2.4. Department of Organometallic Chemistry

Director:

Alois Fürstner (born 1962)

Further group leaders:

Manuel Alcarazo (born 1978)
Group leader since December 2008

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

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, Royal Society of Chemistry
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
2013	Kitasato Medal, Tokyo, Japan

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
2008	Member of the Search Committee, Institute of Science and Technology Austria (ISTA)
2012-	Member of the Scientific Advisory Board, ISIQ Tarragona, Spain
2014-	Chairman, Editorial Advisory Board of *Angewandte Chemie*

Member of the International Advisory Boards of: "*Topics in Organometallic Chemistry*" (1997-); "*Advanced Synthesis & Catalysis*" (2000-); "*Journal of Organic Chemistry*" (2002-2004); "*Progress in Heterocyclic Chemistry*" (2005-); "*ChemMedChem*" (2006-); "*Nachrichten aus der Chemie*" (2007-2012); „*Synthesis*“ and „*Synlett*“ (2009-); „*ChemCatChem*“ (2009-); „*Israel Journal of Chemistry*“ (2010-), "*Angewandte Chemie*" (2010-), "*ChemPlusChem*" (2012-), "*Comptes Rendue de Chimie*" (2013-)

Organometallic Chemistry

The research in the Department is focused on the development of organometallic catalysts of preparative relevance and the investigation of their mode of action. Prof. Fürstner was appointed Director in 1998; since then, the Department has hosted several young scientists at the outset of their independent academic careers. First in line was Prof. Frank Glorius (2001-2004) who is currently Full Professor at the University of Münster; he was followed by Prof. Stefan Hecht (2005-2006), now Full Professor at the Humboldt-University of Berlin, and Dr. Lisbet Kvaerno (2007-2008), who decided to accept a position in industry after her short stint in Mülheim.

Since December 2008, Dr. Manuel Alcarazo is affiliated with the Department. His group has grown to a considerable size, not least because of his winning of a European Research Council Starting Grant in 2011. The work of Dr. Alcarazo is mainly focused on the design of new ligand structures and their use in homogeneous catalysis. His agenda encompasses the development of catalysts of exceptionally strong π-acidity and their applications in organic synthesis, the exploration of novel "frustrated" Lewis pairs for metal-free hydrogenation and related processes, the exploration of main-group elements in low oxidation states, as well as the investigation of new bonding modes (C–M dative double bonds, for example). This program nicely complements the activities of the Fürstner group.

In methodological regard, the major lines of research in the Fürstner group comprise investigations in the following fields of catalysis research, which are partly interwoven:

- alkene and alkyne metathesis
- carbophilic Lewis acid catalysts
- organoiron chemistry and catalysis
- novel reactivity patterns and ligand design

The 2011-2013 evaluation period has seen activities in each of these areas, although with an uneven emphasis. This is partly due to the fact that an important breakthrough was accomplished in the field of alkyne metathesis which therefore attracted much of our attention. Alkyne metathesis is one of the oldest projects in the group that had been initiated over a decade ago. At that time we had to use catalysts that were exceptionally sensitive and therefore difficult to work with. We now managed to develop a new class of catalysts that are not only considerably more active and selective, but can also be

rendered bench-stable; we thought of this as inconceivable before. Because of their largely superior properties, these new tools (which have recently also been commercialized) turn out to be exceptionally versatile and open many new vistas. This is particularly true if alkyne metathesis is used in combination with carbophilic Lewis acid catalysis for the selective manipulation of the resulting products. Considerable efforts were made during the report period to illustrate this notion. In any case, attempts at integrating alkyne metathesis and gold/platinum catalysis gave access to some of the most complex targets that the Fürstner group has ever been able to conquer.

Yet, the 2011-2013 evaluation period has also seen forays into entirely new methodologies, which might eventually lead to new long-term projects. Driven by the need to convert alkynes into *E*-alkenes under conditions that are compatible with sensitive functionality, we were able to demonstrate that metal catalyzed hydrogenation reactions can be carried out in a *trans*-selective fashion. This highly unorthodox outcome challenges the fundamental *cis*-addition rule that dominates heterogenous as well as homogenous hydrogenation since Sabatier's groundbreaking work. Our current mechanistic hypothesis suggests that other reactions could possibly also be forced to follow a non-conventional *trans*-addition mode. Indeed, we have recently managed to reduce the first *trans*-hydroborations of internal alkynes to practice.

As already briefly alluded to above, the methodologies of interest are scrutinized by applications to the total synthesis of structurally complex natural products of biological significance. Because the target molecules themselves are often highly precious and hardly available otherwise, we team up with external cooperation partners to probe their biochemical/biological properties. Where deemed appropriate, we are prepared to adjust the original syntheses such that they allow for larger material throughput and/or for the preparation of non-natural analogues ("diverted total synthesis"). The present evaluation report contains two such case studies, which were chemically highly rewarding but led to stunning biological results.

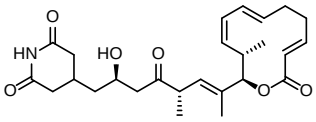
Over the years, close collaborations with Prof. Thiel and coworkers became an integral part of many of our projects. This mutually beneficial work has again resulted in joint publications during the report period. Moreover, it is emphasized that our work would not be possible without the excellent support by the different analytical groups of the Institute.

2.4.1. Research Area "Metathesis" (A. Fürstner)

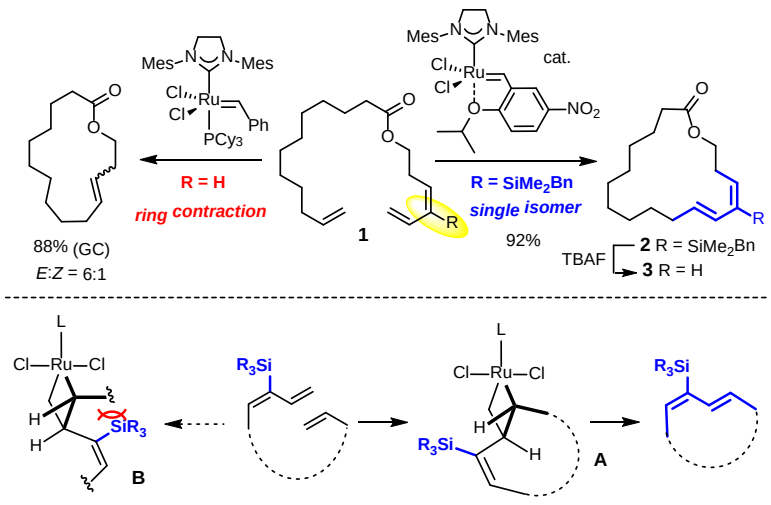
Involved: D. Gallenkamp, J. Heppekausen, V. Hickmann, A. Kondoh, J. Llaveria, R. Llermet, P. Persich, G. Seidel, R. Stade

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 which also furnished some rewarding results.

Results: The development of an efficient and scalable synthesis of ***lactimidomycin*** was a major preoccupation of the group during the report period. This exceedingly rare compound had been claimed to be a highly potent inhibitor of cell migration and might therefore serve as a lead in the quest for anti-metastatic agents. Because of the dauntingly high ring strain of its polyunsaturated macrolide core, we conceived different routes toward this exigent target.



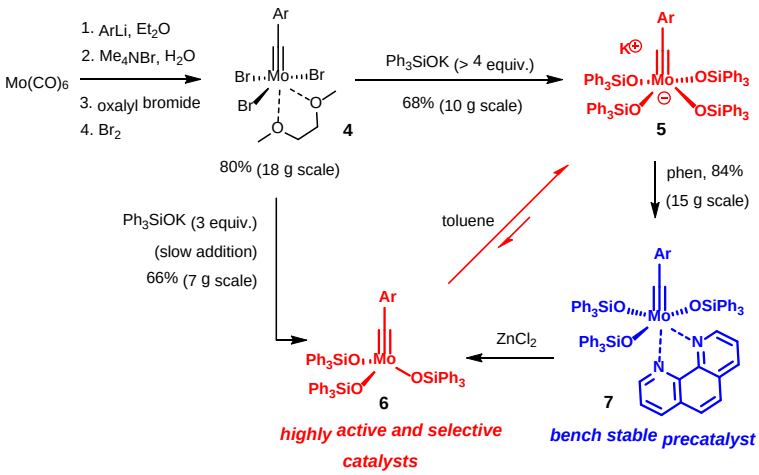
Lactimidomycin



One of them envisaged closure of the 12-membered ring by ordinary olefin metathesis at the diene subunit. 1,3-Dienes, however, are notoriously difficult to make by RCM, because Grubbs-type catalysts are unable to distinguish between the different olefinic sites and therefore often lead to ring contraction; moreover, they are usually stereo-unselective. We conjectured that the introduction of a strategically placed C-silyl group in the substrate might allow these deficiencies to be overcome. In fact, reaction of a model substrate such as **1** (R = $SiMe_2Bn$) with a second generation ruthenium carbene complex furnishes a single metathesis product **2**, from which the desired *Z*,*E*-diene **3** can be released by protodesilylaton. The multitasking silyl group protects the inner double bond against attack by the catalyst and simultaneously acts as a stereo-directing substituent that favors metallacycle **A** over its diastereomer **B**. This tactics turned out to

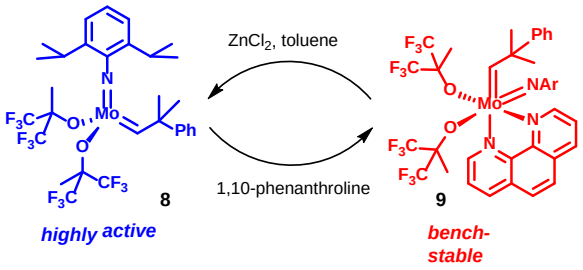
be general; indeed, it opened a first successful route to lactimidomycin. Moreover, silylated products such as **2** can also be subjected to post-metathetic transformations other than protodesilylation.

This success notwithstanding, we pursued a second entry into lactimidomycin based on alkyne metathesis (see Chapter 2.4.4). In the end, this route provided the better solution because it is shorter and scales particularly well; it has powered an extensive investigation of the putative cell migration inhibition properties of this class of compounds and ultimately led to the revision of this claim.



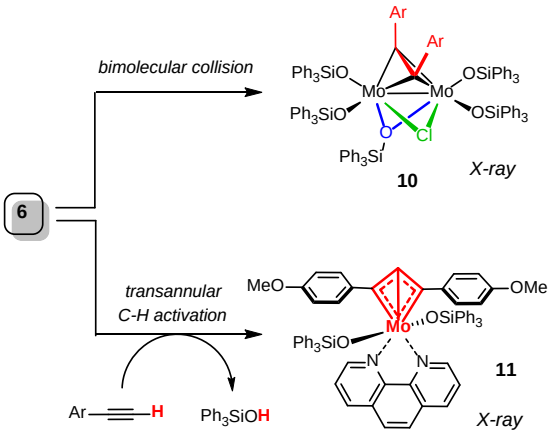
Key to success was a considerable advancement in catalyst design. In the previous evaluation report we had already mentioned that silanolate ligands impart truly outstanding activity onto molybdenum alkylidynes. Following this lead observation, considerable efforts were devoted to this new class of reactive species. To this end, their preparation was fully optimized and can now be carried out on a multi-gram scale. The best entry follows a literature route that allows readily accessible Fischer carbynes to be oxidized to the corresponding Schrock tribromo-alkylidynes **4**. Subsequent ligand exchange via salt metathesis gave access to a large panel of molybdenum alkylidynes in anionic (**5**) or – preferentially – in neutral (**6**) format and allowed the silanolate to be systematically varied. From the application point of view it is rewarding that cheap triphenylsilanol and tris(*p*-methoxyphenyl)silanol gave the most active and selective catalysts.

Importantly, addition of 1,10-phenanthroline or 2,2'-bipyridine provides bench stable adducts **7**. Upon reaction with metal salts ($ZnCl_2$, $MnCl_2$ etc.) that bind phenanthroline more tightly, however, the active alkylidyne **6** can be released undamaged and hence the excellent application profile of these powerful catalysts be harnessed without any special precautions or recourse to Schlenk techniques.



The underlying idea turned out to be more general: Schrock molybdenum alkylidenes such as **8** are amongst the most powerful olefin metathesis catalysts known to date, but mandate very careful handling. This inconvenience can be circumvented via the corresponding phenanthroline- or bipyridine adducts **9**, which are bench-stable and hence very user-friendly; once again, the active species can be regenerated on treatment with $ZnCl_2$ in toluene.

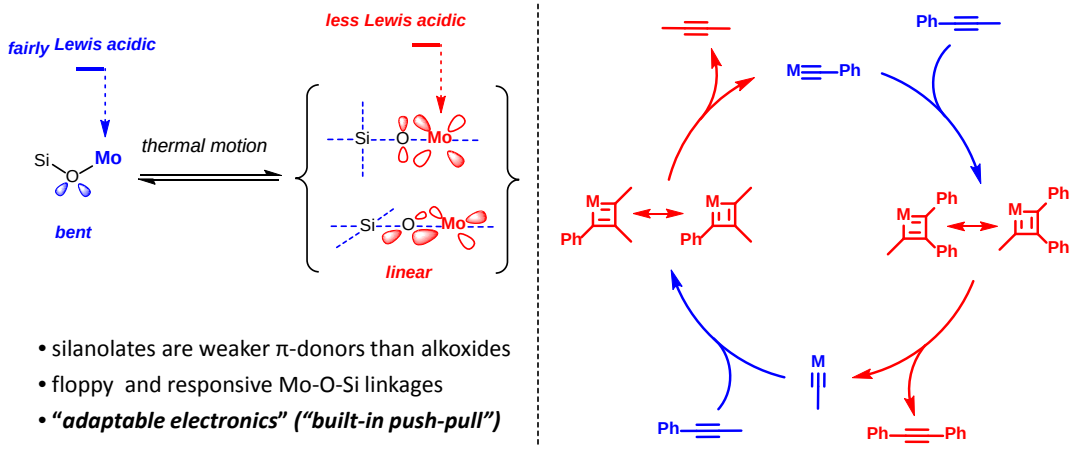
Alkylidynes endowed with silanolate ligands catalyze many alkyne metathesis reactions with unprecedented rates at or even below room temperature; under these conditions however, the released 2-butyne by-product does not evaporate (bp = 27 °C) and hence full conversion would not be reached. It was shown that this problem is easily fixed upon addition of molecular sieves (MS 5Å) which traps 2-butyne; moreover, this additive retards the eventual hydrolytic cleavage of the silanolate ligands and hence exerts a positive effect on the catalyst lifetime.



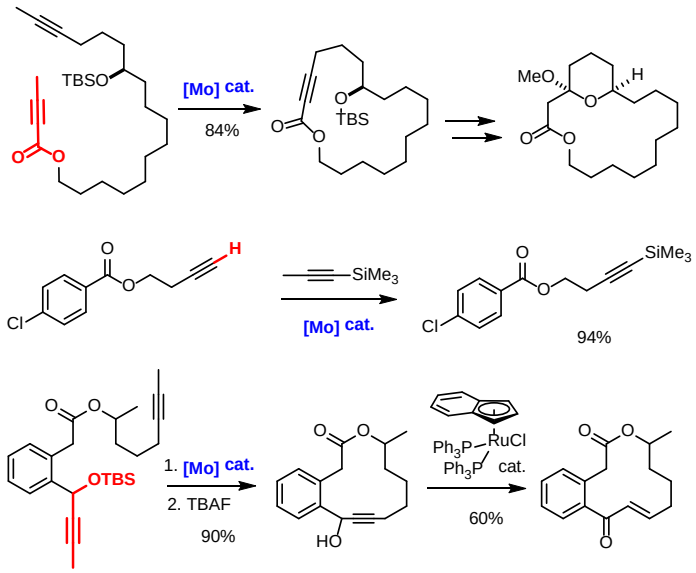
The major decomposition pathways of these catalysts were also carefully investigated. Other than by hydrolysis, they primarily decay via bimolecular collision with formation of dimetallatetrahedrane complexes **10**; gratifyingly though, the "peripheral" bulk of the R_3SiO-groups disfavors this process. Another decomposition pathway operates with terminal alkynes, which are subject to transannular C-H activation after the initial [2+2] cycloaddition; this process, however, requires gentle heating and is retarded due to the fairly low basicity of the silanolates.

Importantly, structural and spectroscopic data gave valuable insights into the origins of the remarkable synergy between silanolate ligands and the operative molybdenum alkylidyne unit. It is believed that their "adaptive electronic properties" are the single most important feature. Thermal motion results in constant stretching and bending of the Mo–O–Si hinges, which gently modulates the donor properties of the ligands and hence the Lewis-acidity of the central metal. This, in turn, allows the catalyst to meet

the different electronic optima of the individual steps of the catalytic cycle and therefore renders the turnover very facile.



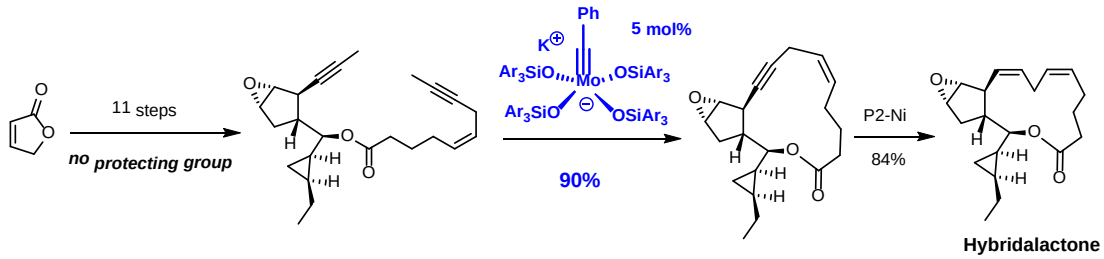
The arguably most rewarding aspect is the outstanding functional group compatibility of **6** and congeners. Although these catalysts comprise a cheap and early transition metal, their tolerance is reminiscent of what one usually expects from noble metals. Even commonly problematic groups such as basic amines or divalent sulfur seem to pose no problem. Limitations are encountered with substituents that are able to protonate the silanolate ligands off as well as with sterically very hindered substrates. Current efforts are directed towards closing these few remaining gaps in coverage.



Furthermore, **6** is sufficiently reactive to accept substrates that were problematic or even totally inert before. This includes electron rich as well as electron poor acetylenes, propargyl alcohol derivatives, and even terminal alkynes. Moreover, the first successful examples of ring opening alkyne cross metathesis reactions could be achieved. This largely increased substrate scope opens many new opportunities.

Importantly, the new alkyne metathesis catalysts rigorously distinguish between the π-systems of alkynes and alkenes; the latter remain untouched independent of whether

they are terminal, internal or conjugated to a functional group. Likewise, only the triple bond of an 1,3-enyne will react. This remarkable chemoselectivity profile predestines alkyne metathesis for applications to polyunsaturated targets as well as to the synthesis of 1,3-dienes, independent of whether they are *E*,*E*-, *E*,*Z*- or *Z*,*Z*-configured.



This notion is corroborated by several advanced syntheses (see the following Chapters). An illustrative example is the protecting-group free approach to the rather fragile marine prostanoid ***hybridalactone***. Attempts at forging the macrocyclic frame containing two *Z*-configured olefins with the help of (*Z*-selective) alkene metathesis catalysts result in instantaneous ring contraction. In contrast, alkyne metathesis allows the site of ring closure to be unambiguously defined. Furthermore, this example showcases that the functional group tolerance of silanolate bearing catalysts is largely superior to that of the classical Schrock alkylidyne $(t\text{BuO})_3\text{W}{\equiv}\text{CCMe}_3$, which destroys the acid sensitive cyclopropylmethyl carbinol subunit in the cyclization precursor.

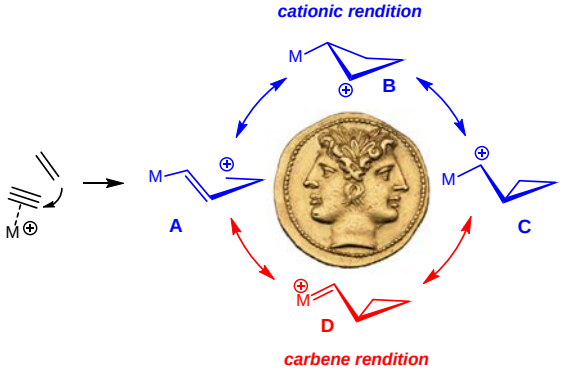
Since acetylenes are privileged substrates for gold/platinum catalysis, alkyne metathesis is obviously serviceable in this context too; several examples compiled in the following Chapter illustrate this aspect. Additional applications to bioactive target molecules, including the scalable route to ***lactimidomycin*** and analogues, are found in Chapter 2.4.4.

Finally, we note that other groups start to use our new alkyne metathesis catalysts, as evident from several applications published in the recent literature. It is hoped that the commercial availability of **6** and the stabilized variant **7** will help to make these powerful tools more popular.

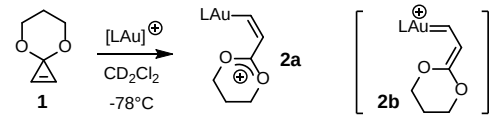
2.4.2. Research Area "π-Acid Catalysis" (A. Fürstner)

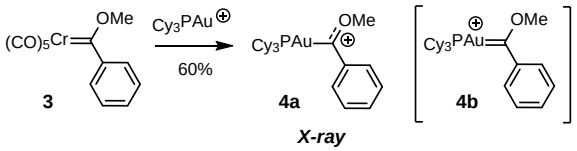
Involved: S. Benson, L. Brewitz, W. Chaladaj, M.-P. Collin, M. Corbet, T. de Haro, J. Llaveria, L. Mantilli, K. Radkowski, C. Regens, G. Seidel, H. Teller, G. Valot, A. Yada

Objective: Guided by our own early mechanistic proposal on how gold-, silver- or platinum-based π-acidic catalysts might operate, we continue to investigate the true nature of the reactive intermediates. In parallel, we try to showcase the significance of carbophilic catalysis by implementations into the late stages of multistep total syntheses. Another line of research concerns asymmetric gold catalysis.

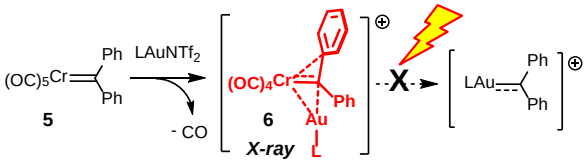


Results: As early as 1998, we proposed a unifying mechanism for π-acid catalyzed addition reactions to alkynes. It implied the intervention of carbenoid species as reactive intermediates which closely resemble (non-classical) cations stabilized by the transition metal center. Although the involvement of carbenoids is now generally accepted, the true nature of such species continues to be a matter of debate. This is largely due to the fact that gold carbenoids basically escaped spectral and structural analysis. The only fully characterized examples pertinent to mechanistic discussion were previously prepared by our group via rearrangement of substituted cyclopropene derivatives such as **1** at low temperature. The resulting products **2**, however, must be viewed as alkenylgold complexes carrying positive charge on the ligand since they exhibit only marginal C–Au double bond character. Other authors have objected that the oxygen substituents – which are needed to avoid substrate polymerization – might unduly disfavor the carbene resonance form.

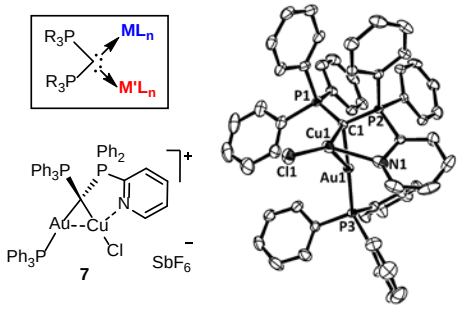




As a consequence, we pursue several complementary approaches towards *unstabilized* gold carbenoids, most notably via carbene transfer. It is well precedented in the literature that Fischer



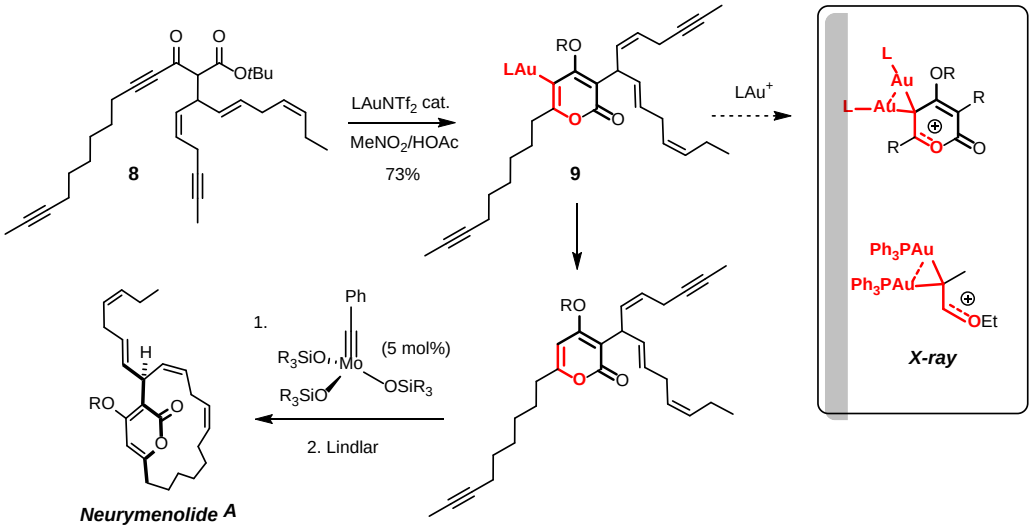
carbenes of tungsten or chromium can be "transmetalated" on treatment with Au(+1). First, we convinced ourselves of the exceptional ease of this reaction, which allowed complex **3** to be transformed into **4** even at –50 °C. As expected, the latter shows a long C–Au but a short C–O bond and is thus best viewed as an oxocarbenium cation in the coordination sphere of gold. When applied to the diphenylchromium carbene **5** however, an analogous transmetalation fails. Rather, the quite unusual bimetallic complex **6** is formed, as confirmed by X-ray diffraction. Although one of the CO ligands of the starting material is lost, breakdown with release of an unstabilized gold "carbene" does not take place; rather, the chromium center engages in a weak interaction with one of the phenyl groups which arguably provides more steric shielding than electronic compensation. Extensive DFT calculations allowed the bonding situation in this and related complexes to be deciphered. Overall, complex **6** basically represents a chromium carbene carrying an η^2-bound gold unit but has little to do with an unstabilized gold carbene. Such species therefore continue to remain elusive form the experimental vantage point, since three of the very best entries into carbene complexes failed to deliver (diazo decomposition, cyclopropene rearrangement, carbene transfer).



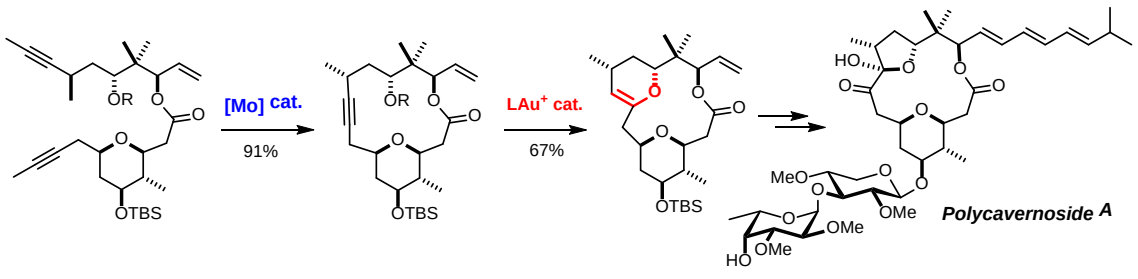
Earlier studies from this laboratory had indicated the possible intervention of *gem*-diaurated complexes in certain gold catalyzed reactions. During the current report period, many additional examples of such species were prepared. Moreover, it was found that *gem*-heterobimetallic complexes are also easy to make. A particularly interesting example is the gold/copper complex **7**, which carries a non-symmetrical carbodiphosphorane ligand (prepared in cooperation with the Alcarazo group). As its central atom C-atom is formally zerovalent, **7** is the first example of a chiral "carbone" complex in which all bonds about the metalated center are arguably capto-dative.

Alkenyl gold species with an oxygen substituent at the β-position are particularly prone to *gem*-diauration. Since the resulting complexes are surprisingly unreactive, we proposed that they might actually be off-cycle and hence constitute unproductive sinks for the precious gold catalysts. This hypothesis allowed the advantageous effect of acetic acid on a conceptually new approach to 4-hydroxypyrones to be rationalized. Driven by the need to make the heterocyclic nucleus of the naturally occurring cyclophane derivative ***neurymenolide A*** under notably mild conditions (this target is

unusually sensitive by virtue of its skipped polyene backbone), we conjectured that alkynyl ketoesters such as **8** might be adequate starting materials.

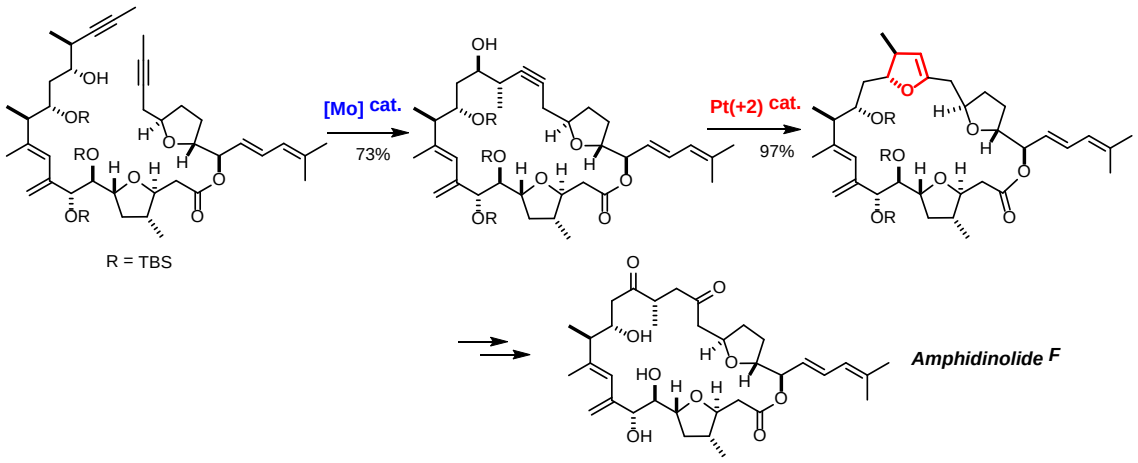


Activation of compound **8** with a carbophilic π-acid engenders a 6-*endo* cyclization with formation of the desired heterocyclic ring. In neutral media, the reaction proceeds rather slowly (12-24 h), whereas addition of small amounts of HOAc results in a dramatic rate acceleration (ca. 15 min). Control experiments suggest that the acid favors the proto-demetalation of the gold complex **9** primarily formed over competing *gem*-diauration. This preparative set-up was quintessential for the total synthesis of neurymenolide, which capitalizes on a substrate containing no less than six different non-conjugated sites of unsaturation (not counting the highly enolized β-oxoester). Alkyne metathesis of the resulting diyne **10** forged the macrocyclic perimeter while leaving all preexisting alkene sites untouched, independent of their configuration.

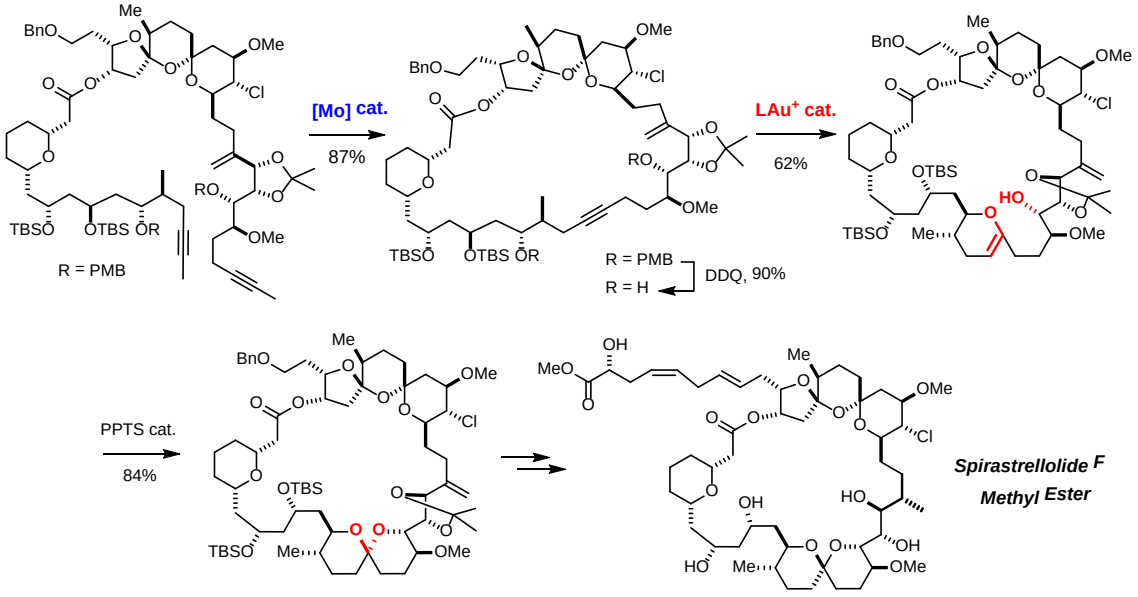


The interplay between alkyne metathesis and alkyne functionalization with the aid of π-acidic catalysts also formed the conceptual basis of several other total syntheses. The most demanding ones were those of ***polycavernoside A***, ***amphidinolide F*** and ***spirastrellolide F***. The densely functionalized macrocyclic frames of these intricate targets could invariably be closed by alkyne metathesis using the newly developed

molybdenum alkylidynes endowed with silanolate ligands, which attests to the excellent performance and functional group tolerance of these new catalysts.

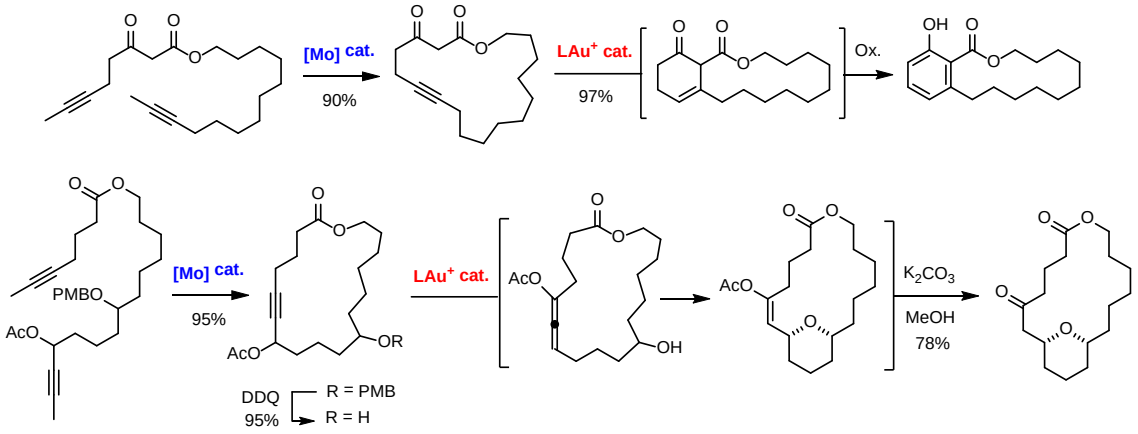


In case of polycavernoside A and amphidinolide F, the resulting cycloalkynes were subjected to exquisitely selective transannular hydroalkoxylation reactions catalyzed by Au(+1) and Pt(+2), respectively. In case of spirastrellolide F, a gold catalyzed spiroketalization was envisaged. Because of severe steric hindrance about one of the two hydroxyl groups, however, the addition stopped at the enol ether stage; yet, the oxygen pattern got properly set and hence a simple Brønsted acid sufficed to complete the acetalization.

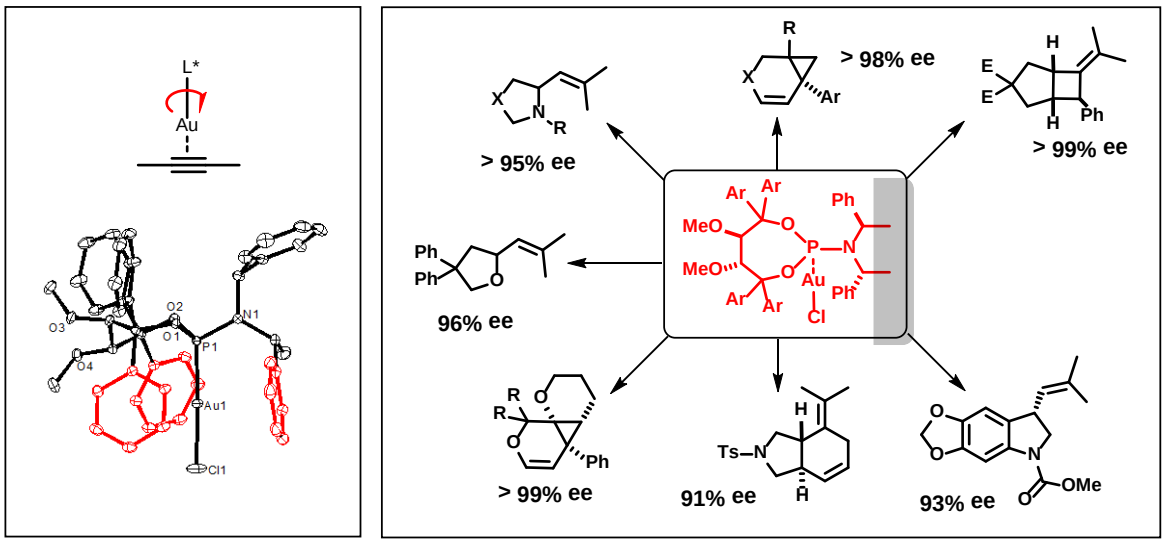


In addition to these massive projects, we were exploring several other opportunities of how metathesis and π-acid catalysis might be integrated in preparatively meaningful

ways. Some of these exploratory studies have already transfigured into “real” synthesis projects in the recent past.

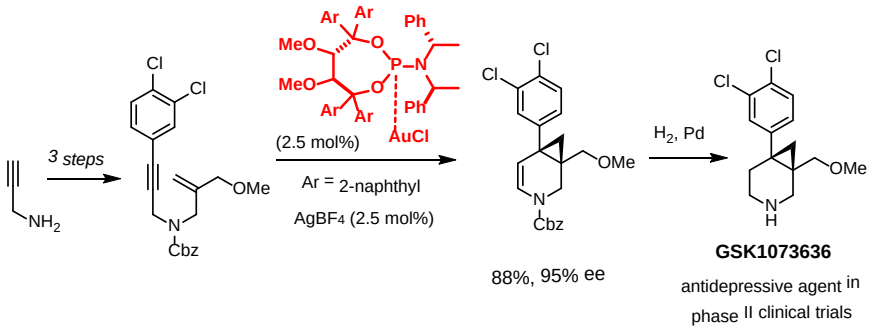


Another important topic is asymmetric gold catalysis, which is particularly challenging due to the peculiarities of the coordination chemistry of Au(+1) and the outer-sphere nature of gold catalyzed processes. In the last evaluation report, we disclosed our basic ligand design that consists of one-point binding phosphoramidites comprising a TADDOL-related scaffold with an acyclic backbone.



This latter structural element is essential, as it allows three of the aryl substituents to craft an effective C_3-symmetric binding site that is deep enough to reach over the gold center and impose asymmetry on the ensuing reaction. Moreover, these ligands are fairly easy to make, allow for substantial structural variation, and have molecular weights that are considerably smaller than those of competing ligands currently used in asymmetric gold catalysis. We optimized their synthesis and extensively studied their

performance. They were shown to impart outstanding enantioselectivities upon a number of mechanistically different transformations, including [2+2] and [4+2] cycloadditions, indoline formations, as well as intramolecular hydroaminations and hydroalkoxylations of allenes. Likewise, they excel in the cycloisomerization of enynes, which enabled a remarkably efficient synthesis of the antidepressive agent (–)-GSK 1360707. Moreover, our understanding of the origin of stereoselectivity has been considerably refined. In cooperation with the Thiel group, we learned how the initially C_3-symmetric pocket of such gold complexes becomes C_1-symmetric after substrate binding, and how a unidirectional rotatory motion of an enyne substrate within this ligand environment explains the enantioselectivity of the ensuing cycloisomerization.

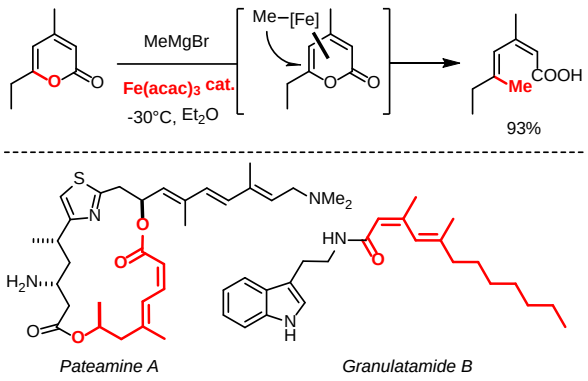


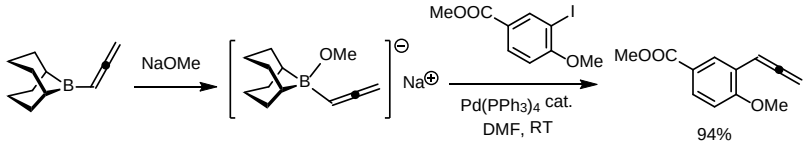
2.4.3. Research Area: "New Reaction Modes" (A. Fürstner)

Involved: L. Leseurre, K. Lehr, A. Kondoh, H. Krause, R. Mariz, K. Radkowski, G. Seidel, C.-L. Sun, B. Sundararaju

Objective: We try to find potentially useful transition metal catalyzed reactions that have little or no precedent in the literature.

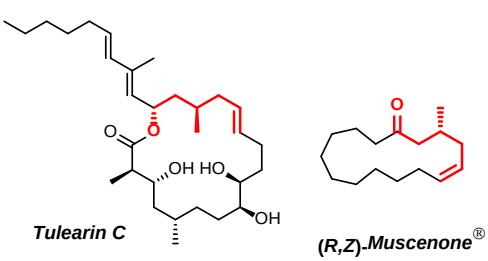
Results: Despite the exceptional level of sophistication in the area of cross coupling chemistry in general, reactions of substrates that contain the leaving group as integral part of a heterocyclic scaffold are extremely scarce. During the report period, we managed to develop a formal ring opening/cross coupling process of 2-pyrones that epitomizes this largely underrepresented reaction mode. Specifically, it was shown that 2-pyrones react with Grignard reagents in the presence of cheap and benign $Fe(acac)_3$ 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. Although the overall transformation hence formally represents a "cross coupling" process, it likely proceeds by a sequence of 1,6-addition followed by electrocyclic ring opening. First applications to the synthesis of the indole alkaloid granulatamide B and to a configurationally labile subunit of the potent translation-initiation inhibitor pateamine A augur well for future projects.



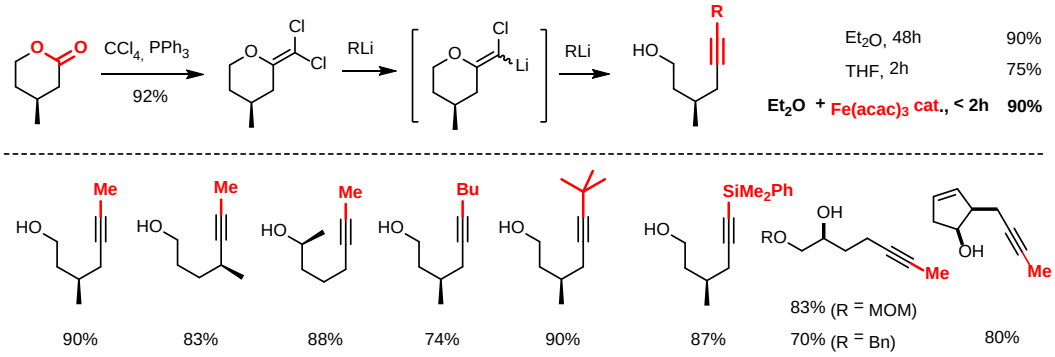


Driven by the need to prepare various types of allenes for use in gold and platinum catalysis, we noticed that cross coupling reactions of allene donors are rare. Despite the tremendously wide scope of the venerable Suzuki–Miyaura reaction, boron-mediated allenylations are basically unknown. We were able to close this gap in structural coverage by demonstrating that the borate complex formed in situ from B-allenyl-9-

BBN and NaOMe in DMF allows aryl- and heteroaryl iodides to be allenylated under mild conditions with good to excellent yields.

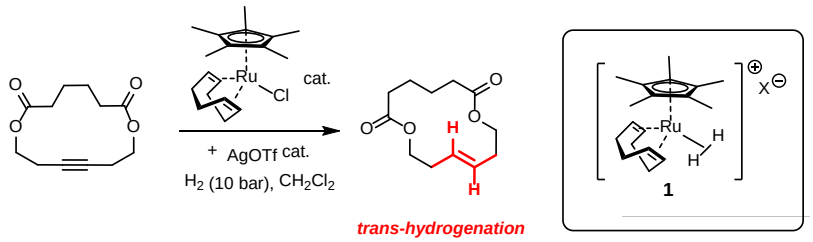


As briefly mentioned in Chapter 2.4.1, the recent literature has witnessed considerable progress toward the development of efficient *Z*-selective alkene metathesis catalysts, whereas inherently *E*-selective catalysts remain elusive. This lack surfaced in an attempted synthesis of ***tulearin C***, where closure of the macrocyclic ring at the *E*-alkene embedded into its framework by RCM afforded poor results. Challenged by this outcome, we devised an alternative entry based on alkyne metathesis followed by formal *trans*-reduction via a hydrosilylation/protodesilylation sequence, which delivered tulearin C in good overall yield and excellent selectivity. In addition, this extensive project had two rewarding methodological spin-offs.

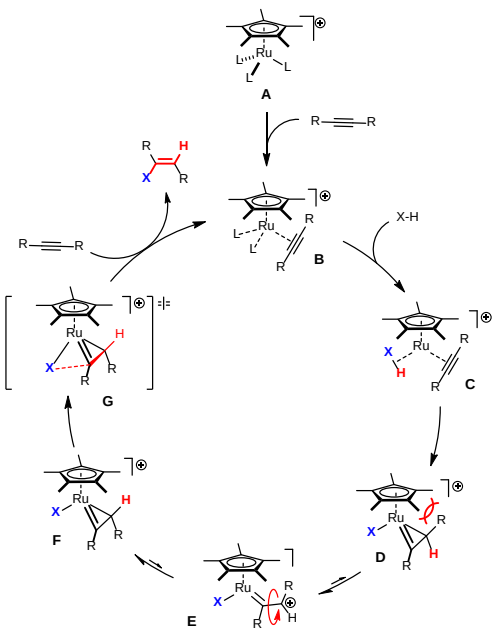


First, we developed a high yielding route to non-terminal alkynes starting from lactones. Transformation into the corresponding *gem*-dichloroalkenes by a literature procedure followed by treatment with an alkyllithium reagent RLi primarily generates lithium carbenoids that are sufficiently electrophilic 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 $Fe(acac)_3$ as a cheap and benign catalyst (in some cases, copper catalysts are optimal). Under these conditions, the method is quite general and does not lead to epimerization of chiral centers. Although parts of this investigation have already been published, the major body of work still needs to be disclosed. One of the alkyne products thus formed on large scale served as a valuable building block in the total synthesis of ***tulearin C*** mentioned above as well as in a particularly short synthesis of the valuable perfume ingredient ***muscenone***® in optically and isomerically pure form.

The tulearin case study relied on a formal *trans*-reduction of the cycloalkyne formed by RCAM via hydrosilylation/proto-desilylation. Although this sequence originally pioneered by Trost and coworkers served our group well on this and several other occasions, we became interested in developing possible alternatives.

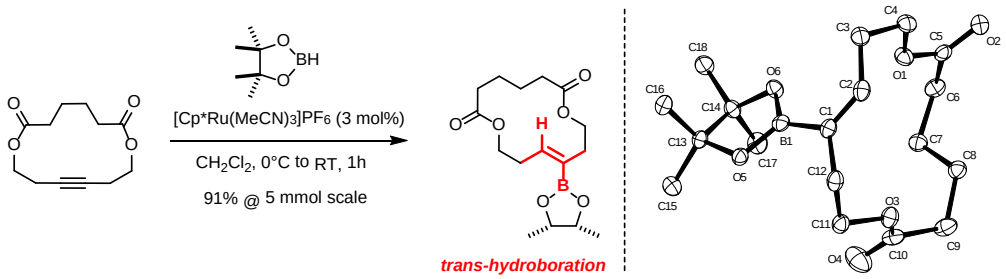


After various unsuccessful trials, we were able to find conditions that allow internal alkynes to be hydrogenated with good to excellent levels of *trans*-selectivity. Although we still need to further improve this transformation (in some cases, over-reduction is observed), it basically constitutes the first broadly applicable and functional group tolerant method that breaks the stereochemical dogma of suprafacial delivery of the two H-atoms to the π-system of the substrate; this rule had remained largely unchallenged for more than a century since Sabatier's groundbreaking work.



Preliminary mechanistic data suggest that a non-classical hydrogen complex might be the active species (or a precursor to it). We assume that binding of an alkyne forms a loaded complex **C**, in which the acetylene moiety acts as a four-electron donor; this explains why alkenes do not react well under the chosen conditions. This particular bonding situation facilitates an inner-sphere delivery of the hydride with formation of a metalla-cyclopropene **D** (η^2-vinyl complex) without prior generation of a discrete Ru–H species. It is well precedented in the literature that the substituents at the β-carbon atom of such complexes are configurationally labile and easily swap places via a $\eta^2 \rightarrow \eta^1 \rightarrow \eta^2$ hapticity change. Because they are approximately orthogonal to the plane of the metallacyclopropene, the sheer size of the Cp* ring will exert a massive influence on the stereochemical outcome. As a result, isomer **F**, in which the hydrogen rather than

the R group is oriented towards the bulky lid, will be largely favored over **D**. The trajectory of the ensuing reductive elimination places the X-group *anti* to the already transferred H-atom and hence leads to an *E*-configured alkene if X = H.



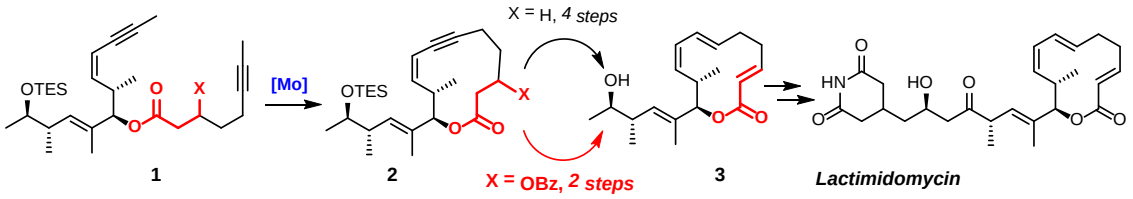
This rationale suggests that reagents H–X with X ≠ H should also be amenable to *trans*-additions across alkynes, provided they are able to form analogous σ-complexes. Indeed, we were recently able to perform the first recorded examples of *trans*-hydroborations of internal alkynes using pinacolborane as a versatile and user-friendly reagent. This transformation is pleasingly facile, rapid, tolerant and high yielding, and might therefore be of some interest. Control experiments showed that the net *trans*-addition observed under our conditions is not the result of a secondary isomerization. From the conceptual viewpoint, this *trans*-addition mode challenges the equally fundament rule that hydroboration proceeds by a *syn*-delivery of boron and hydrogen via a four-membered frontier-orbital controlled transition state. Ongoing investigations intend to explore the scope of these versatile new reactions in more detail. Furthermore, preliminary data suggest that reagents X–H other than H_2 and pin–H can also be forced to follow *trans*-addition pathways.

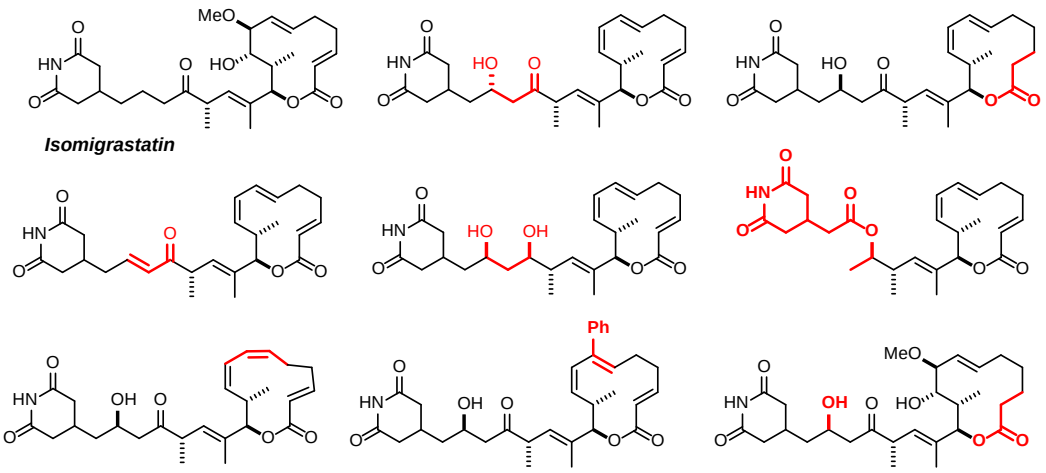
2.4.4 Research Area "Catalysis Based Syntheses and Evaluation of Bioactive Natural Products" (A. Fürstner)

Involved: A. Arlt, S. Benson, S. Handa, N. Kausch-Busies, A. Kondoh, J. Llaveria, K. Micoine, P. Persich, S. Schulthoff, J. Willwacher

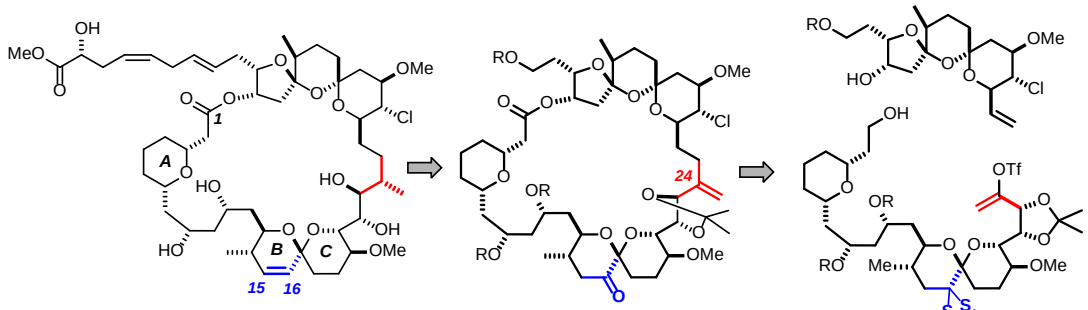
Objectives: We pursue the synthesis of complex natural products by catalysis-based routes, evaluate their biochemical and biological properties in cooperation with external partners, and investigate structure/activity relationships by molecular editing.

Results: As already mentioned in Chapter 2.4.1, ***lactimidomycin*** and related glutarimide macrolides constituted an important focal point of our synthetic work. Although this compound was claimed to be the most potent cell migration inhibitor of a fairly large family of natural products, it had never been made before. In order to close the supply chain and gain access to non-natural analogues for testing, we pursued different routes that might allow the strained head group of this enticing target to be closed. Although the RCM-based entry summarized in Chapter 2.4.1 provided a decent solution, an alternative entry using ring closing alkyne metathesis (RCAM) was ultimately more satisfactory.





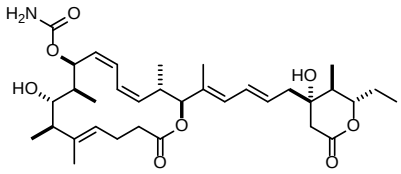
In our first attempt, the macrocyclic ring was closed starting from diyne **1** (X = H), followed by *trans*-reduction of the resulting cycloalkyne **2** (X = H) to set the *E*-configured site of the diene entity. A sequence of selenylation/oxidative deselenylation was then needed to install the yet missing enoate moiety. Although this chemistry worked reasonably well and gave first crops of lactimidomyin for biological testing, it is certainly not ideal for scale-up. Therefore, we pursued a modified route that avoids the selenium chemistry altogether. To this end, the enoate of the target was encoded as an aldol ester derivative. Gratifyingly, RCAM of diyne **1** (X = OBz) with the new molybdenum catalyst still proceeded smoothly (85% @ 2 g scale), without any premature elimination occurring. Subsequent *trans*-hydrosilylation of **2** (X = OBz) followed by treatment with TBAF furnished the key intermediate **3** in excellent overall yield; note that TBAF effects a C- and an O-desilylation as well as concomitant benzoate elimination with formation of the enoate, all in one pot. With the access to **3** being secured, we were not only able to make substantial amounts of lactimidomycin itself, but could also prepare its sister compound ***isomigrastatin*** and a panel of non-natural analogues by diverted total synthesis. These compounds powered an extensive biological (re)assessment of these putative cell migration inhibitors (in cooperation with Pfizer Oncology), which led to a revision of the claims made in the literature; rather, lactimidomycin and analogues were found "just" acutely cytotoxic. Although this was certainly not the expected outcome, their particular mode of action as eukaryotic ribosome inhibitors is perhaps equally interesting.



Spirastrellolide A Methyl Ester

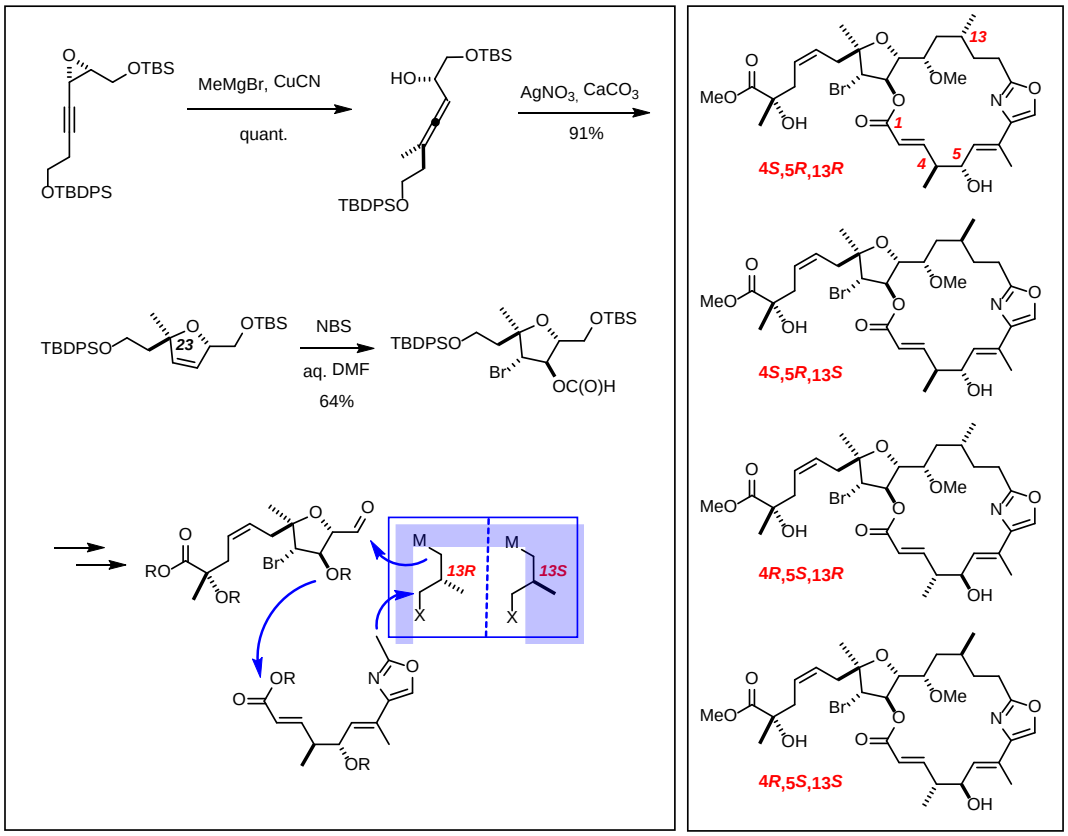
In Chapter 2.4.2, our total synthesis of the potent phosphatase inhibitor ***spirastrellolide F methyl ester*** has been summarized that involves an RCAM reaction followed by a gold catalyzed transannular spiroketalization. In parallel work – but through largely different chemistry – we also managed to make the sister compound ***spirastrellolide A methyl ester***, which contains an additional $\Delta^{15,16}$ double bond within the B-ring. The assembly of this exigent target that exhibits no less than 21 chiral centers plus three

olefinic sites within its complex polyketide frame centered on a late-stage unveiling of the signature C15-C16 alkene, only after the methyl branch at C24 had been properly set by a highly selective substrate-controlled hydrogenation. The elaborate *exo*-methylene precursor was formed by a convergent route using dithiane chemistry, an alkyl-Suzuki coupling, and a Yamaguchi lactonization.

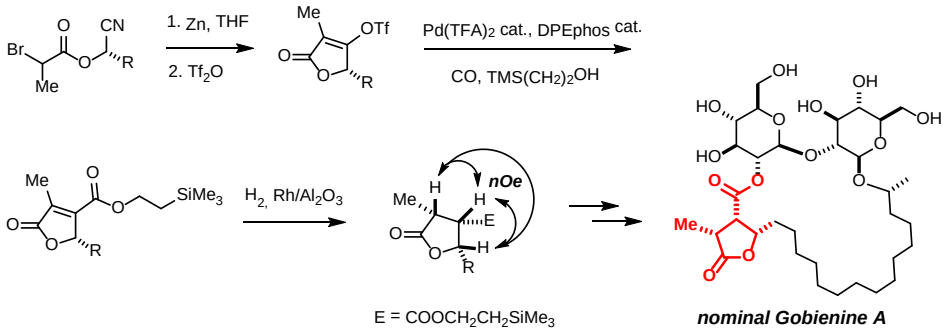


Leiodermatolide

Another massive project concerned the first total synthesis of the antimitotic agent ***leiodermatolide***, an extremely scarce metabolite derived from a marine sponge, whose stereostructure could not be fully established by the isolation team. This macrolide comprises a fragile non-thermodynamic *Z,Z*-diene subunit, which remains beyond reach of any alkene metathesis catalyst known to date. Once again, alkyne metathesis opened a very effective entry into this delicate target and allowed its stereostructure to be unambiguously determined. This compound currently undergoes biological testing (Pfizer Oncology); because of some very encouraging preliminary data, we are now optimizing our route and enter the phase of analogue-making by late-stage digression from the underlying synthesis blueprint.

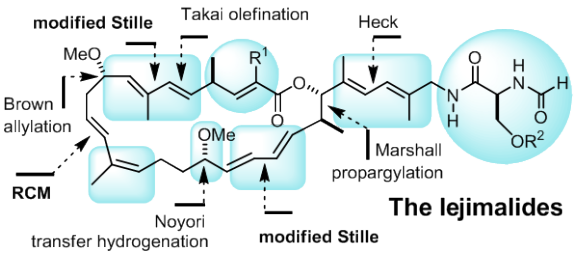


Another deep-sea sponge harvested by submersible in deep waters is the source of ***leiodolide B***, an intricate macrolide of mixed polyketide/non-ribosomal peptide synthetase origin. It attracted our attention because it is practically inaccessible from the producing organism but supposedly very active in the NCI 60 tumor cell line screen. From the purely chemical viewpoint, we felt that the brominated tetrahydrofuran subunit comprising a *tert*-ether site at C23 poses an interesting synthetic challenge. An effective way to form this motif starts off with the vinylogous opening of a propargyl epoxide with a methylcopper reagent, followed by a silver-mediated hydroalkoxylation of the resulting product. This sequence allows for an efficient chirality transfer from a readily available epoxide to the quaternary chiral center using the axial chirality of the allene as a relay. Although this tactics worked exceedingly well and a variety of other problems en route to the target could also be solved, the data of synthetic leiodolide B were not identical with those of the natural product. Careful analysis made us believe that the chiral centers at C4, C5 and C13 are the most likely sites of misassignment by the isolation team. Therefore we went on to make 4 different diastereomers of this complex target through total synthesis; unfortunately, none of them matched the reported data sufficiently closely to claim identity. Since the isolation group could neither provide an authentic sample nor even copies of the original spectra, we felt unable to solve the puzzle.

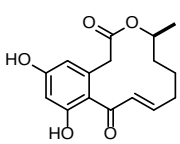


A totally different chemical challenge was encountered during the synthesis of nominal ***gobienine A***, a rather unique lichen-derived glycolipid. It contains an all-*cis* substituted butyrolactone substructure within a macrocyclic frame, which is very epimerization-prone; actually, a literature survey showed no good entry into such a motif. We found a decent solution based on an intramolecular Blaise reaction of an optically active cyanohydrin bromopropionate followed by in situ quenching of the resulting tetronic acid with triflic anhydride. Subsequent methoxycarbonylation and hydrogenation of the resulting tetrasubstituted alkene over Rh/Al_2O_3 gave the desired all-*cis*-configured product in respectable yield and excellent selectivity. This building block was then

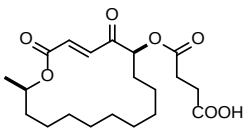
attached to an appropriate disaccharide building block and the macrocycle was closed by RCM before a final hydrogenation released nominal gobienine A. Unfortunately, the structure of this natural product has also been mis-assigned by the isolation team; we could show through extensive studies that the flaw must be “deep seated”. Here again, the lack of authentic reference material makes it impossible for us, without undue effort, to identify the mistake(s) made by the isolation team.



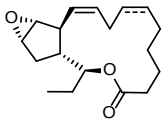
As already mentioned in the previous evaluation report, our group devoted considerable time and effort to the ***iejimalides***, which were reported to exhibit appreciable anti-tumor activities *in vivo* but cannot be obtained in sufficient quantity from the producing sponge for state-of-the-art preclinical studies. After we had demonstrated that it is possible to forge such polyunsaturated products by ring closing olefin metathesis, in which two out of ten different double bonds in the cyclization precursor have to be selectively activated, we were intrigued by the highly promising biological results obtained in the first round of testing. Iejimalide B and several synthetic analogues showed cytotoxicities in the sub-nanomolar (!) or single-digit nanomolar range as well as an encouragingly differential profile with regard to the responsive human tumor cell lines. Therefore we decided to prepare this demanding marine natural product on a gram scale (16 steps longest linear sequence, ca. 42 steps overall) together with a panel of ca. 20 non-natural analogues that map the entire pharmacophore. During the report period, these compounds were extensively tested in tumor colony formation assays, the results of which were at least as encouraging as the original cell-based screens. The most active compounds were then tested in a mouse model, unfortunately with little success. This result corrects the claim of the isolation team that had insinuated an appreciable *in vivo* activity of the natural lead.



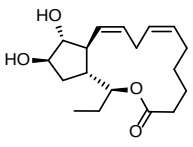
Dehydrocurvularin



(¯)-A26771B



Ecklonialactone A (***Δ6,7***)
Ecklonialactone B



Ecklonialactone C

Additional total synthesis projects completed in between 2010-2013 were concerned with the tubulin-binding agent dehydrocurvularin, the antibiotic A26771B, and the

marine oxylipins of the ecklonialactone family; all of these compounds were prepared in optically pure form. They served to scrutinize various aspects of the metathesis chemistry developed in this laboratory.

2.4.5 Research Area "Cationic Ligands: Synthesis and Applications of Extreme π-Acid Catalysts" (M. Alcarazo)

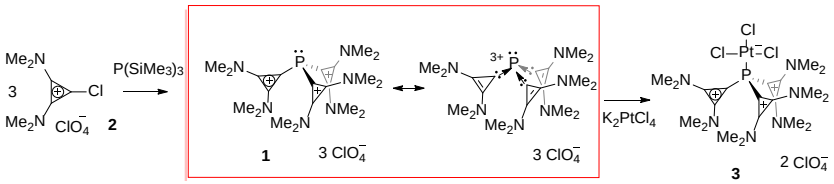
Involved: J. Petuškova, J. Carreras, E. González, L. Gu, Á. Kozma, P. Linowski, G. Mehler, H. Tinnermann, C. Wille, T. Deden, A. Gimeno, P. Gualco, A. Zanardi

Objective: The goal of this project is the synthesis of extreme π-acceptor phosphines through the introduction of positively charged homo- or heteroaromatic substituents directly attached to the phosphorus atom. By exploiting this property, new Au and Pt catalysts have been developed that display a dramatically enhanced capacity to activate π-systems.

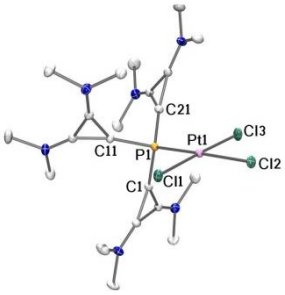
π-Acid catalysis, mainly with Au(I) and Pt(II) based species, has emerged in the last decade as one of the most efficient tools for the promotion of rearrangements in unsaturated organic substrates, which provide an exquisite entry to the synthesis of intricate skeletons that may be otherwise difficult to prepare. The generally accepted mechanism that governs most of these transformations involves three main steps: (i) coordination of the π-acid metal to the alkyne or allene moiety present in the starting material, (ii) nucleophilic intra- or intermolecular attack to the activated substrate forming a vinyl-metal species, and (iii) protodemetallation of the vinyl intermediate with concomitant regeneration of the active catalyst. It seems reasonable to expect that the first two of these steps may be accelerated by strong π-acceptor ancillary ligands, which should increase the Lewis acidity of the metal center they coordinate. In striking contrast, potent σ-donating ligands will weaken the M-C bond in the vinyl intermediates by their *trans*- influence and thus facilitate the protodemetallation step. Hence, the selection of the most appropriate ligand for a particular transformation can only be done based on an in-depth understanding of the nature of the rate-determining step.

Very recently, we reported the synthesis of the first ever isolated carbene-stabilized P_1-centered trication $[L_3P]^{3+}$ (L = 2,3-dialkylaminocyclopropenium) **1** by reaction of the 1-chloro-2,3-(dimethylamino) cyclopropenium salt **2** and $P(SiMe_3)_3$ (Scheme 1). Despite the three positive charges on the groups directly attached to the P atom, this compound can still serve as a ligand for π-acidic metals such as Pt. Thus, when **1** is treated with K_2PtCl_4 in acetonitrile, the bench stable complex **3** is formed. More interestingly, charge decomposition analysis of the metal-ligand interaction in **3** gave the surprising result that the total L→M σ-donation (0.31 *e*) is lower than the M→L π-back donation (0.43 *e*) into the very low-lying LUMO of **1**, which must hence be regarded as the main

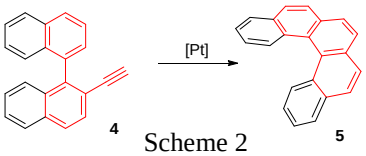
interaction in **3**. This unconventional situation in which the P-ligand removes net electron density from the metal suggests that compound **1** increases the natural π-acidity of Pt(II) centers. It should thus accelerate known reactions, or even permit new ones, in which either the coordination of the substrate or the nucleophilic attack to the activated substrate are the rate-determining steps.



Scheme 1



In a preliminary screening of plausible applications for these ligands, we chose the Pt-catalyzed 6-*endo*-dig cyclization of 2-ethinyl-1,1'-binaphtalene **4** into pentahelicene **5**, as model reaction for two main reasons (Scheme 2).



Scheme 2

(a) The interest in polycyclic homo- and heteroarenes has been refueled during the last years due to their unique optoelectronic properties and their potential applications in organic electronic devices. The chosen cyclisation is a very attractive entry for the preparation of these carbon-rich materials. Moreover, this reaction can be also used to prepare highly substituted phenanthrene moieties that are present in the structure of natural products. Therefore, expeditious syntheses to these compounds may be envisaged.

(b) Due to the relatively weak nucleophile that is employed (an aromatic ring), the nucleophilic attack is expected to be the rate-determining step for this reaction. Hence, the use of strong π-acceptor ancillary ligands such as **1** should facilitate this transformation.

Accordingly, we chose for our studies on ligand effects a series of phosphanes such as PPh_3, $P(OPh)_3$, $P(C_6F_5)_3$ and precatalyst **3** in combination with a silver salt. As expected, both $P(OPh)_3$ and $P(C_6F_5)_3$ performed better than PPh_3 in terms of reactivity (Figure 1).

Interestingly, our ligand **1** produces a much faster reaction, clearly surpassing any of the classical π-acceptor ligands. In fact, complete conversion of the model substrate to

pentahelicene **5** was achieved in less than 20 minutes under the newly developed reaction conditions.

Furthermore, the compatibility of our catalytic system with several functional groups is outstanding. Up to now, our experiments indicate that biaryl substrates containing ethers, free or silylated alcohols, esters, halogen substituents, silyl- and trifluoromethyl groups, thiophenes, and furanes are well tolerated (for representative examples see Scheme 3). Moreover, all products were obtained in few minutes with very good to excellent yields.

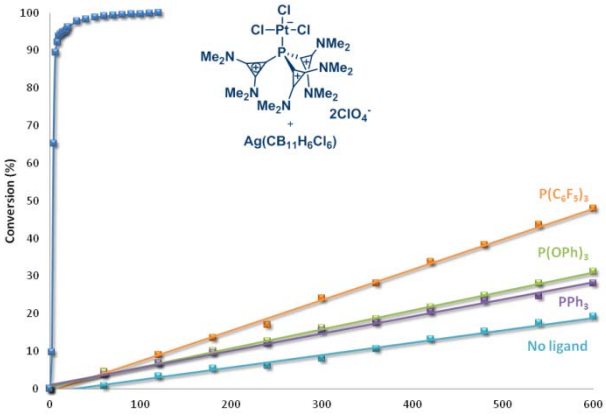
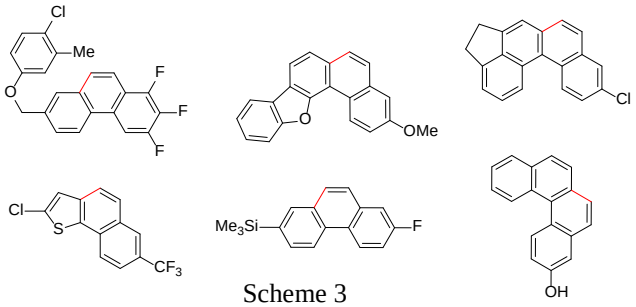


Figure 1



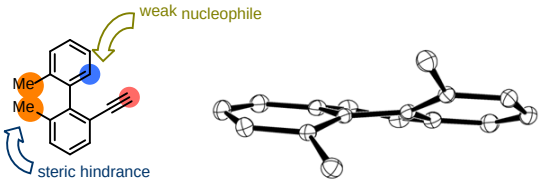
Scheme 3

However, despite of the remarkable activity depicted by **3**, there are still three main aspects regarding this catalyst that deserve further optimization:

a) Catalyst stability needs to be enhanced. With catalysts **3**, no reaction progress is observed after reaction times of about one hour, presumably due to catalysts decomposition.

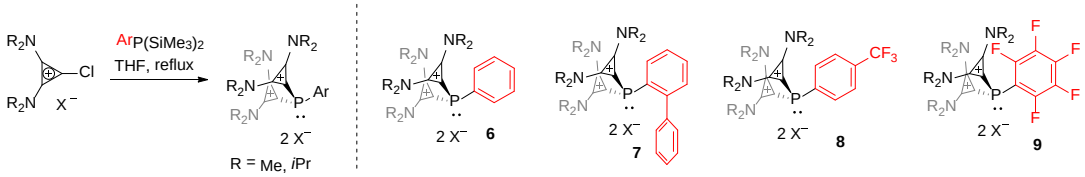
b) Catalyst activity needs to be improved. Although much faster, with the newly developed catalytic system a catalyst loading of 5 mol% and high temperatures (80 °C) are still necessary. In addition no reaction is observed if bulky substituents are located at the *ortho*- positions of the biaryl starting material (See Scheme 4). The employment of a more π-acidic Au(I)-based catalysts instead of a Pt(II)-derived one might be beneficial at this point.

c) Improvement of the substrate tolerance to heteroaromatic rings such as pyridines is desirable.



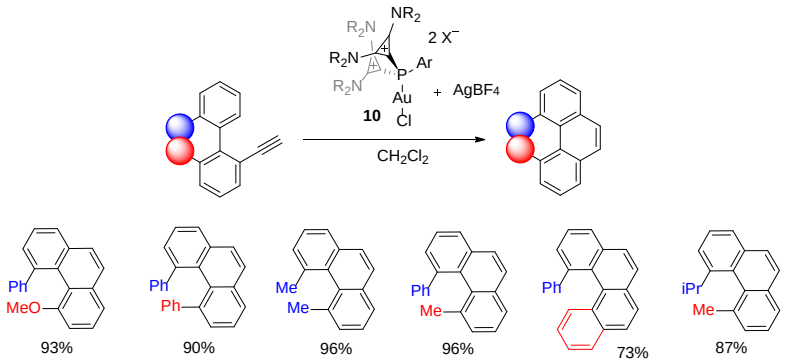
Scheme 4

As already mentioned, Au(I) based catalysts should be more active than Pt(II)-based ones due to the stronger Lewis acidity of Au(I) centers. Unfortunately, all attempts to coordinate gold to ligand **1** were unsuccessful. In contrast, dicationic ligands were found to be more appropriate in Au chemistry because: (i) their Au-derived complexes are much more stable than those derived from tricationic ligands and (ii) their reactivity is comparable. Thus, we planned to synthesize a set of dicationic ligands bearing several R substituents on the phosphorus with different steric demands and electronic nature (Ph, biphenyl, C_6F_5-, *p*-$CF_3C_6H_4$…). Up to now, compounds **6** and **7** and the Au(I) complexes thereof derived have been prepared (Scheme 5).



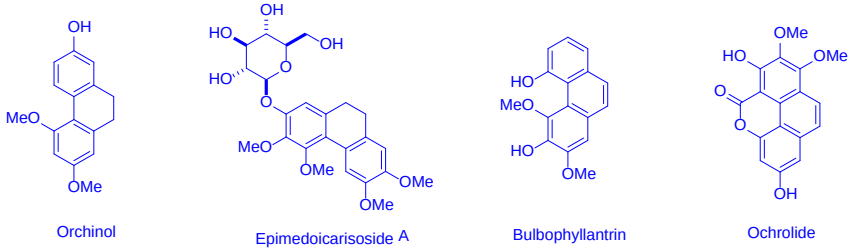
Scheme 5

To evaluate the range of application of these new Au catalysts, we focused on those substrates that were reluctant to react when the Pt-based complex **3** was employed as precatalyst; namely those with substituents in the *ortho*- positions of the biphenyl skeleton or those with electron withdrawing groups attached to the ring that has to accomplish the nucleophilic attack. Some of the substrates that could be prepared employing the new Au(I) catalysts **10** are depicted in Scheme 6.



Scheme 6

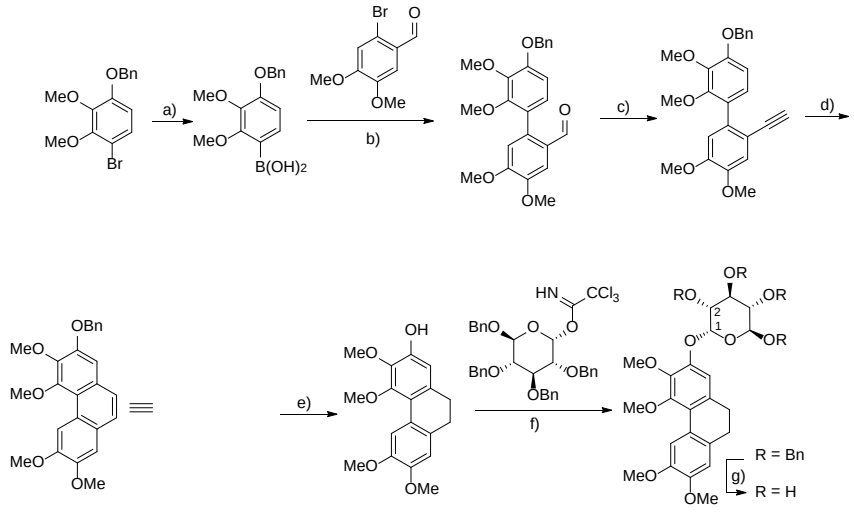
In addition, our synthetic program has already benefitted from these novel tools and natural products such as Orchinol, Ochrolide, Bulbophyllantrin and Epimedoicarisoside A have been prepared using our Pt and Au catalysts for the key hydroarylation step (Scheme 7). As representative example, Scheme 8 depicts the synthesis of Epimedoicarisoside A, a



Scheme 7

compound with potential application in the treatment of cardiovascular and cerebrovascular diseases such as myocardial infection or cerebral thrombosis.

Future directions: Many transformations might benefit from the use of extremely π-acceptor ligands. At the moment we are focused on the application of our ligands in Rh and Pd-catalyzed processes. The synthesis of cationic phosphines containing other –onium substituents different than cyclopropenium is also being investigated.



2.4.6 Research Area "Synthesis and Applications of Simultaneous σ- and π-Donor Ligands: C-M Dative Double Bonds" (M. Alcarazo)

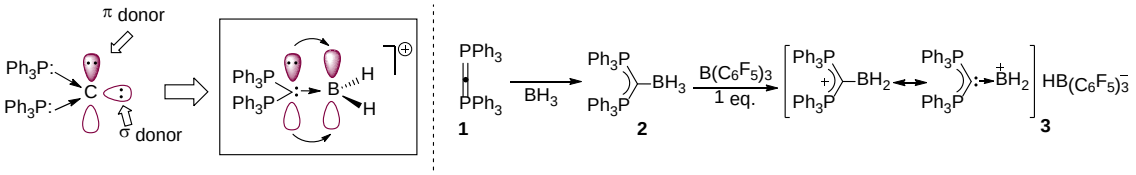
Involved: B. Inés, S. Kahn, R. Azhakar, S. Holle, F. Martín

Objective: The goal was to study new coordination modes of carbon(0) compounds.

In this area, our research has been strongly inspired by the theoretical work of Frenking about the nature of carbodiphosphorane **1** (Scheme 1). His studies revealed that in compound **1** and analogues the central carbon atom retains its four valence electrons that are thus all available for coordination. In fact, carbodiphosphoranes are known to react with two Lewis acids such as AuCl affording diaurated derivatives. However, their ability to donate their four electrons to the same electrophile in a simultaneous σ- and π-donation had not been described.

In this regard, we envisaged that the use carbodiphosphoranes may provide sufficient stabilization to attenuate the reactivity and allow the isolation of dihydrido borenium cations $[L{\rightarrow}BH_2]^+$ (L = carbodiphosphorane), a series of compounds that cannot be isolated when classical σ-donating ligands are employed.

Hence, we allowed carbodiphosphorane **1** to react with borane dimethylsulfide complex and isolated adduct **2** as a bright yellow solid in quantitative yield (Scheme 1). Upon treatment of a solution of **2** with one equivalent of $B(C_6F_5)_3$ the color smoothly vanishes. The ^{11}B-NMR spectrum indicated the generation of the borohydride anion $HB(C_6F_5)_3^-$ (δ = -24.0 ppm; $^1J(^1H,^{11}B)$ = 92 Hz) while complete consumption of $B(C_6F_5)_3$ was confirmed by ^{19}F-NMR. Additionally, the original ^{11}B-NMR resonance of **2** (δ = -22.7 ppm; $^1J(^1H,^{11}B)$ = 84 Hz) disappeared and a new broad signal (δ = 56.6 ppm) emerged. These data suggested the formation of the dihydrido borenium borohydride **3**, an interpretation that was validated by X-ray crystallographic analysis



(Figure 1).

Scheme 1. Synthesis of a dihydridoborenium cation.

In an attempt to clarify the electronic nature of **3**, density functional calculations at the B3LYP/6-31G* level were performed. Inspection of the frontier orbitals reveals that the highest occupied molecular orbital (HOMO) is the C-B π-bonding orbital that is strongly polarized toward the C atom (see Figure 1). Energy decomposition analysis also indicates that σ-donation contributes about twice as much as π-donation to the stability of the C=B bond. Presently, our efforts are directed to the application of the borenium cations in fluorine-free frustrated Lewis pair chemistry as their Lewis acidity has been proved to be very similar to the one depicted by $B(C_6F_5)_3$.

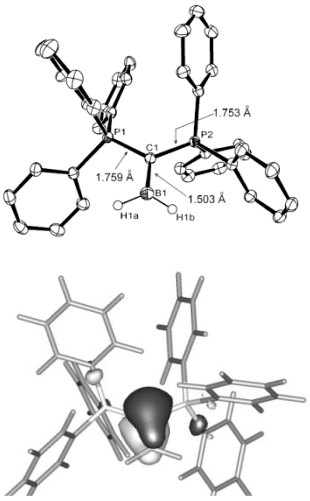
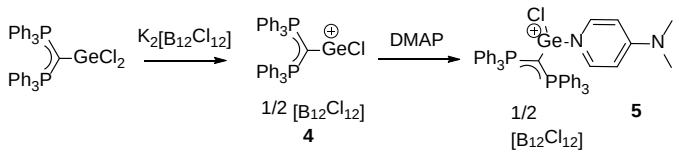
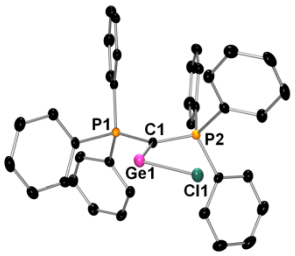


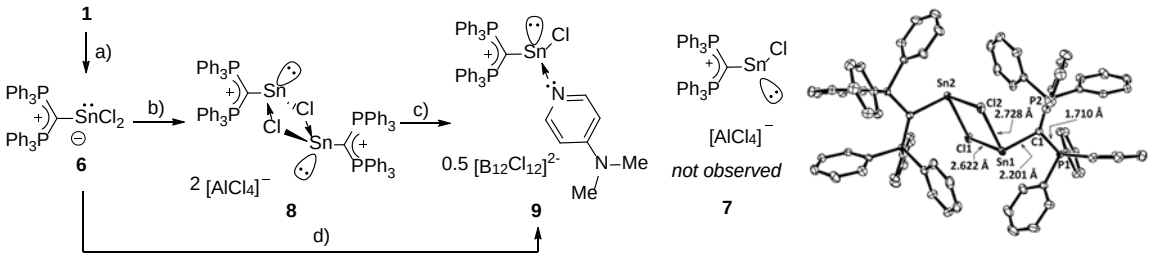
Figure 1. X-ray structure (up) and HOMO(down) of compound **3**.

The employment of **1** as both σ- and π- acceptor ligand is expected to facilitate the isolation of low coordinated p-block cations such as $Si(IV)^{+2}$ or $Ge(II)^{+2}$. Our strategy, that is already producing some positive results, is depicted in Scheme 2. In broad lines it relies on the coordination of carbodiphosphorane **1** to a germanium or silicon chloride and subsequent abstraction of the chloride anions, a task that should be facilitated by the extra π-electrons of the ancillary ligand. Up to now we have been able to synthesize compound **4** which already depicts a σ- and a π-dative bonds between the central carbon atom and the GeCl moiety. Reaction with dimethylamino pyridine affords adduct **5** where the π interaction is not existing anymore. Currently, we are trying to remove the chloride moiety from **5**. In case of success, the first dicoordinated Ge(II) dication will be isolated. The same strategy is being applied for the preparation of Si(IV) dications.





Scheme 2. Proposed synthesis of Ge(II) dications and structure of 4.



Scheme 3. a) **1**, $GeCl_2$·dioxane, DCM, RT, quant.; b) **6**, $AlCl_3$, CH_2Cl_2, 67%; c) **8**, DMAP, CH_2Cl_2, $K_2[B_{12}Cl_{12}]$ (0.5 eq.); d) **6**, DMAP, CH_2Cl_2, $K_2[B_{12}Cl_{12}]$ (0.5 eq.), 53%.

Finally, the extension of this chemistry to Sn(II) was also attempted. Reaction of **1** with $SnCl_2$ afforded the very insoluble and air-sensitive adduct **6** that was subsequently treated with $AlCl_3$. In sharp contrast to the Ge analogue previously described, abstraction of a chloride anion from **6** did not yield the expected cation **7** but its dimer **8** (Scheme 3). The steric hindrances around Ge and Sn in 4 and in a hypothetical complex 7 (see calculated structure, Figure 2) are basically identical. Therefore, the isolation of **8** indicates that the plausible stabilization provided by a π(C-Sn) bond in **7** is so feeble that it is overridden by formation of chloride bridges between the Sn atoms.

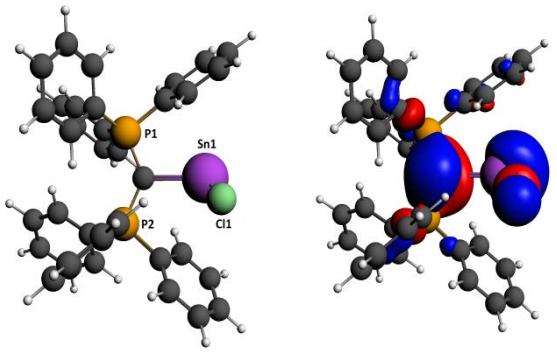


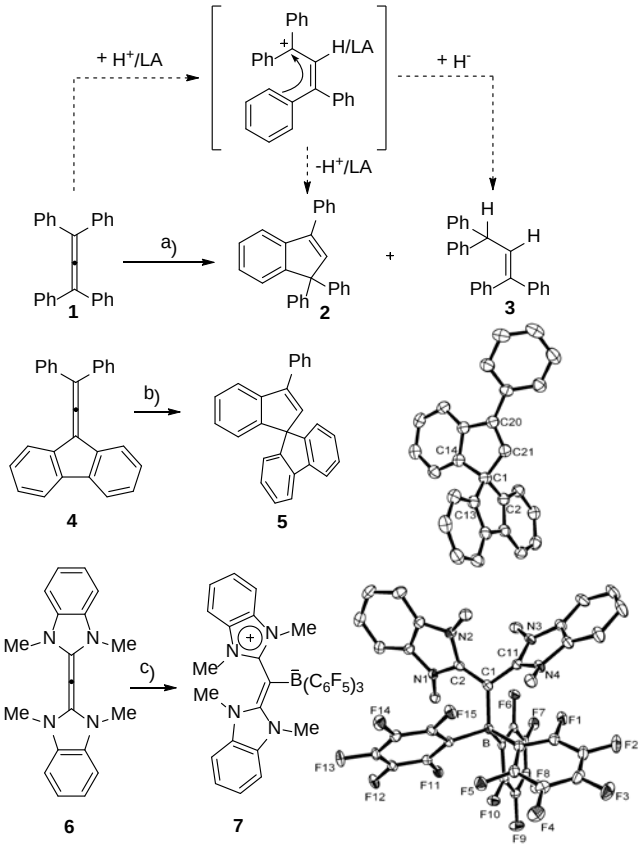
Figure 2. Calculated gas-phase structure of cation **8** (left) and plot of its HOMO (right) at BP86/6-31G* level [LANL2DZ for Sn].

2.4.7 Research Area "Metal-free Hydrogenations" (M. Alcarazo)

Involved: B. Inés, S. Holle, I. Abdellah, J. Nicasio, D. Palomas, S. Steinberg

Objective: The main objective was to expand the scope of frustrated Lewis pair chemistry to the reduction of electron poor allenes and alkenes.

Since its discovery, the chemistry of frustrated Lewis pairs (FLP) has flourished, showing exquisite reactivities towards the activation of small molecules. Thus, it has been reported in recent years that bonds such as C-O, C-H, B-H, S-S, C-C or Si-H can be activated by using this elegant concept. In spite of this, their arguably most remarkable application is still the heterolytic cleavage of H_2, and the subsequent development of metal free catalytic hydrogenations of a number or organic polar substrates such as imines, enamines, nitrogenated heterocycles or silyl enol ethers employing H_2 rather than Hantzsch esters. Surprisingly, despite these achievements, the FLP-promoted catalytic hydrogenation of electron poor unsaturated systems is still underdeveloped. In an attempt to address this limitation, we focused our efforts towards the catalytic reduction of allenes, expecting that the higher reactivity derived from their two adjacent double bonds, could make them appropriate substrates for a preliminary screen of conditions.

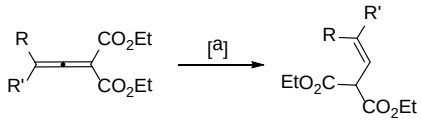


Scheme 1 Reactivity of allenes towards frustrated Lewis pairs. a) $B(C_6F_5)_3/Ph_2NMe$ (15 mol%), toluene, 80 °C, 3 days, **2** (63%), **3** (22%) or $B(C_6F_5)_3/PhNMe_2$ (15 mol%), toluene, 80 °C, 3 days, **2** (0%), **3** (96%); b) $B(C_6F_5)_3$ (15 mol%), toluene, RT, **5** (97%); c) $B(C_6F_5)_3$, toluene, RT, **7** (78%).

Thus, tetraphenylallene **1** was exposed to mixtures of $PhNMe_2$ or Ph_2NMe /$B(C_6F_5)_3$ (15 mol%) and H_2 (60 bar). Interestingly, consumption of **1** was observed and two new products **2** and **3** could be isolated from the reaction mixtures

after column chromatography (Scheme 1). While the formation of alkene **3** proves that reduction of allenes is possible by FLP chemistry, the detection of **2** suggests the existence of a competing reaction pathway. Hence, it can be envisaged that **1** is first protonated at the central carbon followed by hydride transfer to the transient cation produces **3**. Alternatively, intramolecular Friedel-Crafts alkylation affords **2**. In addition, it cannot be excluded that the undesired transformation of **1** into **2** may be directly promoted by $B(C_6F_5)_3$ without the participation of any proton since: (i) allene **4** cleanly cycloisomerizes into **5** solely in the presence of catalytic amounts of $B(C_6F_5)_3$ and (ii) the allene-borane complex **7** is obtained when the more electron rich allene **6** is employed as a substrate. These studies indicate that the hydrogenation takes probably place following a reaction pathway that starts with a Michael-type hydride addition to the allene followed by protonation.

Next, an electron deficient allene **8** unable to interact with the borane through the central carbon atom was chosen as new model substrate. In this case, hydrogenation (80 °C, 60 bar) gave the reduced product in very good yield and no traces of cyclised products were detected. Interestingly, despite the formation of ester-$B(C_6F_5)_3$ complexes is known, this process is probably reversible under the studied conditions and does not seem to affect the desired hydrogenation. Screening of different bases revealed that DABCO is most suitable for this transformation. With this optimized catalytic mixture in hand we were committed to explore the scope of this methodology. To this end, a representative set of diaryl substituted allenes **8**-**12** containing substituents of different electronic nature was synthesized and submitted to the optimized conditions (Table 1).



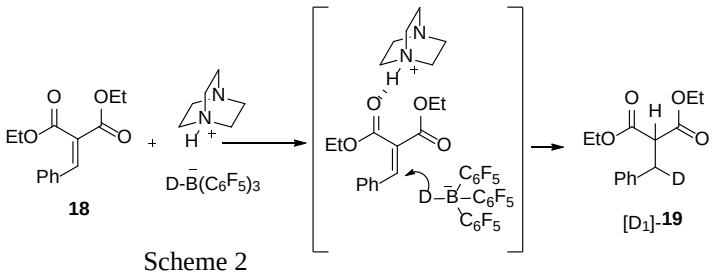
Entry	Allene	Product	Yield (%)[b]
1	**8**; R, R‘ = Ph	**13**	75
2	**9**; R, R‘ = *p*-(Me)Ph	**14**	65
3	**10**; R, R‘ = *p*-(F)Ph	**15**	94
4	**11**; R , R‘= *p*-(OMe)Ph	**16**	68
5	**12**; R-R‘ = 3,5-di(F)-9-fluorene	**17**	43[c]

Table 1. [a] Reaction conditions: Toluene, 80 °C, 3 days; H_2 60 bar and DABCO/$B(C_6F_5)_3$ (15 mol%); [b] isolated yields; [c] the low yields are probably due to dimerization of the allene at the working conditions.

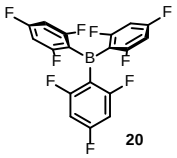
In view of this reactivity, we decided to study whether the additional activation provided by the two double bonds of the allene moiety was necessary to accomplish the desired hydrogenations or if a structurally simpler alkylidene malonate or other electron poor alkenes could also undergo the same transformation.

With this idea in mind, we first carried out a series of experiments to gain some evidence about the operating mechanism. Interestingly, the equimolar reaction of alkylidene malonate **18** with [HDABCO][DB(C_6F_5)$_3$] afforded the hydrogenated product [D_1]-**19** that bears the deuterium label exclusively in the β-position. This clearly indicates that the hydride from the borohydride anion is transferred at the electrophilic position of the substrate (Scheme 1). No reaction was detected when the reduction was attempted with K[HB(C_6F_5)$_3$] followed by quenching with DABCO·HCl, demonstrating that the $[HDABCO]^+$ cation plays an active role during the hydrogenation process. Thus, we rationalized that in this transformation the $[HDABCO]^+$ moiety should activate the substrate, presumably through the formation of a hydrogen bond, followed by nucleophilic attack of the hydride (Scheme 2).

The fact that an activation of the alkylidene malonate is necessary to carry out the desired reduction suggests that for these substrates, hydride transfer from the borohydride moiety is the rate determining step. Hence, the employment of boranes depicting weaker Lewis acidity than B(C_6F_5)$_3$ should facilitate this elemental process. However, weak Lewis acids are not the most adequate ones to promote H_2 cleavage that is necessary for the reduction to take place. Therefore, a compromise situation regarding the Lewis acidity of the borane partner had to be found in order to optimize this transformation in terms of reaction conditions and substrate scope. In our hands, borane **20** exhibits optimum properties (Scheme 3). With this compound we were able to extend this metal-free hydrogenation to alkylidene malonates, nitroalkenes and vinyl sulfones.



Scheme 2



Scheme 3

2.4.8 Publications 2011-2013 from the Department of Organometallic Chemistry

Fürstner group

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Alcarazo group

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