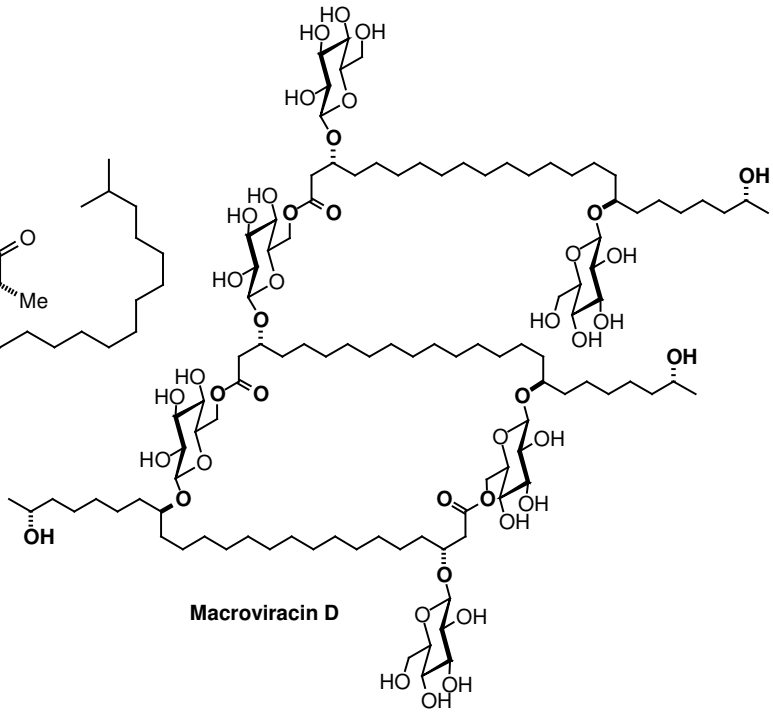
Since our group has been able to develop a highly efficient total synthesis of the marine natural product **latrunculin B** using catalytic methodology developed in the laboratory (see above), it seemed lucrative to divert this synthesis to the preparation of a focused library of fully synthetic analogues which enabled us to investigate this aspect. Gratifyingly, this synthesis campaign resulted in a simplified analogue which is 1-2 orders of magnitude more potent in actin binding than the natural product itself as shown by a cell-based assay.



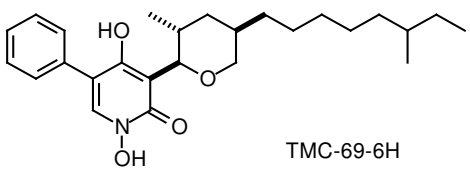
A major effort during the research period concerned the structure elucidation and total synthesis of the antivirally active glycoconjugate **cycloviracin B$_1$** (briefly mentioned in the previous report). While its constitution was known at the outset of our investigations, no information on the absolute stereochemistry of the glycosylated, secondary –OH functions residing on the fatty acid residues was available. In view of these uncertainties and the size of the target, only a very flexible and convergent synthesis plan might allow to reach these goals. Our approach was based on the hidden symmetry of this glycolipid and pursued a two-directional synthesis strategy. The key design element made use of the supposed ionophoric character of the lactide core, which was forged by a highly productive, template-directed macrodilactonization reaction. The different lateral side chains were then attached to this core by a modified Julia-Kocienski olefination and a titanium-catalyzed, asymmetric addition of a functionalized diorganozinc derivative to the aldehyde at C-17'. This strategy allowed us to unambiguously establish the absolute stereochemistry of the 6 chiral centers on the lipidic chains as (3*R*,19*S*,25*R*,3'*R*,17'*S*,23'*R*) and to complete the first total synthesis of this challenging compound. Along similar lines, the related lactide **glucolipsin A** and the even larger glycoconjugate **macroviracin D** have also been conquered by total syntheses, which rigorously established the previously unknown absolute stereochemistry of these glycolipids as shown. In collaboration with external partners,

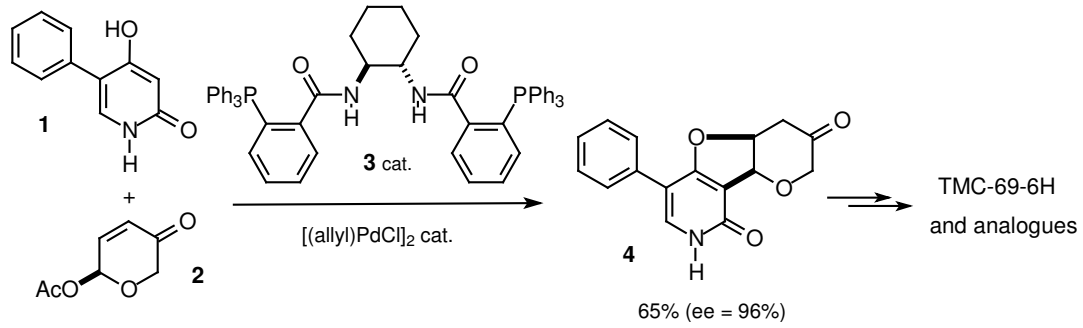
the antiviral acitivity of these natural products has been mapped (cycloviracin turned out to be most active against a *Herpes simplex* virus strain that is resistant to acyclovir). Moreover, it was found that glucolipsin is an effective inhibitor of the phosphatases Cdc25A and PTP1B, two key regulatory enzymes of the cell cycle.



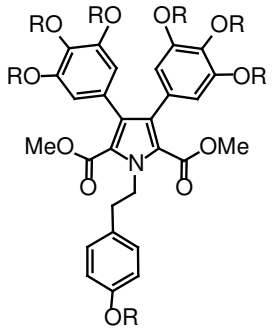


The eminent importance of phosphatases in cell cycle control drew our attention to the cytotoxic agent **TMC-69-6H** recently isolated by an industrial group in Japan. This heterocyclic compound has already proven effective *in vivo* for the treatment of murine leukemia and B16 melanoma in nude mice. The first total synthesis was achieved using a palladium catalyzed C-heteroarylation reaction between pyridone **1** and the enantiomerically enriched 6-acetoxy-pyran-3-one **2** as the key step; this transformation is accompanied by a spontaneous 1,4-addition of the phenolic –OH to the enone of the emerging product. The optically active tricyclic compound **4** thus obtained served as a convenient platform not only for the total synthesis program itself, but also for the preparation of a sizeable library of analogues for biological profiling. The most striking result of these investigation is the finding that TMC-69-6H – in contrast to the claims in the literature – turned out to be only a rather weak inhibitor of the Cdc25A phosphatase, whereas it shows very promising activities against the tyrosine protein phosphatase PTP1B, the dual specific phosphatase VHR, and the serine/theronine phosphatase PP1.

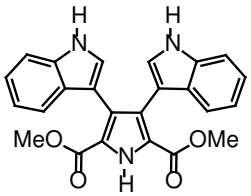

TMC-69-6H



Our long-term project on the synthesis and biological evaluation of pyrrole alkaloids has also been successfully continued. Specifically, palladium-catalyzed cross coupling reactions were used to prepare the core structure of **storniamide A**, a marine natural product able to re-sensitize multidrug resistant tumor cell lines. Moreover, we have shown that this compound is capable to oxidatively cleave DNA, provided that the peripheral –OR groups are unprotected (R = H). Along similar lines, a short synthesis of **lycogalic acid** dimethyl ester has been accomplished.



Storniamide core



Lycogalic acid dimethyl ester

Publications resulting from this research area: 36, 37, 38, 39, 43, 45, 46, 48, 148, 199, 200, 201, 202, 203, 204, 205, 344, 345, 348, 349, 375, 392, 415

External funding: DFG (Leibniz program); Fonds der Chemischen Industrie; Alexander von Humboldt-Foundation (stipends for M. Fenster and J. Mlynarski); Merck Research Council

Cooperations: E. DeClercq (University of Gent, BE; antiviral assays); H. Waldmann, H. Prinz, O. Müller (MPI Dortmund, DE; phosphatase inhibition and actin binding assays)

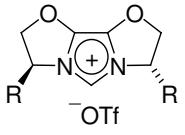
2.4.5 Research Area "New Concepts for Catalysis" (F. Glorius)

Involved: G. Altenhoff, C. Burstein, S. Holle

Objective: The purpose of our research program is to significantly facilitate organic synthesis by the implementation of new concepts for catalysis. We focus on the development of new transformations and on increasing the selectivity and efficiency of chemical processes.

1. New N-heterocyclic carbenes (NHCs) as ligands for transition metal catalysis

Since their first application in transition metal catalysis in 1995, NHC have become indispensable ligands for many different applications like cross-coupling or metathesis reactions. NHC are strong σ-donors with negligible π-acceptor properties and as a result are very strong electron donor ligands. Often, they form chemically and thermally robust and nevertheless extraordinarily active complexes. We have developed a new class of bioxazoline derived NHC ligands (IBiox). These ligands are electronically (less electronrich than "normal" NHC) and sterically (rigid backbone) unique. The latter property allows the synthesis of rigid chiral ligands (**1**,**3**) as well as of achiral ligands with flexible steric bulk (**2**). We have successfully employed these ligands in the enantioselective α-arylation of amides and in the Suzuki cross-coupling of sterically hindered substrates.



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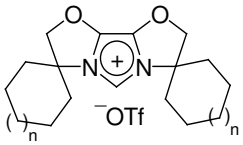

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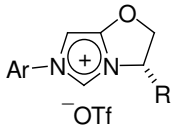
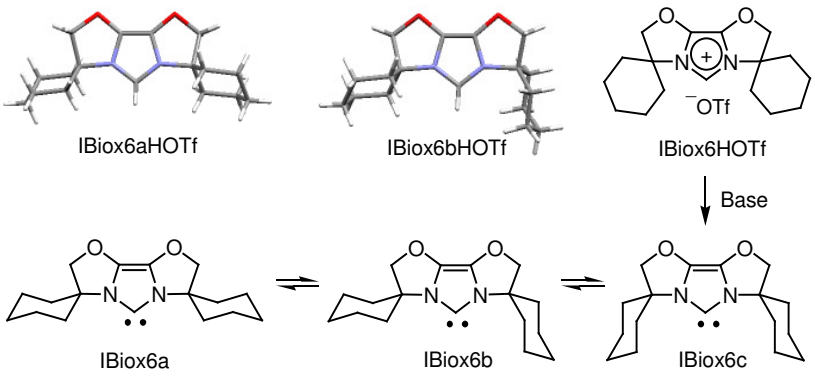
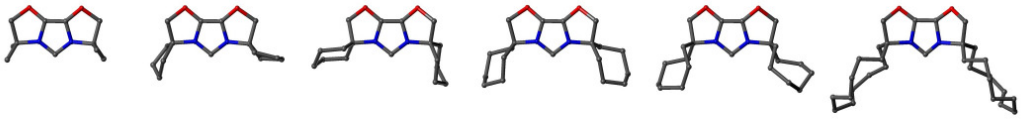


3

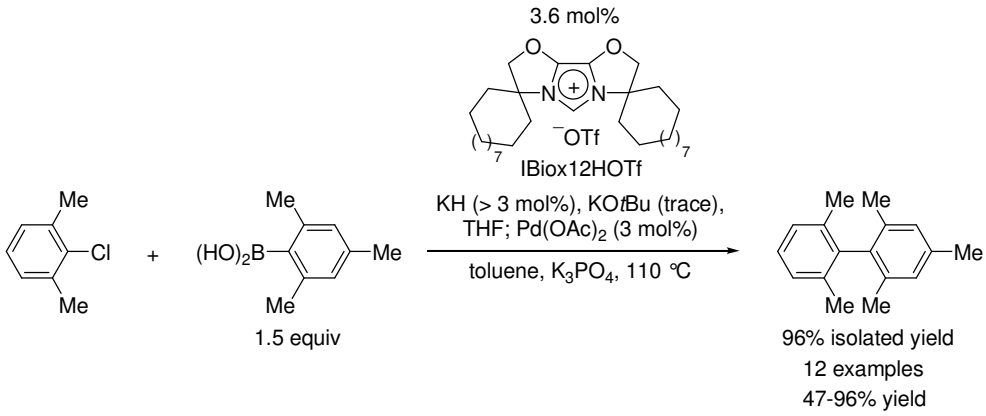
NMR- and X-ray structural analysis showed that IBiox6·HOTf (**2**, n = 1) exists in form of at least two different conformers which rapidly interconvert at room temperature. We reasoned that the flexible steric bulk caused by chair flipping of the cyclohexyl rings proves beneficial in the catalytic cycle of the Suzuki-Miyaura coupling reaction and that the sterically more demanding conformations would favor the formation of a catalytically active monoligated $Pd(IBiox6)_1$ species. However, while IBiox6·HOTf was successfully employed for the synthesis of many different ortho-substituted biaryls, the challenging formation of tetraortho-substituted biaryls remained out of reach. We have synthesized a series of structurally related imidazolium salts with cycloalkyl rings of varying ring size (cyclopentyl to cyclododecyl, Scheme 1). The electronic properties of these IBiox ligands are very similar whereas the steric demand gradually



increases within the series. These characteristics render these ligands valuable for the optimization of the catalyst system for a particular application. For the first time, these ligands allow the transformation of arylchlorides into tetra-ortho-substituted biaryls via palladium catalyzed Suzuki cross-coupling. IBiox12, the ligand containing two cyclododecyl rings, was best suited for this reaction, generally giving the highest yields of biaryl product.



Scheme 1. X-Ray structures of the imidazolium salts (hydrogen atoms and triflate counterion are omitted for clarity).

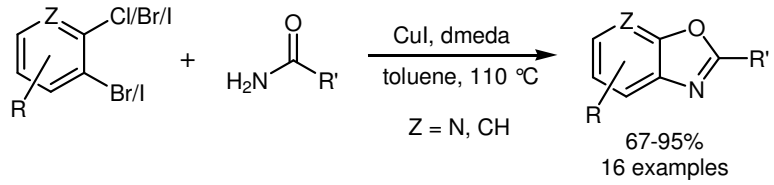


2. Innovative C-C- and C-heteroatom-bond forming reactions

C-C- and C-heteroatom bond forming reactions are at the heart of organic chemistry. In the common Heck reaction aryl halides (C-sp^2-centers) are used as coupling partners. In stark contrast, we have developed a Heck reaction in which chloroacetamides (C-sp^3-centers) react with different olefines significantly expanding the scope of the Heck reaction.

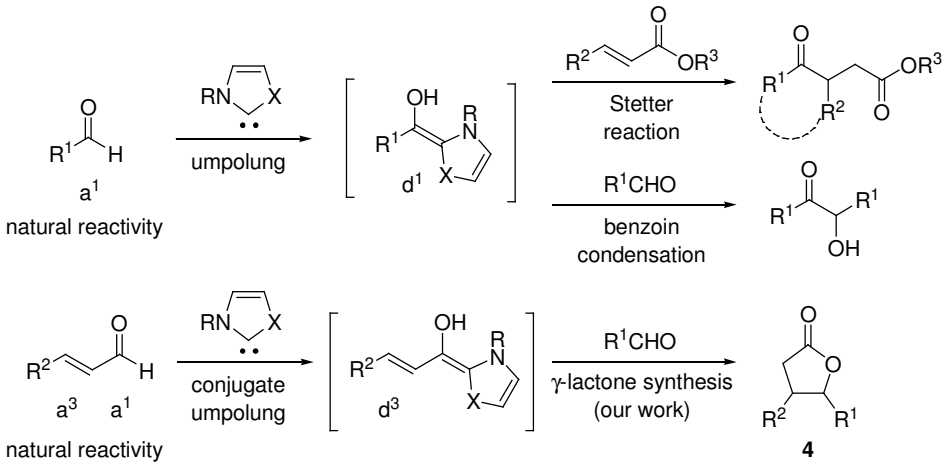
Furthermore we have developed a novel copper catalyzed domino-C-N-/C-O-bond formation. This allows the one step synthesis of benzoxazoles starting from o-dihalobenzenes and primary amides. Different strategic bonds are formed following

traditional syntheses of benzoxazoles, which employ 2-aminophenols and carboxylic acid derivatives as starting materials. Our method provides ready access to this versatile class of heterocycles.



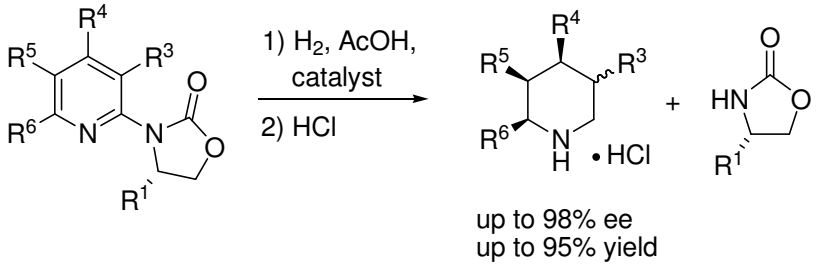
3. Conjugate Umpolung for the synthesis of γ-butyrolactones

Most transformations of organic synthesis are polar and can be described as the reaction of a nucleophile (donor d) with an electrophile (acceptor a). The umpolung of the "natural" reactivity of a functional group opens up an avenue to a new set of reactions. It has been known for a long time that the umpolung of electrophilic aldehydes can be achieved by using catalysts like cyanide or thiazolium derived carbenes. The resulting d^1-nucleophiles can react with aromatic aldehydes (benzoin condensation) or with electron poor, polarized olefins (Stetter reaction). However, for selectivity reasons these reactions are generally limited in scope. The benzoin condensation is mostly run as a self-condensation, whereas the Stetter reaction is generally conducted in an intramolecular fashion. However, some enzymes are intriguingly selective catalysts and enable the crossed and asymmetric benzoin condensation. In contrast to the a^1-to-d^1-umpolung described above, we use the term "conjugate" umpolung to describe the transformation of α,β-unsaturated aldehydes into d^3-nucleophiles (homoenolate equivalents) by attack of a nucleophilic catalyst onto the aldehyde function. We have discovered this new type of umpolung and have utilized it for the synthesis of substituted γ-butyrolactones, the *cis*-isomer being predominantly formed. The reaction is very sensitive to the choice of catalyst. Many well known umpolungs catalysts fail to provide any of the desired product **4**. Intriguingly, using IMes as the catalyst under optimized conditions γ-butyrolactones result in good yields, while the possible benzoin condensation and Stetter reaction products are hardly formed. We have shown that variation of the cinnamaldehyde and benzaldehyde component is tolerated, so that differently substituted butyrolactones are accessible. Fortunately, even ketones can be used as electrophiles. In contrast to the classical aldehyde umpolung reactions the conjugate umpolung has the advantage that it cross-couples two different aldehydes in an intermolecular fashion, giving products with two new stereocenters.



4. Asymmetric hydrogenation of pyridines

The asymmetric hydrogenation of aromatic compounds is a powerful transformation since numerous aromatic substrates exist and multiple stereocenters can be created simultaneously. Three highly enantioselective partial hydrogenations of annulated heterocycles (chinolines, indoles, pyrazines) have been reported, leading to the formation of only one chiral center. In these hydrogenations, the annulated benzene ring is required for increasing reactivity and selectivity, albeit severly limiting the substrate scope. Highly selective and general methods for the complete hydrogenation of aromatic substrates have not been developed. We have developed a conceptually novel, practical and efficient synthesis of optically active piperidines, an important substructure of many biologically active compounds. This process is distinguished by the fact that piperidines with multiple stereocenters can be formed in very good yields and excellent optical purities. For the first time, this transformation allows highly selective chirality transfer and nondestructive and traceless cleavage of the chiral auxiliary in one reaction. In addition, the piperidinium hydrochloride and the auxiliary can be easily separated by extraction and the auxiliary recycled. In collaboration with Professor Fürstner, this methodology was applied in the total synthesis of isooncinotine.



Publications resulting from this research area: 50, 150, 213, 308, 330, 351, 415

External funding: Fonds der Chemischen Industrie; BMBF (Liebig fellowship to F. Glorius); DFG

Cooperation: A. Fürstner (Mülheim/Ruhr, DE)