2.4 Department of Organometallic Chemistry

Director:

Alois Fürstner (born 1962)

Further group leader:

Manuel Alcarazo (born 1978)
Group leader from December 2008 - June 2015

Curriculum Vitae: Alois Fürstner

1962	Born in Bruck/Mur, Austria
1980-1987	Studies at the Technical University Graz, Austria; Ph.D. with Prof. H. Weidmann
1990-1991	Postdoctoral Fellow, University of Geneva, Switzerland, with Prof. W. Oppolzer
1987-1992	"Habilitation", Technical University Graz, Austria
1993-1997	Research group leader at the Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr, Germany
1998-	Director at the Max-Planck-Institut für Kohlenforschung, Mülheim/Ruhr, and affiliated as Professor ("apl. Prof.") with the TU Dortmund University, Germany
2009-2011	Managing Director of the Institute
2016-2017	Managing Director of the Institute

Awards and Honors

1994	Chemical Industries Prize ("Dozentenstipendium"), Chemical Industry Fund
1998	Ruhr Prize for Arts and Sciences, Mülheim/Ruhr
1999	Leibniz Award, German Research Foundation
2000	Thieme-IUPAC Prize for Synthetic Organic Chemistry
2000	Astra-Zeneca Award for Organic Chemistry
2001	Victor Grignard - Georg Wittig Lecture, Société Francaise de Chimie
2002	Arthur C. Cope Scholar Award, American Chemical Society
2002	Member, National Academy of Sciences Leopoldina
2004	Centenary Lecture, Royal Society of Chemistry
2004	Member, North Rhine-Westphalian Academy of Sciences, Humanities and the Arts
2004	Corresponding Member, Austrian Academy of Sciences
2004	Tetrahedron Chair
2005	Junior Award, International Society of Heterocyclic Chemistry
2005	First Mukaiyama Award, Society of Synthetic Organic Chemistry, Japan
2006	Otto Bayer Prize
2006	Heinrich Wieland Prize
2008	Janssen Pharmaceutica Prize for Creativity in Organic Synthesis
2009	Lord Todd-Hans Krebs Lectureship, RSC

2011	Lilly European Distinguished Lectureship Award
2011	Prelog Medal, ETH Zurich, Switzerland
2013	Elhuyar-Goldschmidt Lectureship, Royal Spanish Society of Chemistry
2013	Prix Jaubert, University of Geneva, Switzerland
2013	Karl Ziegler Prize, German Chemical Society
2014	Hans Herloff Inhoffen Medal, Braunschweig
2014	Gay-Lussac/Humboldt Pize, France
2014	Thomson Reuters Highly Cited Researcher
2015	Thomson Reuters Highly Cited Researcher
2015	Adolf-Windaus-Medal, University of Göttingen
2016	H. C. Brown Award for Creative Research in Synthetic Methods, ACS

more than 30 Name Lectureships (in the report period: Siegfried Hünig Lecture (DE, 2014); Heathcock Lecture (US, 2014); Irvine Organic Synthesis Lecture (US, 2015); Adolf Windaus Memory Lecture (DE, 2015); Sandin Lecture (CA, 2015); Adolf Lieben Lecture (AU, 2016)

Special Activities

2001-2006	Member, Board of Editors of "*Organic Syntheses*"
2001-2007	Scientific Editor, "*Chemical Communications*"
2002-2009	Member of the Scientific Advisory Board, Leibniz Institute for Catalysis at the University of Rostock (LIKAT Rostock)
2002-2010	Member and since 2006 Chairman of the Selection Committee of the Alexander-von-Humboldt Foundation (Feodor-Lynen-Program)
2004-2011	Member, Board of Governors, German Chemical Society
2012-	Member of the Scientific Advisory Board, ISIQ Tarragona, Spain
2013-	"*Angewandte Chemie"* Chairman of the Editorial Board
2014	Chairman, BOSS-XIV Symposium, Louvain-la-Neuve, Belgium
2015-	Member of the Selection Committee of the Alexander-von-Humboldt Foundation (Humboldt-Professorship)

International Advisory Boards (active memberships only): "*Topics in Organometallic Chemistry*" (1997-); "*Advanced Synthesis & Catalysis*" (2000-); "*Progress in Heterocyclic Chemistry*" (2005-); "*Science of Synthesis*" (2009-); „*Israel Journal of Chemistry*" (2010-), "*Angewandte Chemie*" (2010-), "*Comptes Rendus de Chimie*" (2013-); "*Bull. Chem. Soc. Jpn*." (2015-)

Organometallic Chemistry

The research in this Department is focused on the development of organometallic catalysts of preparative relevance, the investigation of their mode of action, and on applications to the synthesis of natural products of biological significance.

Several group leaders started successful careers while affiliated with the Department: Frank Glorius (2001-2004; now Full Professor in Münster), Stefan Hecht (2005-2006; now Full Professor in Berlin), Lisbet Kvaerno (2007-2008, left for a position in industry), and Manuel Alcarazo (2008-2015), who became Professor of Organic Chemistry (W3) at the University of Göttingen. His research encompassed the design of new ligands that impart exceptional π-acidity on the derived metal complexes. Moreover, he developed a promising class of high valent sulfur compounds as stable alternatives to hazardous hypervalent iodine reagents commonly used in the literature.

A new research group leader will be appointed to the Department to fill the vacancy. An offer has been made, the acceptance of which is currently bending.

The major lines of research in Prof. Fürstner's own group comprise investigations in the following fields of catalysis research, which are partly interwoven:

- metathesis
- carbophilic Lewis acid catalysis
- stereochemical unorthodox *trans*-addition chemistry
- organoiron chemistry and catalysis
- natural product total synthesis

Following our early work on alkene metathesis (macrocyclization reactions; ruthenium indenylidene catalysts etc), the related metathesis of alkynes has become a focal point of research since the turn of the millennium. This reaction had no practical relevance at that time; gratifyingly though, a new generation of catalysts developed in our laboratory shows remarkable activity and functional group compatibility and hence upgrades alkyne metathesis to the strategy level. Our catalysts are now commercial available and increasingly used by others. Furthermore, we recently showed that triple bond metathesis might even be relevant for the activation of small molecules since our catalysts cleave the N≡N-bond of aryldiazonium salts with remarkable ease. This transformation serves as prospect for an unconventional way of nitrogen activation.

With alkyne metathesis rapidly maturing, the focus of our attention is gradually shifting to the downstream chemistry which ultimately defines the outreach of this method. Many creative ways of using alkynes can be envisaged, but some seemingly simple transformations remain surprisingly difficult to accomplish. Thus, it is by no means trivial to convert alkynes into *E*-alkenes under conditions that are compatible with sensitive functionality. This challenge was met in 2013 when we described an alkyne *trans*-hydrogenation that tolerates relevant functional groups. This unorthodox outcome seemingly violates the basic rules of hydrogenation reigning since Sabatier's ground-breaking work. The underlying concept has been generalized in that practical methods for *trans*-selective hydroboration, hydrogermylation and hydrostannation of alkynes were developed quickly thereafter. Detailed experimental and computational studies provided insights into the mechanism of these perplexing transformations.

While the use of carbophilic π-acids based on Au, Pt, Rh, Ru etc. has become tremendously popular since the turn of the millennium, the field is in its childhood with regard to firm mechanistic analyses. Of key relevance is a better understanding of the structure and reactivity of the metal carbenes commonly invoked. During the report period, we managed to isolate the first reactive gold carbenes and determined their structure by X-ray diffraction and NMR. Along the same lines, the first reactive rhodium carbenes were isolated and characterized, which had defied experimental inspection for decades.

In the area of iron catalysis, we were able to find several previously unknown reaction modes. This includes an unconventional way of ring opening/cross coupling of a heterocyclic scaffold, as well as an unprecedented merger of cross coupling and cycloaddition chemistry. Moreover, the intricate redox behavior of a prototype iron precatalyst was largely clarified, which had been subject to debate in the past.

All methodologies of interest to our group are scrutinized by applications to the total synthesis of structurally complex natural products of biological significance. Because the target compounds are highly precious and hardly available otherwise, we team up with external cooperation partners to study their biochemical and/or biological properties. Where deemed appropriate, we are prepared to adjust the original syntheses such that they allow for larger material throughput as well as for the preparation of non-natural analogues ("diverted total synthesis").

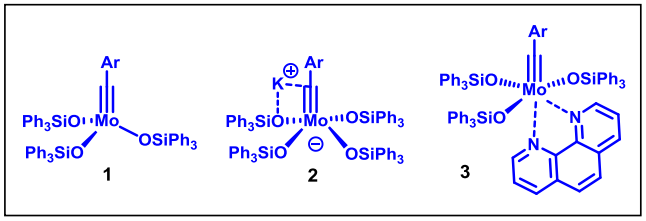
Over the years, close collaborations with Prof. Thiel and coworkers have become an integral part of many of our projects. Moreover, it is emphasized that our work would not be possible without the excellent support by and cooperation with the different analytical groups of the Institute. These mutually beneficial collaborations have led to several joint publications during the report period.

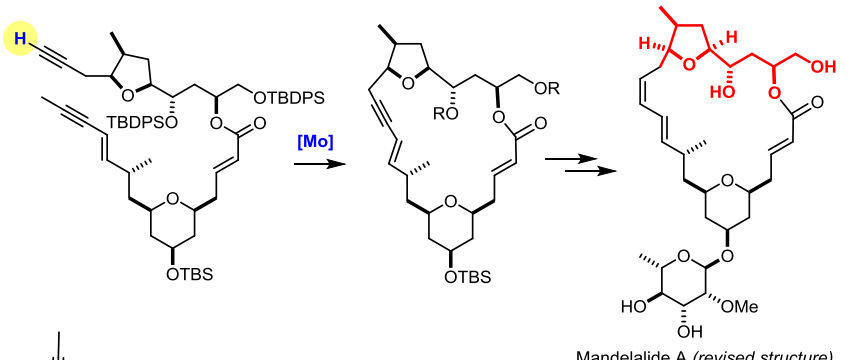
2.4.1 Research Area "Metathesis" (A. Fürstner)

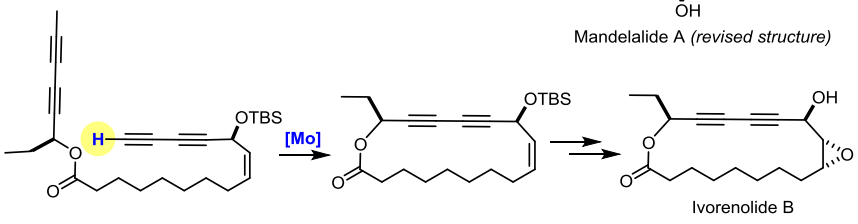
Involved: K. Gebauer, L. Hoffmeister, M. K. Ilg, A. Lackner, R. Llermet, S. Schaubach, J. Willwacher, F. Ungeheuer

Objectives: Teaching olefin metathesis "simple" stereochemistry is arguably the single most important issue of contemporary metathesis research. Whereas other laboratories managed to develop prototype examples of *Z*-selective alkene metathesis catalysts, our group pursues complementary approaches via triple bond metathesis. The alkyne products have the distinct advantage of providing access to many different structural motifs upon adequate downstream functionalization. Finally, it is shown that metathesis provides – at least in principle – even opportunities for the activation of N≡N triple bonds as exemplified by the cleavage of the [N_2]-unit of aryldiazonium salts.

Results: During the preceding report period (2011-2013), our group had developed a new generation of catalysts for alkyne metathesis such as **1**-**3** which outperform all ancestors in terms of activity and functional group compatibility. They capitalize on the synergy between a molybdenum alkylidyne core and a silanolate ligand sphere; moreover, reversible adduct formation with phenanthroline renders them bench-stable and hence easy to use. These catalysts are now commercially available and have been used by a number of groups worldwide in exigent applications.

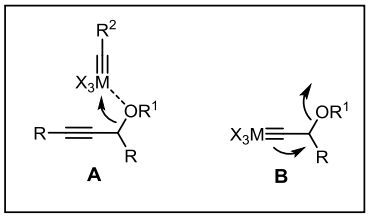




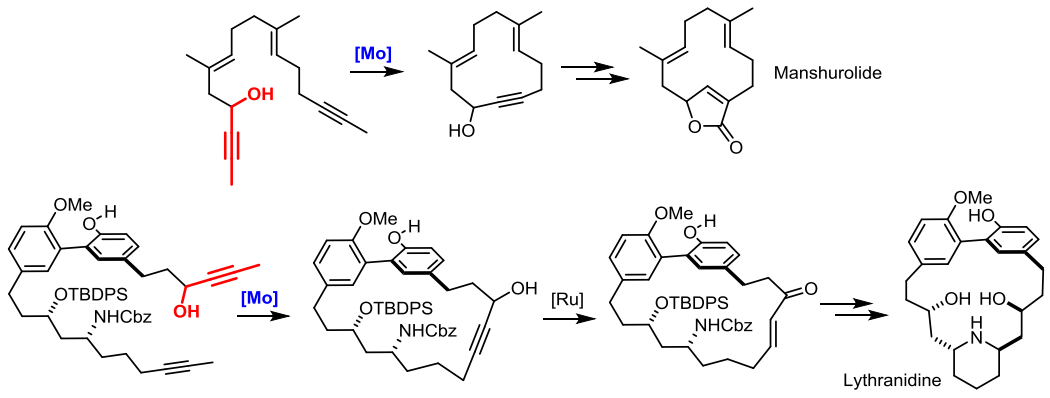


While our work had previously been focused on the understanding of these catalysts, attention has now shifted towards exploitation of their truly enabling application profile.

Terminal acetylenes are an important class of substrates that were traditionally beyond reach of alkyne metathesis because they polymerize on contact with a metal alkylidyne. Gratifyingly though, complex **3** is capable of inducing highly effective alkyne cross metathesis as well as ring closing alkyne metathesis reactions of terminal alkynes that were basically inconceivable before. Likewise, conjugated 1,3-diynes proved well behaved. The robustness of this methodology is apparent from applications to natural products such as ivorenolides A and B as well as mandelalide A. The latter project also led to the revision of the structure originally proposed by the isolation team: since the stereochemistry of the entire northern sector had been mis-assigned, this goal was reached only after a massive synthetic effort.



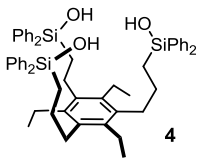
Propargyl alcohol derivatives are another class of challenging substrates for two major reasons: all alkyne metathesis catalysts are Schrock alkylidynes, and as such comprise an early transition metal in its highest oxidation state. Unless appropriately tempered by the ligand set, the inherent Lewis acidity endangers substituents at any activated position; propargylic alcohol derivatives fall into this category (see the generic structure **A**) because of the resonance stabilization of the resulting carbocations. Even if this serious pitfall is overcome and the chosen catalyst engages productively with the triple bond, the ensuing alkylidyne of type **B** might decompose by extrusion of the potential leaving group next to the nucleophilic site. Therefore it was gratifying to learn that our molybdenum alkylidynes allow such substrates to be metathesized with ease.



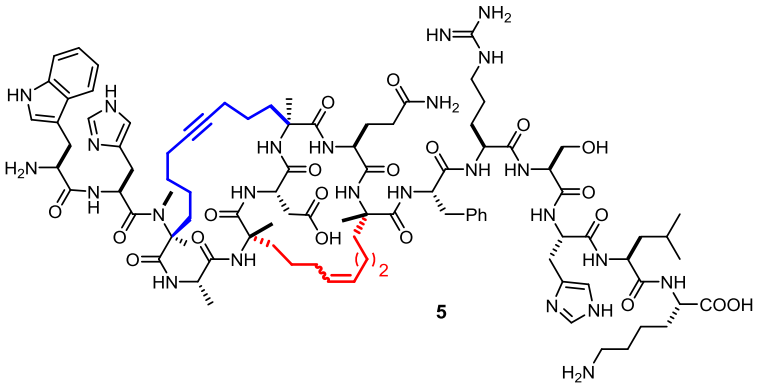
Because of the rich follow-up chemistry of propargyl alcohol derivatives, this outcome is particularly rewarding. The total syntheses of the strained sesquiterpene lactone manshurolide and the biphenyl alkaloid (–)-lythranidine illustrate just two of the many possibilities. As a spin-off of our studies, we developed a much improved catalyst for

the redox isomerization of propargyl alcohols, which is subject to further investigations in the laboratory.

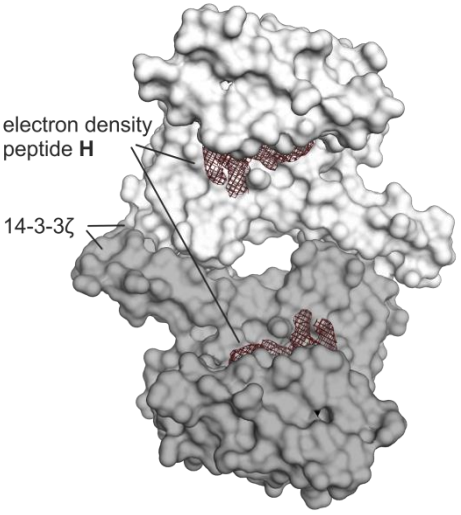
These examples illustrate yet another important point: because Schrock alkylidynes are nucleophilic at carbon, none of the classical catalysts had shown any meaningful compatibility with protic groups; in contrast, our molybdenum alkylidynes work well even in the presence of alcohols, phenols, amines, amides, sulfonamides etc. It is perhaps not surprising that formal replacement of the Ph_3SiO- ligands in the standard precatalyst **1** by a potentially chelating ligand environment, as materialized in **4**, imparts even higher stability (although the corresponding catalyst is oligomeric rather than a well-defined monomeric entity). In any case, the functional group tolerance of molybdenum alkylidynes endowed with silanolates as ancillary ligands is remarkable. Several total syntheses referred to in the different chapters of this report illustrate this aspect.



4

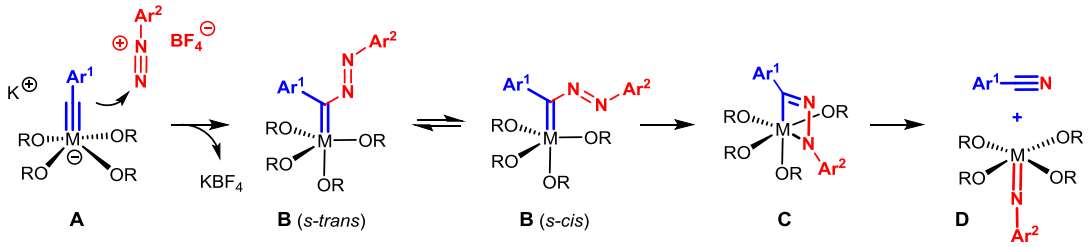

5

Another instructive case pertains to the formation of stapled peptides, which also represents the first application of alkyne metathesis on solid support. The compatibility of the molybdenum catalysts with olefins of all sorts made it even possible to prepare bicyclic peptide architectures such as **5** via consecutive ring closing alkene/alkyne metathesis. Compound **5** shows high affinity to an activated Rab GTPase; this protein superfamily comprises several clinically relevant yet particularly challenging drug targets that are key regulators of intracellular vesicular transport and trafficking.



In parallel work, alkyne metathesis was used to prepare a monocyclic stapled peptide that could be co-crystallized with its protein target; therefore it serves as a valuable tool to study the 14-3-3ξ

binding motif of the exo-enzyme virulence factor S of *Pseudomonas aeruginosa*.



The power of triple bond metathesis is also evident from an entirely different application to aryldiazonium salts. This choice may seem counterintuitive since these compounds loose N_2 with ease, whereas the formal N≡N triple bond itself is very stable. Yet, on treatment with molybdenum or tungsten alkylidyne ate-complexes endowed with triphenylsilanolate ligands, the [N_2] unit is metathesized even at low temperature. The reaction transforms the alkylidyne unit into a nitrile and the aryldiazonium entity into an imido ligand to the metal center, as unambiguously confirmed by X-ray diffraction. Since the bonding situation of an aryldiazonium salt is similar to that of certain metal complexes with end-on bound dinitrogen, this unprecedented transformation might represent a conceptually novel strategy for dinitrogen cleavage that is devoid of any redox steps and hence orthogonal to the established methods.

Future directions: Fill the few remaining gaps with regard to functional group tolerance, find strategic applications were alkyne metathesis is uniquely enabling, and expand the scope of triple bond metathesis beyond ordinary alkynes.

Publications resulting from this research area: 3-10, 17, 19-22, 24, 25, 27, 29, 30, 32-34, 39, 44, 46

External funding: Alexander-von-Humboldt Foundation (fellowship to A. Lackner), Fonds der Chemischen Industrie (fellowships to S. Schaubach and J. Willwacher)

Cooperations: T. N. Grossmann (Amsterdam, NL), W. Thiel (Mülheim/Ruhr, DE), H. Waldmann (MPI Dortmund, DE)

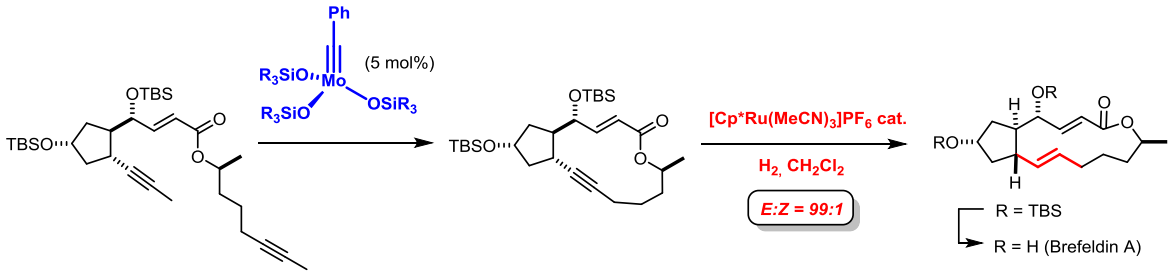
2.4.2 Research Area: "*trans*-Addition Chemistry" (A. Fürstner)

Involved: T. G. Frihed, M. Fuchs, K. Michigami, J. Preindl, K. Radkowski, D.-A. Rosca, S. Rummelt, S. Schaubach, H. Sommer, B. Sundararaju

Objective: We try to find broadly applicable catalytic addition reactions to π-bonds that violate the reigning paradigms of organometallic chemistry.

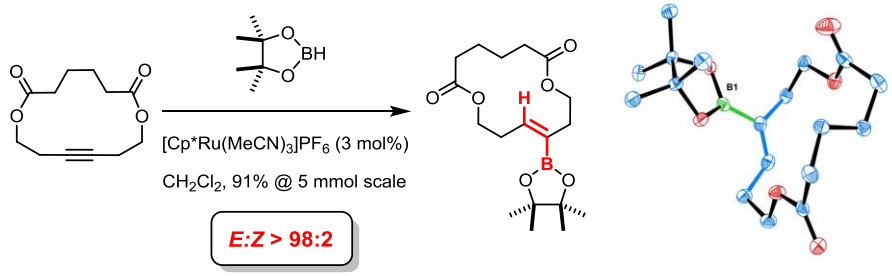
Results: Alkyne metathesis in combination with a Birch-type reduction opens a stereoselective entry into *E*-alkenes; this sequence fills an important gap in methodological coverage, since inherently *E*-selective alkene metathesis catalysts are unknown. With the advent of the powerful and practical alkyne metathesis catalysts described in the previous chapter, however, it became increasingly clear that the weak point of this tactics is the semi-reduction step, which, in its classical format, requires strongly reducing conditions that preclude many functional groups.

At the outset of our project, the best current alternative was the *trans*-hydrosilylation chemistry introduced by Trost and coworkers shortly after the turn of the millennium. When combined with a subsequent proto-desilylation of the resulting alkenylsilanes, *E*-alkenes can be formed in an indirect manner. This remarkable discovery was rapidly embraced by the synthesis community, despite the fact that non-symmetrical substrates almost always lead to the formation of regioisomers.

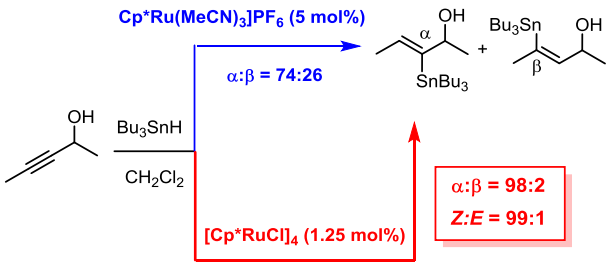


Intrigued by the then unknown reasons for this unorthodox stereochemical outcome and spurred by the potential preparative significance of *trans*-addition chemistry in general, we initiated a long-term research program in this area. A first notable success was reached when we managed to develop a method that allows internal alkynes to be directly hydrogenated with remarkable levels of *trans*-selectivity; this perplexing result had been briefly mentioned in the last progress report. A number of control experiments proved that the net stereochemical outcome is not the result of a canonical *cis*-reduction followed by isomerization; rather, it is an inherent virtue of the ruthenium catalyst

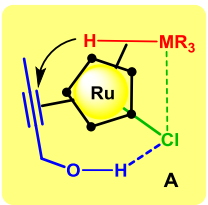
which seemingly violates the fundamental rule of suprafacial *syn*-selective hydrogen delivery that governs hydrogenation since the pioneering work of Sabatier. The novel *trans*-hydrogenation proved compatible with many (reducible) functional groups and already stood the test of natural product total synthesis. Specifically, it served as the cornerstone of a highly productive entry into brefeldin A, which is a widely used probe molecule in the biosciences for its ability to target the Golgi apparatus.



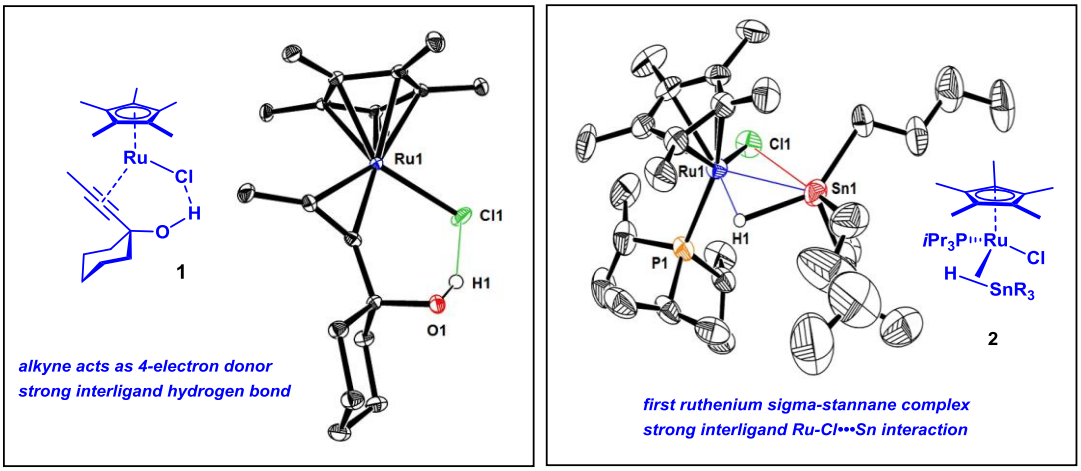
A first mechanistic study provided strong evidence for the intervention of a σ-H_2 complex on the catalytic cycle. Since silanes are also capable of forming σ-complexes, this preliminary information suggested that *trans*-hydrogenation and *trans*-hydrosilylation basically follow the same principles. Under this premise, other reagents able to form ruthenium σ-complexes might also qualify for *trans*-addition chemistry. This notion was quickly proven correct: it allowed us to establish the *trans*-hydroboration, *trans*-hydrogermylation and *trans*-hydrostannation of internal alkynes, which again violate the paradigms of organometallic chemistry and prove highly versatile in synthetic terms.



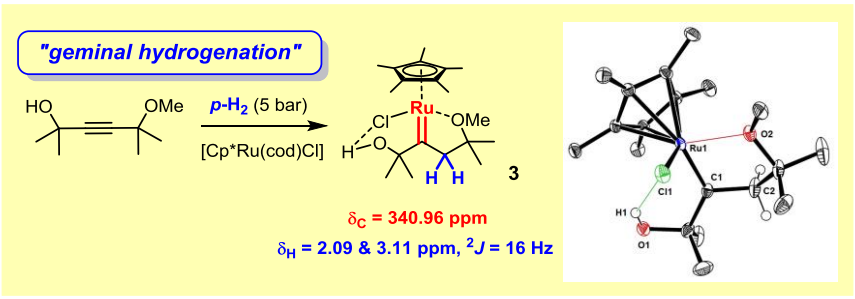
Irrespective of the stereochemical outcome, any hydrometalation of an unsymmetrical π-bond gives mixtures of regioisomers. In the present context, however, this severe handicap is easily circumvented by using neutral precatalysts comprising a [Ru–Cl] bond. Under the proviso that the alkyne substrate carries a protic functional group, the R_3M unit is faithfully delivered to the acetylene-C-atom proximal to the steering substituent. The effect is massive and therefore of considerable preparative significance (see below). It originates from the ability of the polarized [Ru–Cl] bond to engage in hydrogen bonding with the protic group, which helps upload, activate and lock the alkyne substrate in the coordination sphere. An additional interligand contact of the



chloride with the –MR_3 center (M = Si, Ge, Sn) positions the incoming reagent in the loaded complex of type **A** in a matching orientation that ultimately translates into high regioselectivity.

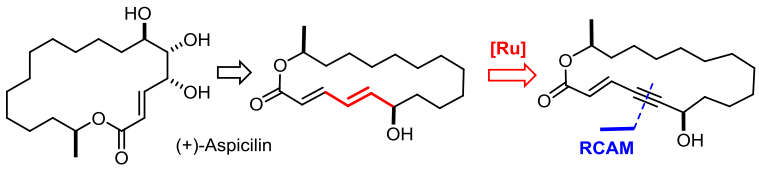


The proposed secondary interactions are manifest in a host of spectral and crystallographic data. Specifically, a number of ruthenium alkyne π-complexes such as **1** were isolated that feature strong interligand hydrogen bonds between an –OH group in the substrate and the Ru–Cl entity of the catalyst. Likewise, the first ruthenium complex with a σ-bound stannane ligand was obtained, which corroborates the notion that σ-coordination is instrumental for alkyne *trans*-addition chemistry. The strong peripheral Ru–Cl···MR_3 contacts manifest in complex **2** are in excellent accord with model **A** meant to describe the loaded complex formed en route to product. Importantly, these experimental data are in full agreement with high level DFT calculations of the entire reaction path.

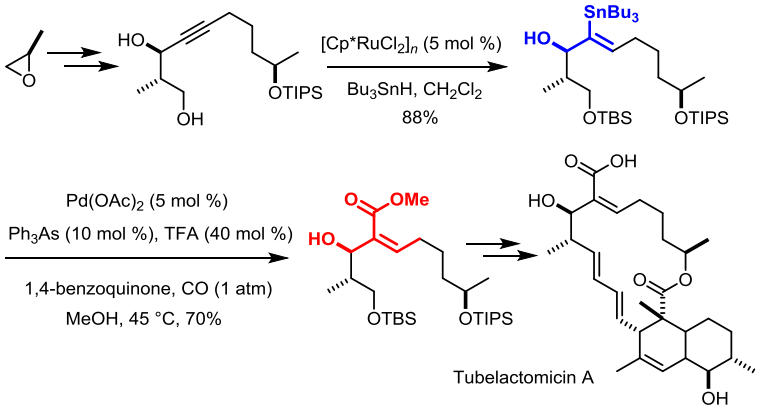


Valuable insights into the origins of the unorthodox *trans*-addition mode were gained by *para*-hydrogen (*p*-H_2) induced polarization (PHIP) transfer NMR spectroscopy. Surprisingly, it turned out that the productive *trans*-reduction concurs with a pathway in which both H-atoms of H_2 are delivered to a single alkyne C-atom of the substrate, whilst the second alkyne C-atom converts into a metal carbene. This intriguing "*geminal*-hydrogenation" is unprecedented in the realm of organic chemistry; it was confirmed by isolation and

structural characterization of the ruthenium carbene complex **3** stabilized by secondary interligand interactions. An in-depth DFT study showed that the *trans*-alkene and the carbene complex originate from a common metallacyclopropene intermediate. Moreover, the computational analysis and the PHIP NMR data concur in that metal carbenes analogous to **3** are a gateway to olefin isomerization and over-reduction, which interferes with regular alkyne *trans*-hydrogenation.

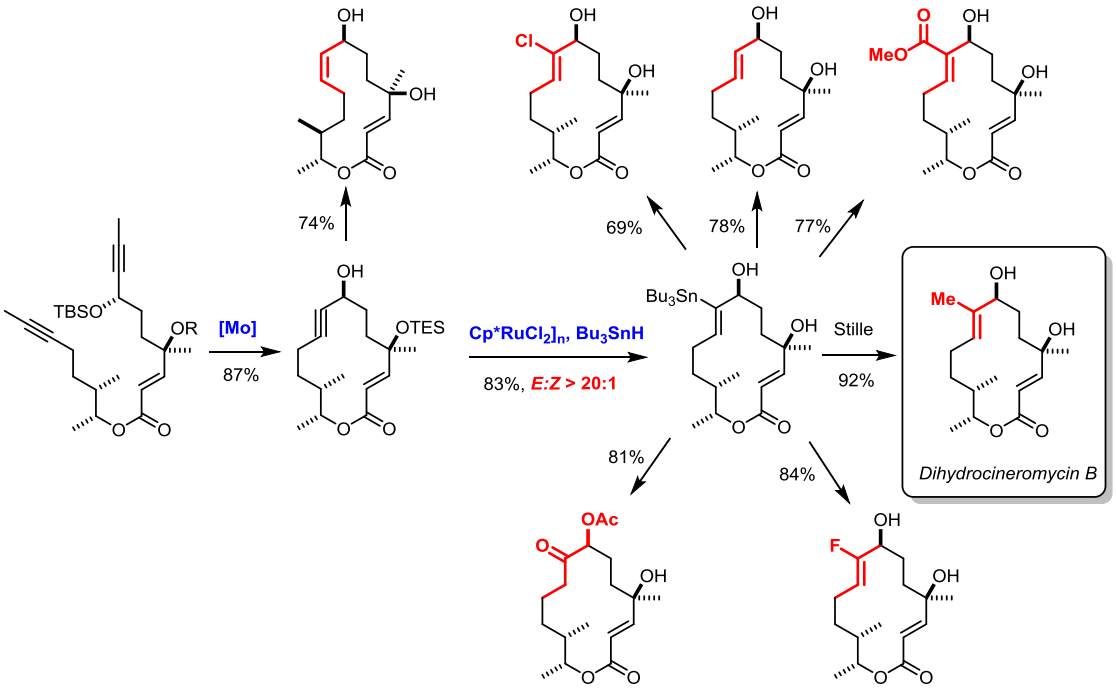


In parallel work, we were striving to showcase the preparative significance of the emerging *trans*-addition chemistry by increasingly complex applications to target oriented synthesis. In addition to the brefeldin case mentioned above, formal total syntheses of the lichen-derived macrolide aspicilin and the antibiotic tubelactomicin A were accomplished. The former project served to illustrate that a strategically-placed hydroxyl group allows substrates to be activated that are not amenable to *trans*-addition otherwise (e. g. 1,3-enynes). The tubelactomicin project, on the other hand, provided an opportunity to develop conditions for the direct methoxycarbonylation of alkenylstannanes. Key to success was the use of 1,4-benzoquinone in combination with trifluoroacetic acid for the regeneration of the palladium catalyst. The acid is essential for lowering the LUMO of the quinone and for marshaling the critical assembly of the reaction partners. Under the optimized conditions, competing proto-destannation is marginal.



Countless natural products of polyketide origin comprise an (*E*)-configured 2-methyl-but-2-en-1-ol substructure. An unconventional entry into this important motif was developed as part of a total synthesis of the antibiotic 5,6-dihydrocineromycin B. Our approach consisted of a sequence of alkyne metathesis followed by a hydroxyl-directed *trans*-hydrostannation and an uncommon methyl-Stille coupling. The excellent yield and remarkable selectivity with which the signature trisubstituted alkene site of 5,6-dihydrocineromycin B was procured is best appreciated when compared with the rather

poor outcome of a classical RCM reaction that had previously been exercised to form this motif.



Finally, we showed how the unorthodox ruthenium-catalyzed *trans*-hydrostannation can be used as a handle for diversity-oriented synthesis. To this end, it proved necessary to develop new conditions that allow the C-Sn bond of alkenylstannanes to be oxidized, fluorinated, methoxycarbonylated or protodestannated under conditions that are sufficiently mild to leave other vulnerable groups untouched. None of these transformations has had a satisfactory solution prior to our work; the generality of the new procedures is currently under investigation.

Future directions: Explore the scope and limitations of the ruthenium catalyzed *trans*-addition reactions and search for alternative and complementary catalyst systems; development of the downstream chemistry of readily available hydrometalated motifs.

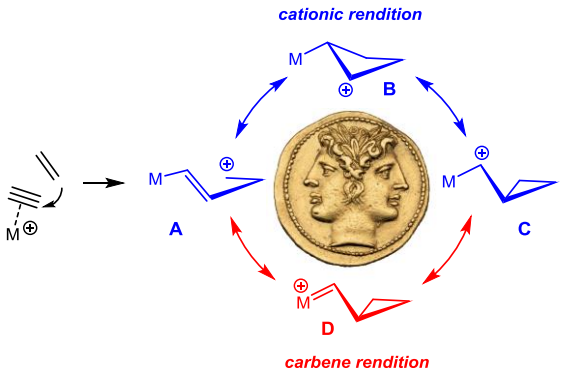
Publications resulting from this research area: 3, 11, 19, 25-28, 36, 45, 46

External funding: Alexander-von-Humboldt Foundation (fellowships to D.-A. Rosca and B. Sundararaju), Fonds der Chemischen Industrie (Kekulé stipend to S. Schaubach), FWF Austria (fellowship to M. Fuchs), Villum Foundation Denmark (fellowship to T. G. Frihed), JSPS (fellowship to K. Michigami).

Collaboration: C. Farès (Mülheim/Ruhr, DE), W. Thiel (Mülheim/Ruhr, DE)

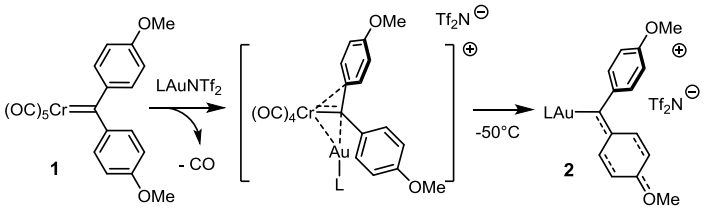
2.4.3 Research Area "Carbene Chemistry and π-Acid Catalysis" (A. Fürstner)

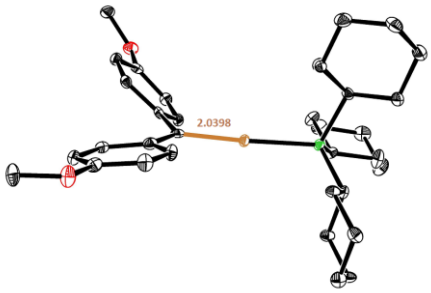
Involved: M. Ilg, L. Mantilli, G. Seidel, C. Werlé



Objective: Guided by our own early mechanistic proposal, we investigate the mode of action of carbophilic catalysts. Other lines of research concern asymmetric gold catalysis and rhodium carbene chemistry.

Results: The intervention of carbene intermediates in platinum or gold catalysis has originally been proposed by our group as early as 1998 and is now largely undisputed. Structure and bonding in these species, however, has been subject to considerable debate because they defied direct inspection. During the report period, we finally managed to isolate and fully characterize the first reactive gold carbene able to cyclopropanate styrene even at –30°C. The structure of complex **2** in the solid state shows that there is only very little back donation of electron density from gold to the carbene center and hence truly modest Au–C double bond character; rather, it is the organic ligand framework that is responsible for stabilizing the species by resonance delocalization of the accumulated positive charge. Following this lead finding, other groups reported related gold carbenes and reached similar conclusions. These data nicely confirm our previous view that such intermediates exhibit significant cationic character. Therefore we strongly recommend not to use the very popular but largely misleading [Au=C] notation whenever referring to distinct intermediates of this type in condensed phase.

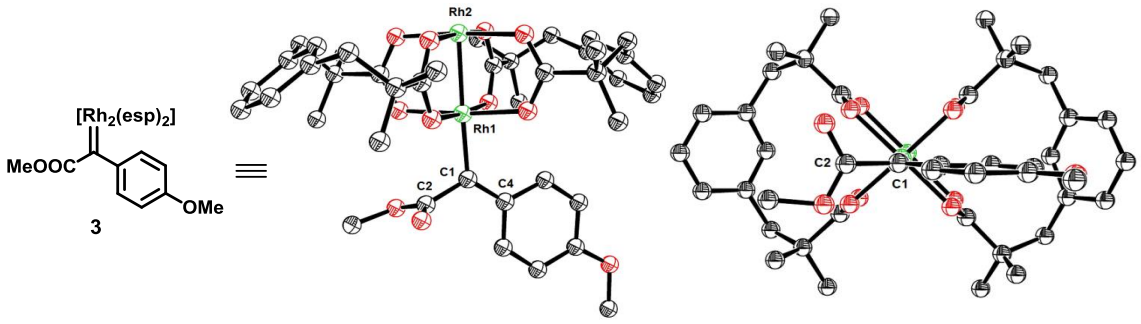




Access to this prototype gold carbene **2** was originally gained by transmetalation of a tailored Fischer chromium

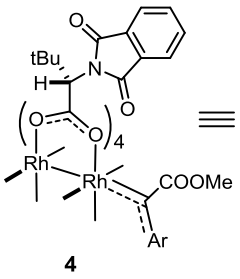
carbene complex **1**. While this approach proved highly effective, it is not overly practical for a more systematic investigation. A much more convenient alternative was found by "transmetalation" of transient dirhodium carbenes with an appropriate $[LAu]^+$ source, which in turn allows readily available diazoalkanes to be used as substrates (that tend to decompose on attempted direct reaction with $[LAu]^+$). This new method furnished a number of additional gold carbenoids differing from **2** in the ancillary ligand and/or the carbene backbone. Several representative examples could be characterized by X-ray diffraction; therefore structural information about this class of reactive intermediates – which was nil prior to our 2014 paper – is now deemed fairly consolidated.

During this study we became aware that structural information about dirhodium carbenes themselves is also largely missing. The only experimental reference point was a singular ^{13}C NMR and EXAFS spectrum reported by Davies, Berry and coworkers in 2013. This situation is more than inappropriate in view of the tremendous importance that rhodium carbenes in general have gained during the last decades, not least in the areas of asymmetric catalysis and C–H activation.

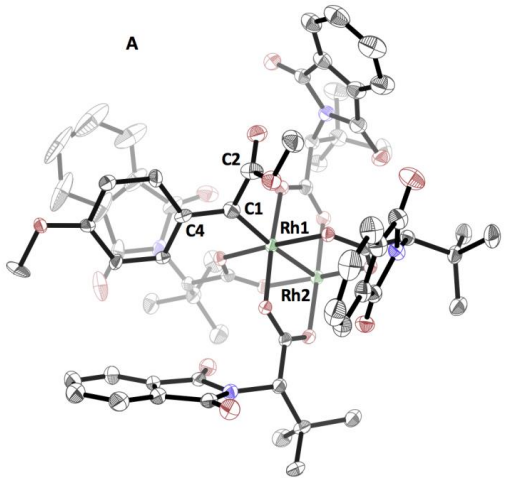


In an attempt to fill this gap, we made massive efforts to isolate representative members of this class of "superelectrophilic" intermediates in pure form. Because of their exceptional sensitivity, the project proved unusually challenging. Major difficulties arose from the fact that even the pure crystalline material decomposes in less than 12 h at –20°C; solute CH_2Cl_2 and toluene are necessary to ensure meta-stability but tend to be highly disordered within the unit cell. Considerable experimentation was necessary to find conditions that allowed crystals of sufficient quality to be grown. These serious issues notwithstanding, we were able to determine the structures of a dozen reactive dirhodium(II) tetracarboxylate and mononuclear half-sandwich Rh(III) carbenes in the solid state.

Our experimental data correct and/or refine previous computational studies and allow the stereochemical course of rhodium catalyzed reactions to be rationalized. They reveal the importance of stereoelectronic rather than steric arguments as the major selectivity-determining factors. The carbene ligand occupies an axial coordination site on the dirhodium cage and the Rh2-Rh1–C1 axis is almost linear. The Rh1–C1 bond distance is substantially longer than that previously computed for various model compounds. This fact suggests that back-donation of electron density from the metal into the carbene center is minute. To compensate, C1 strongly engages with the flanking arene, whereas the electron withdrawing ester group of the donor/acceptor carbene is positioned orthogonal to the carbene lobe to disrupt any destabilizing electronic communication. In all cases investigated, the carbene entity adopts a staggered conformation relative to the O–Rh–O unit, whereas previous computations had predicted an eclipsing orientation.

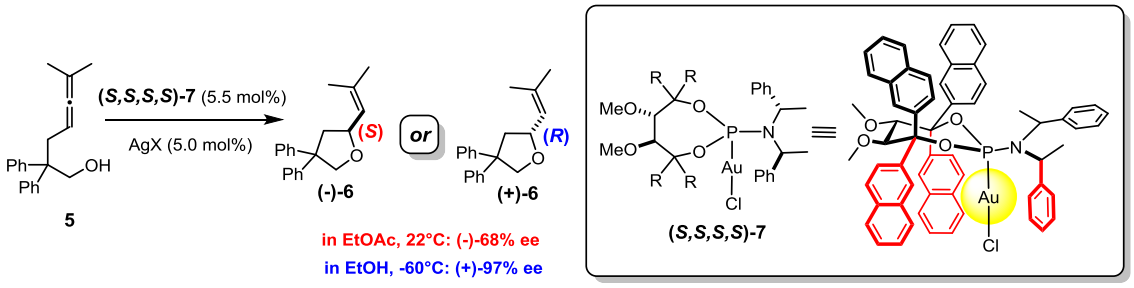


4



An extension of this study to dirhodium carbenes endowed with chiral ligand sets proved unexpectedly difficult. It was only after considerable experimentation that two representative chiral complexes were obtained in crystalline form. They carry the widely used *N*-phthalimide protected amino acid derivatives (PTTL) as auxiliary ligands originally introduced by Hashimoto and coworkers. The chiral binding pocket is primarily defined by the conformational preferences of the *N*-phthaloyl protected amino acid ligands and reinforced by a network of interligand interactions. NMR data confirm that the structure determined by X-ray diffraction persists in solution and provide additional information about the dynamics of this species. Our experimental results resolve the controversial issue as to which conformation of the chiral binding site is responsible for asymmetric induction. For the very first time, we could interpret the stereochemical course of an asymmetric cyclopropanation solely on the basis of experimental data without need to make any assumptions about the chiral ligand environment.

The last project to be mentioned in this chapter refers to the perplexing observation that the cyclization of the hydroxy-allene **5** to the tetrahydrofuran **6** catalyzed by the chiral gold complex **7**, after ionization with an appropriate silver salt AgX, is one of the most striking cases of enantioinversion known to date. The sense of induction can be switched from (*S*) to (*R*) solely by changing either the solvent or the temperature or the nature of the counterion X.



The governing TADDOL-related phosphoramidites featuring an acyclic (rather than acetal) backbone had been introduced as powerful ligand set for asymmetric gold catalysis by our group a few years ago. A combined experimental/computational study showed that the major reason for the stereoinversion phenomenon is likely found in the bias of the organogold intermediates to undergo assisted proto-deauration. Such assistance can be provided either by a protic solvent, by a reasonably coordinating counterion, or even by a second substrate molecule itself; in this way, the reaction free energy profile gains a strong entropic component that ultimately dictates the stereochemical course. At the meta-level, our analysis shows that particular attention must be paid to the entropic changes along a reaction coordinate that are often disregarded in discussions of asymmetric catalysis in general.

Future directions: Refine our mechanistic understanding of π-acid catalysis, calibrate mechanistic studies by the isolation of pertinent reactive intermediates, expand the scope of asymmetric gold catalysis, and scrutinize the methodology by selected applications

Publications resulting from this research area: 1, 3, 5, 8, 12, 13, 22, 23, 30, 31, 33, 38, 41, 42

External funding: Swiss National Science Foundation (fellowship to L. Mantilli), Fonds der Chemischen Industrie

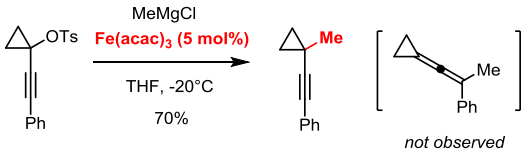
Cooperations: C. Farès (Mülheim, DE), R. Goddard (Mülheim, DE), W. Thiel (Mülheim, DE)

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

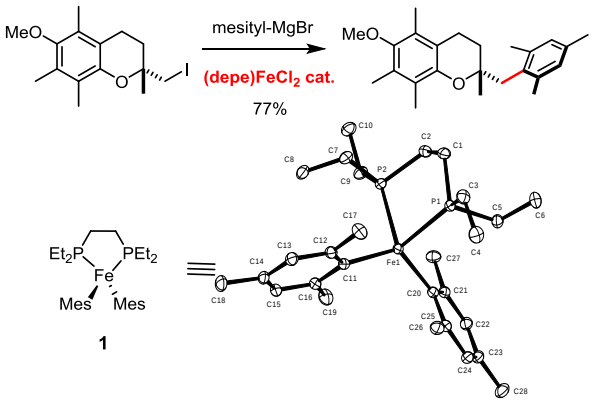
Involved: A. Casitas, P.-G. Echeverria, H. Krause, K. Lehr, S. Schulthoff, C.-L. Sun, D. J. Tindall, Y. Ueda, C.-X. Zhuo

Objectives: Centered in the middle of the d-block and able to support formal oxidation states ranging from –II to +VI, iron hold the promise of being able to encompass organic synthesis at large. Catalysts based on this metal are expected to serve reductive as well as oxidative regimes, can emulate "noble tasks", but are also able to adopt "early" transition metal character. Our group strives to discover useful transformations and to investigate their mechanistic background, most notably in the areas of cross coupling, cycloaddition and cycloisomerization chemistry.

Results: Homogeneous iron catalysis has been a topic of considerable interest for the group since we reported the first successful examples to alkyl-aryl cross coupling shortly after the turn of the millennium. These studies were predicated on the conception that iron is potentially capable of serving as a cheap, benign and readily available substitute for noble metal catalysts. In parallel, we try to harness the peculiarities of this element, which is located in the center of the d-block and hence endowed with "early" as well as "late" transition metal character.

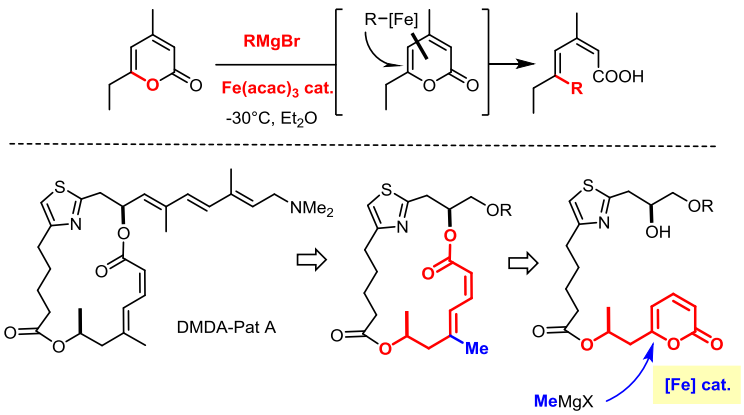


Notable progress in the cross coupling arena relates to the successful coupling of 1-alkynylcyclopropyl tosylates with alkyl-magnesium halides in the presence of catalytic [$Fe(acac)_3$] under net propargylic substitution; allene formation, which is the prevalent reactivity mode of propargylic substrates otherwise, is insignificant. (1-Alkylcyclopropyl)ethynyl groups, as readily accessible by this new method, are present in a number of drug candidates and crop protection agents. To the best of our knowledge, this transformation represents the first successful iron catalyzed cross coupling of a *tert*-alkyl electrophile.

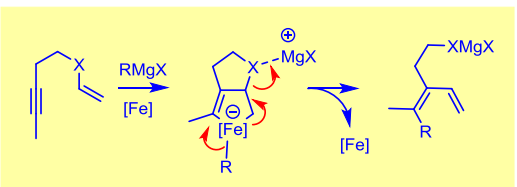


Another largely unmet chemical need concerns the coupling of sterically hindered Grignard reagents which often fail and/or lead to competing homo-dimerization. We found that

commercially available bis(diethyl-phosphino)ethane (depe) is an adequate ancillary ligand for such purposes. This chelating bis-phosphine is slim enough not to interfere with the loading of the iron center even by *ortho,ortho*-disubstituted arylmagnesium halides, yet capable of preventing premature reductive coupling of the resulting organoiron complex [(depe)Fe(mesityl)$_2$] (**1**); this species was isolated and characterized by X-ray diffraction; it proved competent in a number of stoichiometric as well as catalytic control experiments. The method is compatible with various polar functional groups as well as substrates containing β-heteroatom substituents; it allows even encumbered neopentylic electrophiles to be arylated with donors as bulky as mesitylmagnesium bromide, which had not been possible before.

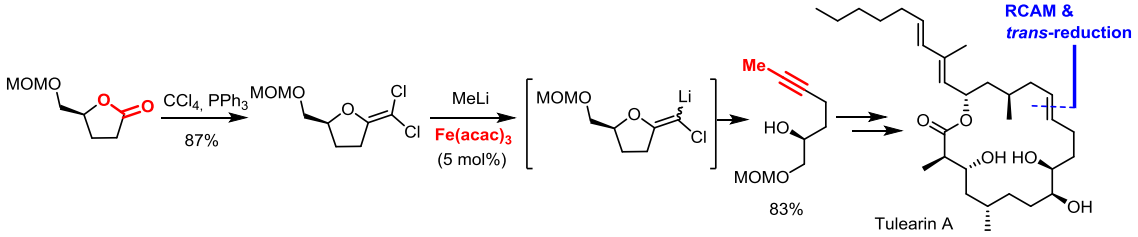


In late 2013 we described a formal ring opening/cross coupling process that epitomizes a largely underrepresented reaction mode. 2-Pyrones react with Grignard reagents in the presence of Fe(acac)$_3$ to give diene carboxylic acids after work up. In all cases investigated, the reaction was stereospecific in that the incoming nucleophile replaces the lactone leaving group with retention of configuration. Therefore this unorthodox transformation formally represents a "cross coupling" process, although it likely proceeds via 1,6-addition followed by electrocyclic ring opening. It served as the key step of a concise synthesis of desmethyl-desamino-pateamine A (DMDA-Pat A), a highly potent translation inhibitor endowed with remarkable *in vivo* activity against two different melanoma mouse models. Our novel entry is significantly more productive than the literature route; it capitalizes on the masking of the signature *Z,E*-configured dienoate subunit as a 2-pyrone ring, which was crafted by a gold catalyzed cyclization also developed in our laboratory (see the following chapter of this report). While the robustness of the heterocycle greatly facilitated the entire assembly stage, the highly isomerization-prone seco-*Z,E*-dienoic acid could be unlocked in due time for macrolactonization by iron catalyzed ring opening/cross coupling.

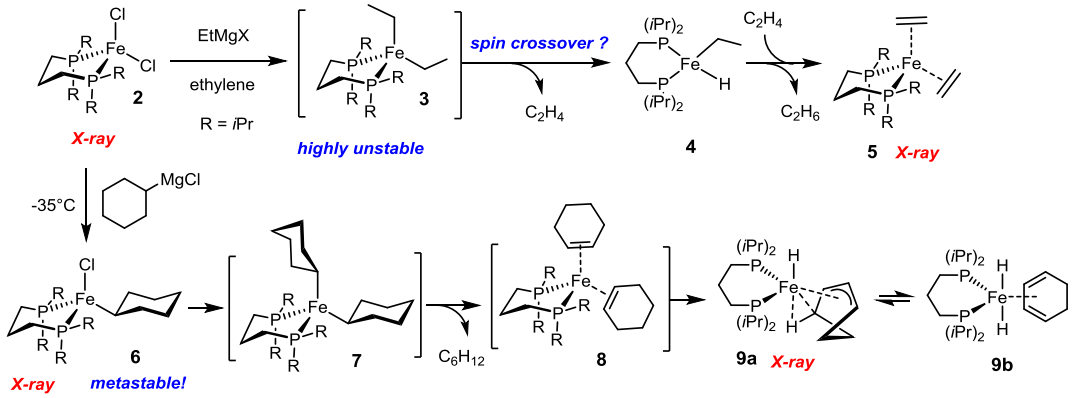


Treatment of readily available enynes with alkyl-Grignard reagents in the presence of

catalytic amounts of $Fe(acac)_3$ engenders a reaction cascade that results in the net formation of two new C–C bonds while a C–X entity in the substrate backbone is broken. Not only does this manifold lend itself to the extrusion of heteroelements (X = O, NR), but it can even be used for the cleavage of activated C–C bonds. The reaction likely proceeds via metallacyclic intermediates, the iron center of which gains ate-character before reductive elimination does occur. The overall transformation represents a previously unknown merger of cycloisomerization and cross coupling chemistry and provides ready access to functionalized 1,3-dienes comprising a stereodefined tetrasubstituted alkene unit, which are difficult to make by conventional means.

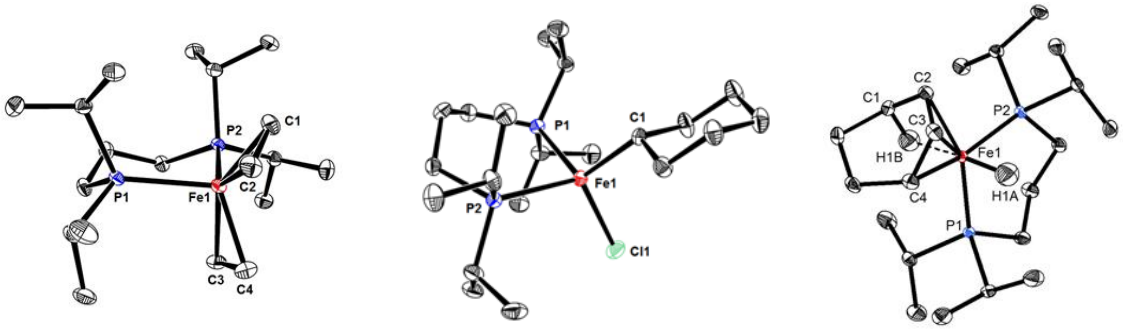


As briefly mentioned in the previous report, a high-yielding route to non-terminal alkynes starting from lactones was developed. Formation of the corresponding *gem*-dichloroalkenes followed by treatment with RLi generates lithium carbenoids that are sufficiently electrophilic to intercept an additional equivalent of RLi prior to collapse and release of the product. Although the reaction proceeds uncatalyzed in Et_2O or THF, it is best performed in the presence of either catalytic $Fe(acac)_3$ or $Cu(acac)_2$. Under these conditions, the method is broadly applicable and preserves chiral centers at the α-position; it has already powered our total syntheses of tulearin A and C, brefeldin A, muscenone, kendomycin and 5,6-dihydrocineromycin B.



Finally, the report period has seen extensive mechanistic investigations into organoiron catalysis. In a first foray, we studied the alkylation of the iron complex **2** (and related species) with Grignard reagents containing β-hydrogen atoms. Although seemingly trivial, this process is of considerable relevance for the understanding of C–H activation

as well as C–C bond formation mediated by low-valent iron species. Specifically, reaction of **2** with EtMgBr under an ethylene atmosphere affords the Fe(0)-complex **5** almost quantitatively, which is an active precatalyst for prototype [2+2+2] cycloaddition reactions and a valuable probe for mechanistic studies.



On the other hand, alkylation of **2** with 1 equivalent of cyclohexylmagnesium bromide furnished the unique iron alkyl species **6** with a 14-electron count that contains no less than four β-H atoms but is meta-stable against β-hydride elimination. In contrast, exhaustive alkylation of **2** with cyclohexylmagnesium bromide in the presence of cyclohexene triggers two consecutive C–H activation reactions mediated by a single iron center. The resulting complex has a diene-dihydride character in solution (**9b**), whereas its structure in the solid state is more consistent with an η^3-allyl iron hydride rendition featuring an additional agostic interaction (**9a**). These well-defined species are the starting point for ongoing investigations into low-valent iron complexes of relevance for cross coupling, CH-activation and cycloaddition chemistry.

Future directions: Search for unconventional and useful transformations catalyzed by iron complexes, and investigations into their mechanistic background.

Publications resulting from this research area: 3, 5, 15, 18, 25, 35, 37, 40, 43, 47

External funding: Alexander-von-Humboldt Foundation (fellowships to C.-L. Sun and C.-X. Zhuo), Fundación Ramón Areces (fellowship to A. Casitas), Kyoto University Education Program (scholarship to Y. Ueda)

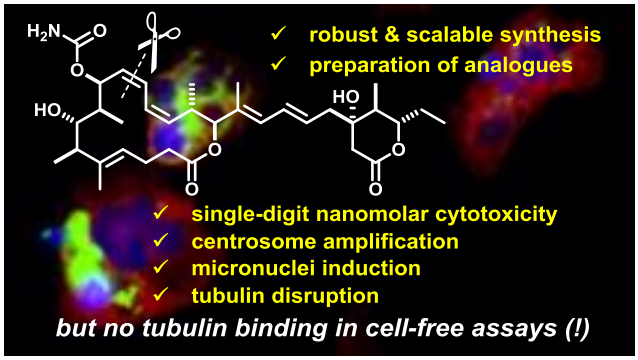
Cooperations: E. Bill (MPI for Chemical Energy Conversion, Mülheim, DE)

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

Involved: A. Ahlers, T. Fukuda, T. de Haro, L. Hoffmeister, K. Jouvin, D. Mailhol, P. Persich, G. Pototschnig, J. Preindl, S. Schulthoff, J. Willwacher, G. Valot

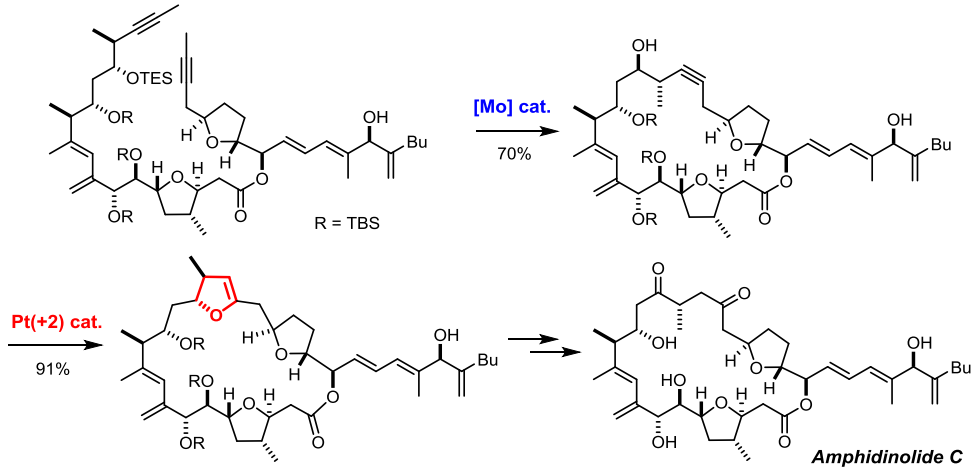
Objectives: We pursue the synthesis of complex natural products by catalysis-based routes, evaluate their biochemical and biological properties in cooperation with external partners, and investigate structure/activity relationships by molecular editing.

Results: In addition to the total syntheses mentioned in the previous sections, further projects were pursued that were meant to scrutinize the methodology developed in the group in complex settings; in most cases, questions concerning the biochemical and biological properties of the target compounds are of equal importance. This aspect is apparent in a rather comprehensive project aiming at the synthesis, molecular editing and biological assessment of the marine cytotoxin leiodermatolide. In the first foray, we managed to elucidate the previously unknown stereostructure of this demanding target by preparation of two possible diastereoisomers which the isolation team had proposed but was unable to distinguish. This synthesis illustrates that ring closing alkyne metathesis (RCAM) is particularly well-suited for applications to polyunsaturated targets where olefin metathesis (RCM) often finds its limits; a *Z*,*Z*-diene unit, as present in leiodermatolide, is certainly beyond reach of contemporary RCM catalysts.



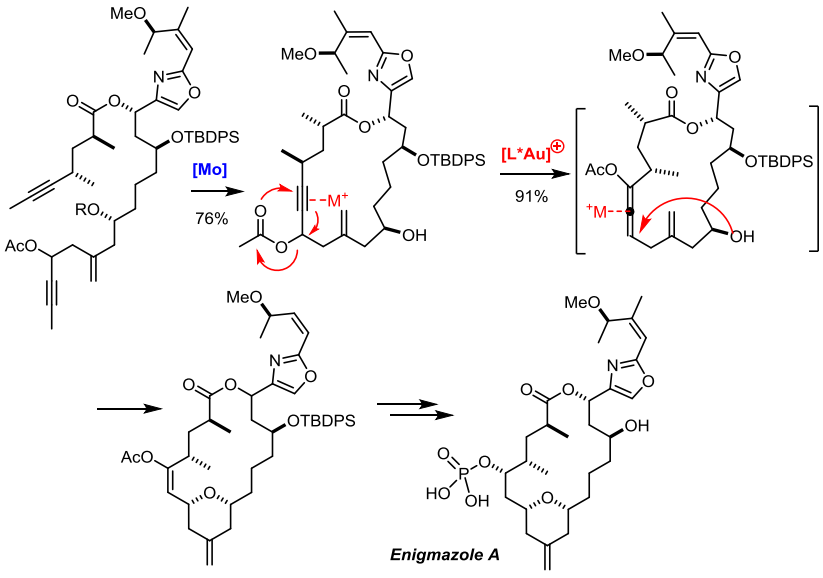
With the target unambiguously defined, our mission changed to secure a meaningful supply of this exceedingly rare natural product derived from a deep-sea sponge. To this end, a scalable route was developed in the second phase of the project that nicely showcased the scalability of alkyne metathesis; moreover, a Binol-catalyzed allylation of a highly enolizable β-keto-lactone allowed the conspicuous axial carbon branch on the δ-lactone ring to be set in a practical manner. Deliberate digression from this robust blueprint brought a series of non-natural analogues into reach for the study of the lead qualities of this compound. Leiodermatolide was shown to be a highly potent cytotoxin in human tumor cell proliferation assays, distinguished by GI_{50} values in the ≤ 3 nM range even

for cell lines expressing the Pgp efflux transporter. It causes mitotic arrest, micronucleus induction, centrosome amplification and tubulin disruption, even though it does not bind tubulin itself in cell-free assays. This paradoxical profile has little – if any – precedent: indirect evidence points at centrosome declustering as a possible mode of action, which holds promise of being inherently selective for malignant over healthy human tissue.

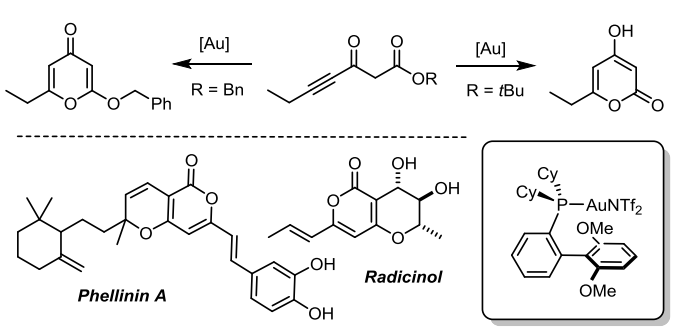


As part of our long-term commitment to the amphidinolides, a family of exceptionally potent secondary metabolites derived from marine dinoflagellates, we were able to finish the total synthesis of amphidinolide C as one of the most cytotoxic and – at the same time – structurally most complex members of this series. Our approach hinged upon alkyne metathesis with the in-house molybdenum alkylidynes followed by platinum catalyzed transannular hydroalkoxylation; notably, this simple carbophilic catalyst nicely selected for the triple bond over no less than five alkenes. This delicate strategic maneuver at a very late stage of the synthesis is deemed one of the most challenging applications of π-acid catalysis known to date.

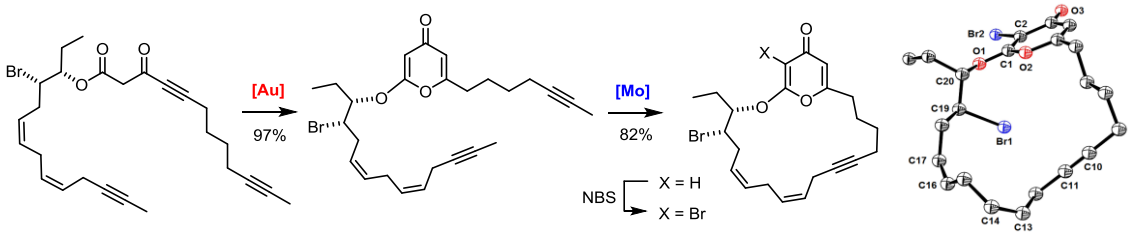
Of arguably similar complexity is the key reaction cascade en route to the phosphorylated macrolide enigmazole A. It commenced with a gold catalyzed [3,3]-sigmatropic rearrangement that walks a propargyl

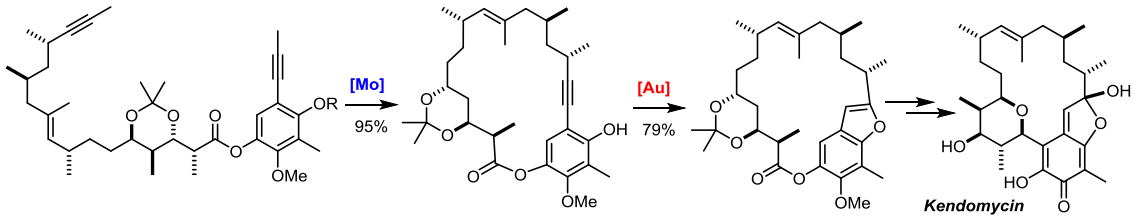


acetate along the periphery of the macrocyclic scaffold forged by RCAM; the resulting transient allenyl acetate immediately succumbs to a regio- and stereoselective transannular hydroalkoxylation. This transformation mandated the use of a chiral gold catalyst to override the inherent substrate bias. Another noteworthy step of this synthesis is the preparation of the oxazole building block by palladium catalyzed CH-activation.

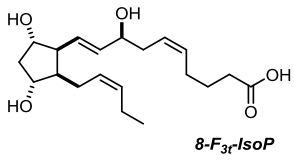


We developed a new entry into pyrones derivatives based on the cyclization of 3-oxo-5-alkynoic acid esters upon treatment with a carbophilic catalyst. Depending on the choice of the ester group, 2-pyrones or 4-pyrones can be selectively prepared. The reliability of the method was first proven by applications to various members of the radicinol and phellinin families. Subsequently, it stood a truly challenging test during the total synthesis of an unnamed 4-pyrone of algal origin, which also allowed us to determine the previously unknown stereostructure of this remarkable natural product: it comprises a rare brominated 4-pyrone nucleus linked via a ketene-acetal to a polyunsaturated macrocyclic scaffold comprising a homoallylic bromide entity. Our synthesis was based on the elaboration and selective functionalization of an exceptionally fragile cyclization precursor endowed with no less than six (skipped) sites of unsaturation, including the enolized oxo-alkanoate function. Yet, the formation of the 2-alkoxy-4-pyrone ring by a novel gold catalyzed transformation worked nicely, engaging only the acetylenic β-ketoester substructure while leaving all other π-bonds untouched. The synthesis was completed by RCAM to forge the signature cycloalkyne motif, followed by selective bromination of the ketene-acetal site without touching the skipped diene-yne substructure resident within the macrocyclic tether.





A total synthesis of kendomycin provides yet another illustration of the power of alkyne metathesis in concord with π-acid catalysis. The intriguing *ansa*-architecture of this target had provided inspiration for many groups in the past; our synthesis is conceptually different from the literature precedent in that it disconnects the macrocyclic frame of kendomycin at the rather sensitive heterocyclic *para*-quinonemethide/lactol substructure. In the forward sense, this motif was formed by RCAM followed by a gold-catalyzed benzofuran synthesis/oxidation sequence of the type previously developed in our laboratory. This foray proved rewarding in that it opened the arguably most productive entry into this strongly cytotoxic agent.



Finally, studies on isoprostanoids such as 8-F_{3t}-IsoP need to be briefly mentioned. These scarce compounds are non-enzymatic metabolites of polyunsaturated fatty acids and, as such, stress markers of high medicinal interest. In order to enable detailed preclinical and clinical investigations, authentic samples were prepared by a flexible strategy that allows for considerable structural variation.

Future directions: Identify, synthesize and evaluate (hopefully) relevant targets; prepare functional analogues by diverted total synthesis; sustain the network of collaborations with academic and industrial partners to ensure professional testing

Publications resulting from this research area: 1, 3, 5-8, 10, 17, 19-22, 25, 27, 29, 30, 32-34, 36, 38, 39, 43-46

External funding: Fonds der Chemischen Industrie (fellowship to J. Willwacher), FWF Austria (fellowship to G. Potoschnig), JSPS (fellowship to T. Fukuda), Swiss National Science Foundation (fellowship to T. de Haro)

Cooperations: Pfizer Oncology and Medicinal Chemistry (Groton, US); J.-M. Galano (Montpellier, FR)

2.4.6 Research Area "α-Cationic Phosphines" (M. Alcarazo)

Involved: H. Tinnermann, E. González, J. Dube, S. Holle, E. Haldón, L. Gu, P. Linowski, A. Zannardi, L. Nicholls

Objective: Synthesis of structurally differentiated α-cationic phosphines/arsines and evaluation of their potential as ancillary ligands in catalysis.

Introduction: The world of ligands is dominated by anionic and neutral species. This is not surprising considering that they have been designed to coordinate metals, which usually behave as Lewis acids. Cationic ligands are exceptions and when they are used, the positive charged group is mostly located at a remote position from the donating atom. However, beneficial effects can be expected from the incorporation of positive charges in close proximity to the donor position. The strong –I inductive effect of positive charges reduces the σ-donor abilities of α-cationic phosphines. Simultaneously, the new very low lying σ*(P-C^+) orbitals increase their π-acceptor character and, as a consequence, the global electron donation of these ligands to the metal is quite low.

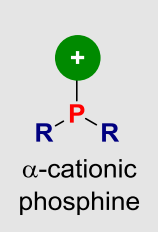
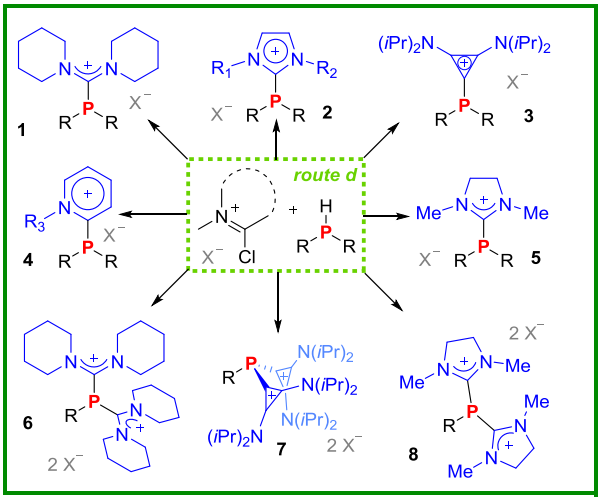


Fig. 1

This may have interesting consequences in catalysis: if the rate-determining step of a catalytic cycle is facilitated by an increase of the Lewis acidity at the metal center, an acceleration of the process is expected by the use of such ancillary ligands. Interestingly, this situation is found more frequently than one might think: many common elementary steps involved in catalytic cycles, such as reductive eliminations, coordination of substrates to metals, or the attack of nucleophiles to coordinated substrates, belong to this category and are often fostered by electron poor metal centers.

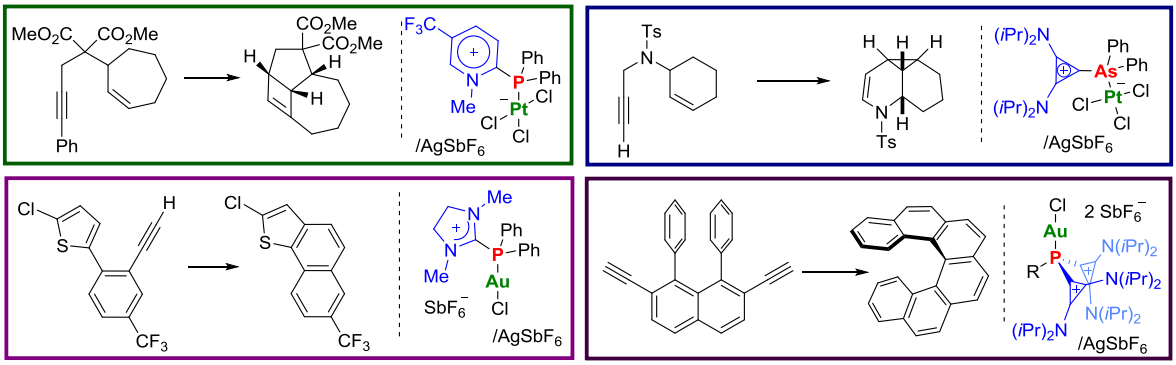
Results: We have implemented a general synthetic method for the synthesis of α-cationic phosphines based on the reaction of secondary phosphines and Vilsmeier-type salts. The availability of both starting materials and the high yields of the condensation reactions make this route very reliable even on multigram scale.
Since then, the repertoire of α-cationic phosphines incorporated to the ligand tool box has been truly expanded, and it now includes cyclopropenio-, imidazolinio-, pyridinio-, and formamidiniophosphines, **1**-**8** respectively (Scheme 1). Moreover, α-dicationic phosphines and α-cationic arsines can be prepared after only small variations of this synthetic methodology.



Scheme 1. Synthetic route for the preparation of mono- and dicationic phosphines.

The structural analysis of compounds **1-5** reveals two parameters that are crucial in understanding their coordination properties. The central phosphorus atom of **1-5** displays a pyramidal environment (sum of angles around P1: 300-318°, depending on the steric demand of the substituents), while all P-C(+) bonds lengths are, within experimental error, very similar to those of the other two P-C(Ph) bonds. These observations suggest that the non-shared electron pair is retained at phosphorus. For this reason the coordination chemistry of cations **1-5** seems to be as rich as that of traditional phosphines; up to now the formation of complexes with Au, Ag, Cu, Pt, Pd, Ni, Ir and Rh have been described. On the other hand, dicationic phosphines are less prone to coordinate metals. Up to now, we have only been successful on the preparation of Pt(II), and Au(I) derivatives of **7**.

Illustrative examples of the use of the newly prepared cationic phosphines in π-acid catalysis are depicted in Scheme 2. In these cyclisation processes the rate determining step is usually the attack of the nucleophile to the activated alkyne; therefore, the employment of cationic ligands that augment the Lewis acidity at the metal center proves beneficial. The reaction rates observed with cationic ancillary phosphines are between 20 and 500 times faster than those measured when Ph_3P-derived catalysts are used under otherwise identical conditions.



Scheme 2. Selected examples of the use of α-cationic phosphines in π-acid catalysis.

Future directions: We anticipate that the intensive acceleration effects observed in π-acid catalysis by the use of α-cationic phosphines might have tremendous implications in the area of asymmetric catalysis, where catalysts able to work at lower temperatures are usually required to obtain good enantiomeric excess. The development of chiral versions of the ligands prepared is one of our current research topics.

Publications resulting from this research area: 49, 51, 53-55, 57, 59, 60

External funding: Deutsche Forschungsgemeinschaft (projects AL1348 4-2 and AL1348 5-1); NSERC Canada (stipend to J. Dube); China Scholarship Council (stipend to L. Gu).

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

2.4.7 Research Area "Development of New Electrophilic Transfer Reagents" (M. Alcarazo)

Involved: G. Talavera, J. Pena, B. Waldecker, A. Barrado, Y. Zhang, A. Zielinski

Introduction: The unique ability of hypervalent iodine compounds to act as electrophilic group-transfer reagents has been extensively exploited during the last several years in a variety of synthetically useful transformations. These include trifluoromethylation, alkynylation, arylation, amination, halogenation and cyanation of a wide variety of electron-rich substrates under mild conditions. Considering this tremendous synthetic utility, it is surprising that other structurally related scaffolds, yet not based in iodine, have not been evaluated for similar purposes. We recently envisaged that imidazolium sulfuranes **A,** that are isolobal to I(III) species **B** and exhibit the key three-center four-electron bond motif, might be considered alternative platforms for the development of new electrophilic group-transfer reagents (Figure 1).

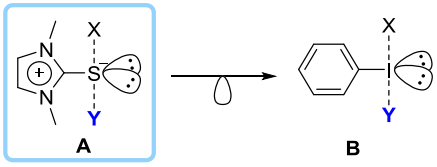
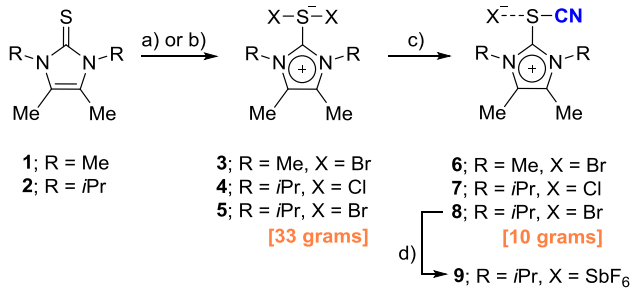


Fig. 1. Isolobal relationship between I(III) species and sulfuranes.

Objective: The implementation of this working hypothesis to the specific design of new sulfur-based electrophilic transfer reagents. Specifically, we have already developed cyanation, alkynylation and thioalkynylation reagents.

Results: We submitted thioureas **1** and **2** to previously described halogenation conditions, and obtained the corresponding hypervalent sulfur compounds **3-5** as bright yellow to orange solids in high yields and analytic purity (Scheme 1). Subsequent addition of one equivalent of Me_3SiCN caused the immediate disappearance of the color and formation of the desired imidazolium thiocyanates **6-8**. Compounds **6-8** were isolated as air stable pale yellow solids in excellent yields, and can be stored at room temperature for months without evident decomposition. Interestingly, compounds **6-9** depicted excellent ability to transfer



Scheme 1. Synthesis of 2-thiocyanoimidazolium salts.

the CN group to organic nucleophiles such as amines, sulfides, enolates, enamines, activated methylenes and electron rich aromatic compounds (Figure 2).

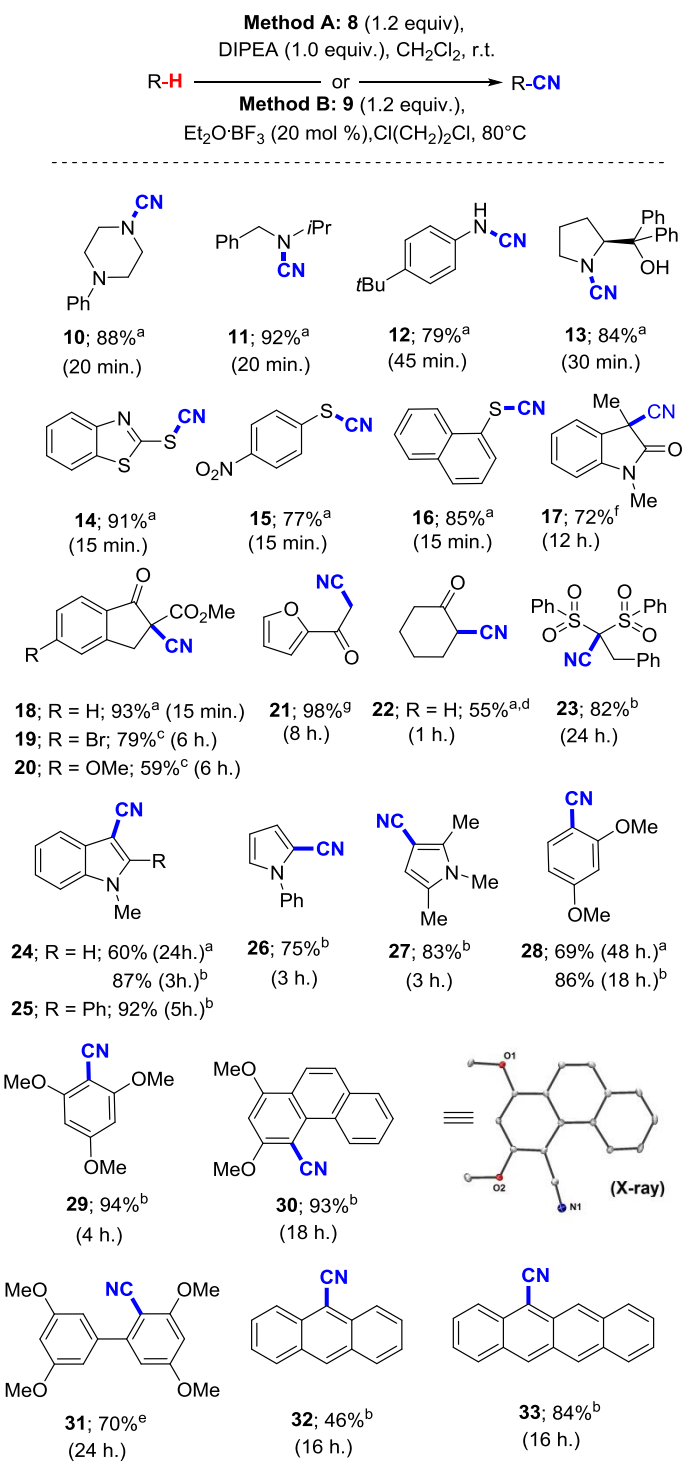
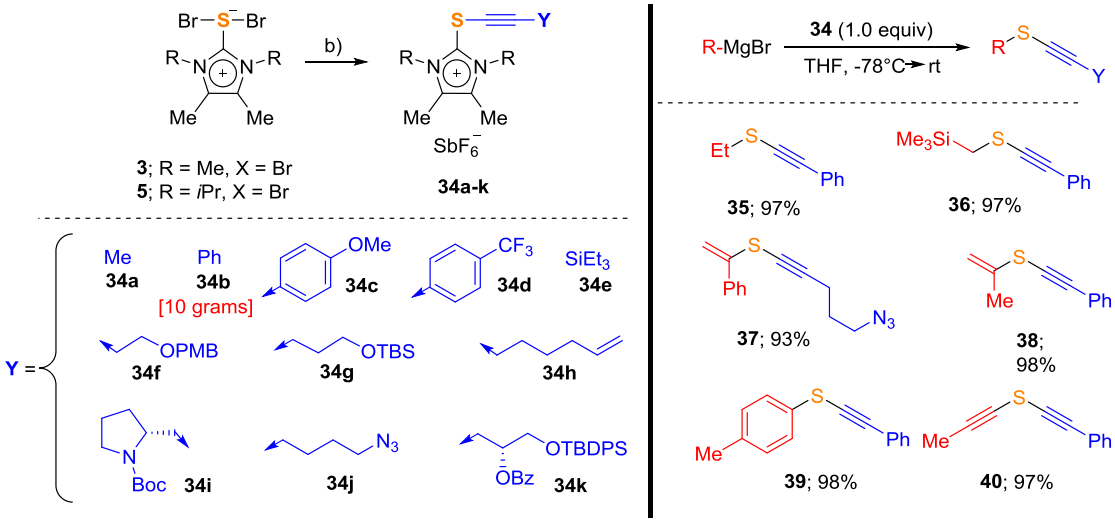


Fig. 2. Substrate scope of the electrophilic cyanation using 2-thiocyanoimidazolium salts **6-9**.

Encouraged by this discovery we set up to explore whether alkynylthioimidazolium salts **34a-k** could also participate in this transformation. Thus, a series of these compounds bearing different functionalizations on the alkyne rests was prepared by reaction of **5** with the desired alkynylzinc bromide. However, already during preliminary investigations, we came across an unexpected finding: simple commercially available Grignards regioselectively attack these salts *at the sulfur atom* affording the corresponding alkynylthioethers in excellent yields (Scheme 2). This unique behavior makes alkynylthioimidazolium salts convenient synthetic equivalents of a formal $[R-C\equiv C-S]^+$ cation.

Alkyl-, aryl-, alkenyl- and even alkynyl-Grignard reagents were found to smoothly react under optimized conditions with salts **34a-k**, providing a library of alkynylsulfides **35-40** in good to excellent yields. Specifically, the robustness and applicability of this transformation is highlighted by the successful preparation of

fairly hindered thioethers, vinylthioacetylenes, and a series of asymmetric bis(alkynyl)thioacetylenes that are non-obvious to obtain through other routes. Note however, that the preparative significance of this method is limited at this stage by the use of Grignard reagents.



Scheme 2. Synthesis and reactivity of 2-alkynylthioimidazolium salts.

Future directions: The potential of imidazolium sulfuranes to become platforms for the development of new reagents able to promote the umpolung of synthetically useful organic groups has been demonstrated. Ongoing studies in our laboratory intend to demonstrate the generality of the concept, and to further evaluate the synthetic utility of the new reagents.

Publications resulting from this research area: 58

External funding: Deutsche Forschungsgemeinschaft (project AL1348 7-1); Regional Government of the Basque Country, Spain (stipend to G. Talavera).

2.4.8 Publications 2014-2016 from the Department of Organometallic Chemistry

Fürstner group

(1) Fürstner, A. *Acc. Chem. Res.* **2014**, *47*, 925-938.
(2) Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 8-9.
(3) Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 8587-8598.
(4) Fürstner, A. In *Comprehensive Organic Synthesis*; Molander, G. A., Knochel, P., Eds., 2nd ed.; Elsevier: Oxford, 2014; Vol. 5; pp 1357-1399.
(5) Fürstner, A. *C. R. Chim.* **2014**, *17*, 1065-1070.
(6) Gebauer, K.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 6393-6396.
(7) Guy, A.; Oger, C.; Heppekausen, J.; Signorini, C.; De Felice, C.; Fürstner, A.; Durand, T.; Galano, J.-M. *Chem.–Eur. J.* **2014**, *20*, 6374-6380.
(8) Hoffmeister, L.; Persich, P.; Fürstner, A. *Chem.–Eur. J.* **2014**, *20*, 4396-4402.
(9) Lhermet, R.; Fürstner, A. *Chem.–Eur. J.* **2014**, *20*, 13188-13193.
(10) Mailhol, D.; Willwacher, J.; Kausch-Busies, N.; Rubitski, E. E.; Sobol, Z.; Schuler, M.; Lam, M.-H.; Musto, S.; Loganzo, F.; Maderna, A.; Fürstner, A. *J. Am. Chem. Soc.* **2014**, *136*, 15719-15729.
(11) Rummelt, S. M.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 3626-3630.
(12) Seidel, G.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 4807-4811.
(13) Seidel, G.; Gabor, B.; Goddard, R.; Heggen, B.; Thiel, W.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 879-882.
(14) Seidel, G.; Fürstner, A. *Organometallics* **2014**, *33*, 4336-4339.
(15) Sun, C.-L.; Krause, H.; Fürstner, A. *Adv. Synth. Catal.* **2014**, *356*, 1281-1291.
(16) Wang, F.; Mielby, J.; Richter, F. H.; Wang, G.; Prieto, G.; Kasama, T.; Weidenthaler, C.; Bongard, H.-J.; Kegnæs, S.; Fürstner, A.; Schüth, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 8645-8648.
(17) Willwacher, J.; Fürstner, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 4217-4221.
(18) Casitas, A.; Krause, H.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 1521-1526.
(19) Fuchs, M.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 3978-3982.
(20) Fürstner, A. In *Handbook of Metathesis, Vol. 2: Applications in Organic Synthesis*; Grubbs, R. H., O'Leary, D. J., Eds.; Wiley-VCH: Weinheim, 2015; Vol. 2; pp 405-501.
(21) Fürstner, A. In *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Trost, B. M., Li, C.-J., Eds.; Wiley-VCH: Weinheim, 2015; pp 69-111.

(22) Hoffmeister, L.; Fukuda, T.; Pototschnig, G.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 4529-4533.
(23) Ilg, M. K.; Wolf, L. M.; Mantilli, L.; Farès, C.; Thiel, W.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 12279-12284.
(24) Lackner, A. D.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 12814-12818.
(25) Lehr, K.; Schulthoff, S.; Ueda, Y.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 219-227.
(26) Leutzsch, M.; Wolf, L. M.; Gupta, P.; Fuchs, M.; Thiel, W.; Farès, C.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 12431-12436.
(27) Rummelt, S. M.; Preindl, J.; Sommer, H.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 6241-6245.
(28) Rummelt, S. M.; Radkowski, K.; Roşca, D.-A.; Fürstner, A. *J. Am. Chem. Soc.* **2015**, *137*, 5506-5519.
(29) Ungeheuer, F.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 11387-11392.
(30) Valot, G.; Mailhol, D.; Regens, C. S.; O'Malley, D. P.; Godineau, E.; Takikawa, H.; Philipps, P.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 2398-2408.
(31) Werlé, C.; Goddard, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15452-15456.
(32) Willwacher, J.; Heggen, B.; Wirtz, C.; Thiel, W.; Fürstner, A. *Chem.–Eur. J.* **2015**, *21*, 10416-10430.
(33) Ahlers, A.; de Haro, T.; Gabor, B.; Fürstner, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 1406-1411.
(34) Cromm, P. M.; Schaubach, S.; Spiegel, J.; Fürstner, A.; Grossmann, T. N.; Waldmann, H. *Nat. Commun.* **2016**, *7*, 11300.
(35) Echeverria, P.-G.; Fürstner, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 11188-11192.
(36) Frihed, T. G.; Fürstner, A. *Bull. Chem. Soc. Jpn.* **2016**, *89*, 135-160.
(37) Fürstner, A. *Adv. Synth. Catal.* **2016**, *358*, 2362-2363.
(38) Preindl, J.; Jouvin, K.; Laurich, D.; Seidel, G.; Fürstner, A. *Chem.– Eur. J.* **2016**, *22*, 237-247.
(39) Schaubach, S.; Gebauer, K.; Ungeheuer, F.; Hoffmeister, L.; Ilg, M. K.; Wirtz, C.; Fürstner, A. *Chem.– Eur. J.* **2016**, *22*, 8494-8507.
(40) Tindall, D. J.; Krause, H.; Fürstner, A. *Adv. Synth. Catal.* **2016**, *358*, 2398-2403.
(41) Werlé, C.; Goddard, R.; Philipps, P.; Farès, C.; Fürstner, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 10760-10765.
(42) Werlé, C.; Goddard, R.; Philipps, P.; Farès, C.; Fürstner, A. *J. Am. Chem. Soc.* **2016**, *138*, 3797-3805.
(43) Zhuo, C.-X.; Fürstner, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 6051-6056.

(44) Cromm, P. M.; Wallraven, K.; Glas, A.; Bier, D.; Fürstner, A.; Ottmann, C.; Grossmann, T. N. *ChemBioChem* **2016**, *17*, 1915-1919.
(45) Sommer, H.; Fürstner, A. *Org. Lett.* **2016**, *18*, 3210-3213.
(46) S. Schaubach, K. Michigami, A. Fürstner, *Synthesis* **2016**, *48*, DOI 10.1055/s-0035-1562381.
(47) A. Fürstner, *ACS Cent. Sci.* **2016**, *2*, 778-789.
(48) H. Sommer, A. Fürstner, *Chem.– Eur. J.* DOI org/10.1002/chem.201605444.

Alcarazo group

(49) Alcarazo, M. *Chem.–Eur. J.* **2014**, *20*, 7868-7877.
(50) Alcarazo, M. *Synlett* **2014**, *25*, 1519-1520.
(51) Gu, L.; Gopakumar, G.; Gualco, P.; Thiel, W.; Alcarazo, M. *Chem.–Eur. J.* **2014**, *20*, 8575-8578.
(52) Inés, B.; Holle, S.; Bock, D. A.; Alcarazo, M. *Synlett* **2014**, *25*, 1539-1541.
(53) Kozma, Á.; Deden, T.; Carreras, J.; Wille, C.; Petuškova, J.; Rust, J.; Alcarazo, M. *Chem.–Eur. J.* **2014**, *20*, 2208-2214.
(54) Tinnermann, H.; Wille, C.; Alcarazo, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8732-8736.
(55) Haldón, E.; Kozma, Á.; Tinnermann, H.; Gu, L.; Goddard, R.; Alcarazo, M. *Dalton Trans.* **2015**, *45*, 1872-1876.
(56) Holle, S.; Escudero, D.; Inés, B.; Rust, J.; Thiel, W.; Alcarazo, M. *Chem.–Eur. J.* **2015**, *21*, 2744-2749.
(57) Kozma, Á.; Rust, J.; Alcarazo, M. *Chem.–Eur. J.* **2015**, *21*, 10829-10834.
(58) Talavera, G.; Peña, J.; Alcarazo, M. *J. Am. Chem. Soc.* **2015**, *137*, 8704-8707.
(59) Dube, J. W.; Zheng, Y.; Thiel, W.; Alcarazo, M. *J. Am. Chem. Soc.* **2016**, *138*, 6869-6877.
(60) Mehler, G.; Linowski, P.; Carreras, J.; Zanardi, A.; Dube, J. W.; Alcarazo, M. *Chem.– Eur. J.* **2016**, *22*, 15320-15327.

Publications by Other Members of the Department

(61) **Roşca**, D.-A.; Wright, J. A.; Bochmann, M. *Dalton Trans.* **2015**, *44*, 20785-20807.
(62) **Weber**, D.; Gagné, M. R. In *Homogeneous Gold Catalysis*; Slaughter, L. M., Ed.; *Top. Current Chem.*; Springer International Publishing, 2015; Vol. 357; pp 167-211.