Catalysis in Mülheim

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Catalysis for Total Synthesis: A Personal Account

*Alois Fürstner**

Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

gold · iron · molybdenum · natural product synthesis · ruthenium

It was the arguably most respected organic chemist of the early 20th century, Prof. Emil Fischer (Figure 1), who masterminded the initiative that finally led to the foundation of the Max-Planck-Institut für Kohlenforschung in Mülheim an der Ruhr (then "Kaiser-Wilhelm-Institut"). In a presentation

Figure 1. Plaque displayed in the staircase of the Institute with the heads of Emil Fischer (left) and Franz Fischer (right), who was the first director of the Institute.

given in July 1912,[1] which was part of a fund-raising campaign, he elaborated on the importance of coal research. This particular focus certainly met the expectations of the local officials and must have enchanted potential benefactors who had made their fortune with coal mining and/or heavy industry that dominated the economy of the Ruhr area in those days. Yet, Emil Fischer managed to lay out—as an overtone—a much more visionary second agenda, in that he foresaw in those early days the tremendous importance that catalysis would gain in the future. *This chapter of catalysis is virtually unlimited, and thorough investigations in this area promise considerable success.*[1] For example, he anticipated that catalysis might allow coal to be converted into liquid fuel (the later (Franz) Fischer–Tropsch process (Figure 1), which was discovered at the Institute in the early 1920s);[2] he even saw the need to find catalysts for use in fuel cells (*galvanischen Elementen*), and emphasized that such a development could revolutionize energy production.[1]

Though ingenious, these statements also show that Emil Fischer associated catalysis solely with "large-scale" operations, which best allow the advantages of a process-integrated way of saving energy, reducing waste, and securing productivity to be harnessed. This may be the reason why he did not see—or at least not mention—any link between catalysis research and organic synthesis or natural product chemistry,[3] even though he himself was the undisputed master of these fields. In cases where natural product chemistry had reached industrial practice then, stoichiometric reactions were acceptable.[4] In fact, metal-catalyzed transformations—apart from hydrogenation and related reductions—had fairly little impact on the logic and practice of target-oriented synthesis in the first decades of the 20th century—some beautiful early exceptions notwithstanding.[5,6] Their true relevance was appreciated only when organic chemists learnt how to liaise catalysis with their own preoccupations of chemo-, regio-, and stereoselectivity. Since then, however, the organic community has been one of the strongest advocates of this discipline. I am no exception to this rule, as will become evident from the vignettes outlined below which are a personal reverence to the Kohlenforschung Institut. They are meant to highlight how catalysis and total synthesis cross-fertilize each other. It is my strong believe that the "ideal synthesis" must not only adhere to the various "economies" that have already been amply discussed in the literature,[7] but should also aim at being largely or even solely catalysis-based. To date, hardly any multistep endeavor reaches this standard, which shows how much is left to do. The total synthesis of complex target molecules hence provides a constant stimulus for catalysis research and, at the same time, remains the most rigorous benchmark. Therefore I find it appropriate and enriching to pursue natural product chemistry at a research institution like "the Kohlenforschung", whose founding fathers originally had a very different agenda in mind.

A noble trail from pyrrole alkaloids to transannular macrolide functionalization: The enticing structures and biological promise of a small set of pyrrole alkaloids captured our attention in the mid-1990s.[8–10] Our early work on ring-closing olefin metathesis (RCM) had taught us that the synthesis of even fairly strained medium-sized rings was within the range of this methodology;[11,12] yet, attempts at translating this knowledge into a viable route to streptorubin B were not encouraging. Therefore we considered an alternative approach that was inferred from a timely publication by Murai, Chatani, and co-workers.[13] These authors described a rather unusual cycloisomerization of enynes effected by bare $PtCl_2$. Although the exact mechanism had remained unclear, this transformation served our purpose very well and gave (starting from **1**) access to compound **2**,

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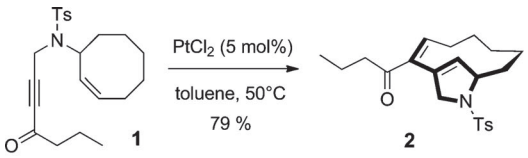
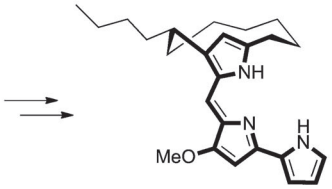
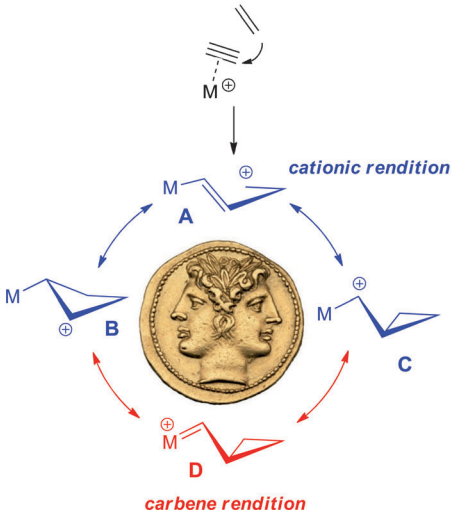




Streptorubin B

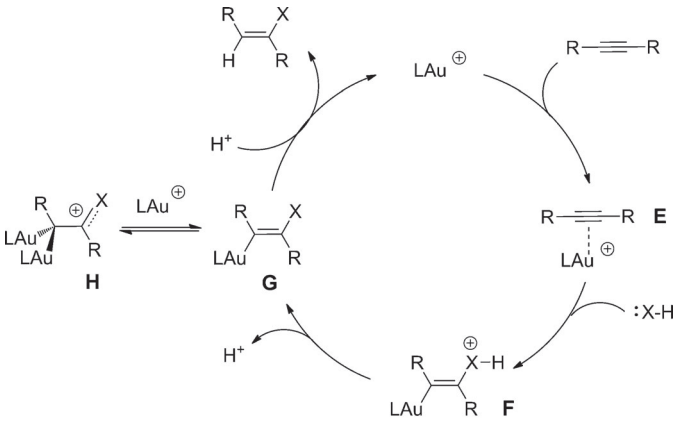


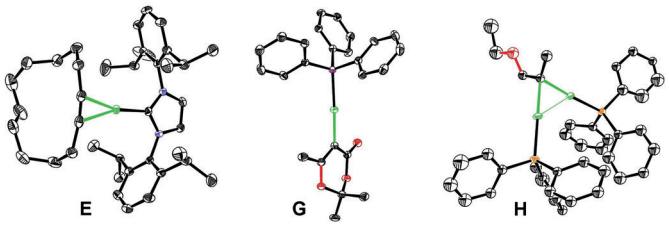
Scheme 1. Top: Enyne cycloisomerization used to forge the core region of streptorubin B. Bottom: The inferred mechanism invoking carbenoid intermediates with delocalized charge density.

which was elaborated into the core of the target alkaloid (Scheme 1).[14] The reaction scaled up well, even though **2** is highly strained by virtue of the *meta*-bridging ten-membered ring and the "bridgehead" 1,3-diene substructure embedded in the bicyclic edifice.

Intrigued by this result, we ventured into a mechanistic study of noble-metal-catalyzed cycloisomerizations. We soon found that the Pt^{II} cation is by no means uniquely capable of effecting such transformations, although it is particularly efficient at activating alkynes toward an outersphere attack by an adjacent olefin which enters *trans* to the metal.[14,15] Because the formation of the new C–C bond formally leads to the build-up of positive charge at the homoallylic position, the resulting putative species **A** (Scheme 1) represents only one form of an ensemble of resonance extremes **A**–**D** that, collectively, provide an adequate description of the reactive intermediate; the congruent form **C** clearly visualizes the carbenoid character, as formal positive charge and a C–M bond concur at the same carbon atom.[14–16]

This interpretation eventually became the generally accepted rationale of π-acid catalysis (Scheme 2).[17–21] It implies that other carbophilic metal cations might induce similar transformations, amongst which Au^{I} became the most popular. Since only one π-system gets activated, many





Scheme 2. Top: Generalized mechanism of π-acid catalysis, including *gem*-diauration as an off-cycle event, which competes with protodeauration. Bottom: Some crystallographic evidence for proposed intermediates of types **E**, **G**, and **H** (only the complex cations are shown for clarity); color code: Au = green, O = red, N = blue, P = orange.

Alois Fürstner (born 1962) graduated from the Technical University of Graz, Austria (Prof. H. Weidmann). After postdoctoral studies with the late Prof. W. Oppolzer at the University of Geneva, Switzerland, and a Habilitation in Graz (1992), he joined the Max-Planck-Institut für Kohlenforschung, Mülheim, Germany, as a group leader (1993). In 1998, he was promoted to the rank of Director. His work is focused on organometallic chemistry and homogeneous catalysis, including applications to the total synthesis of structurally complex natural products of biological significance.

nucleophiles other than olefins should qualify; likewise substrates other than alkynes can be used, as long as they exhibit sufficient affinity to the chosen π-acidic catalyst. Moreover, the proposed dual carbenoid/cationic character of the key intermediates opens a gateway to considerable structural diversity.[22]

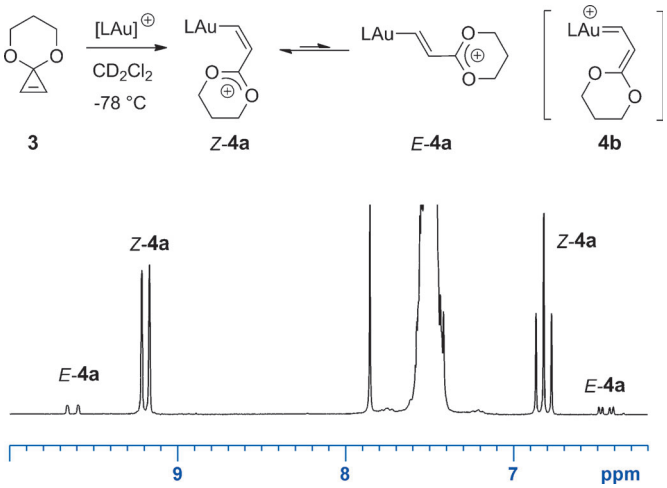
Our mechanistic hypothesis allowed several transformations to be anticipated with little or no precedent in the literature.[17,22] This predictive power notwithstanding, the scenario shown in Scheme 2 was nothing but a sketch as long as the true nature of the proposed intermediates remained speculative. It was perhaps the environment of the Mülheim

Institute with its long tradition in structural and mechanistic organometallic chemistry that encouraged us to become more deeply involved. As a first foray, a series of polyunsaturated probe molecules was designed; upon treatment with gold catalysts, they were shown to undergo reaction cascades via highly ordered, charge-delocalized transition states that are reminiscent of the "Stork–Eschenmoser paradigm" evoked to explain cationic polycyclization processes.[23]

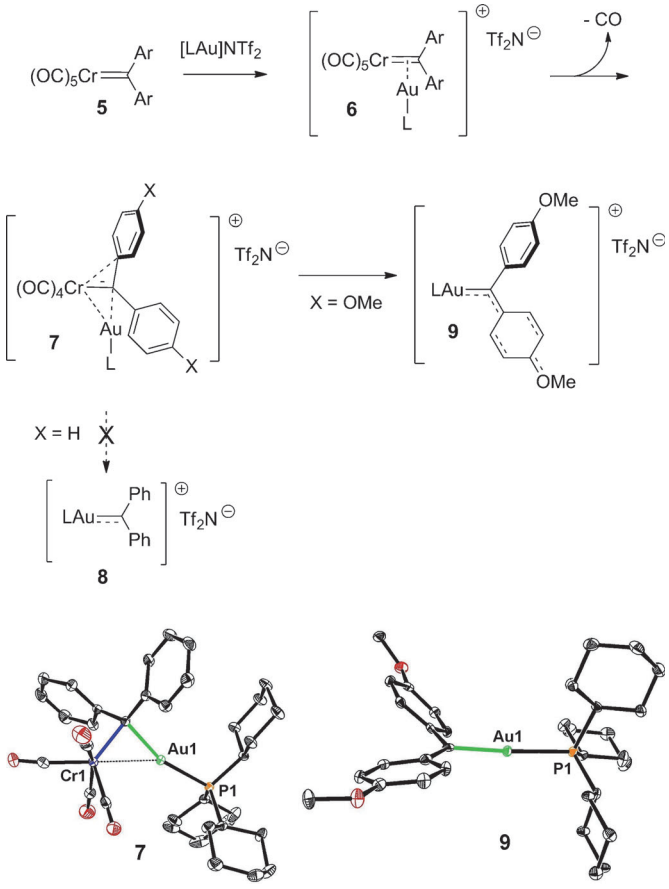
In parallel work, considerable efforts were made to obtain direct spectroscopic and crystallographic information about the reactive species.[24] This program was complemented by computational studies which we performed in cooperation with the Thiel group, and which were instrumental more than once for the interpretation of the acquired structural data (Scheme 2). For example, the effects imposed onto a given alkyne substrate upon coordination to either neutral or cationic Au^I fragments were systematically studied;[25] the spectroscopic and structural fingerprints made it possible to interpret the bonding situation in some detail within the framework of the Dewar–Chatt–Duncanson model.[26,27] Moreover, we managed to emulate the slippage process by which carbophilic acids are supposed to polarize a coordinated π-bond.[28]

An unexpected observation was made during investigations into the seemingly trivial final step of the proposed catalytic cycle. It was found that enol ether derived alkenylgold species are aurophilic to the extent that *gem*-diauration with formation of complexes of type **H** starts to compete with the seemingly trivial protodeauration.[29,30] This bias implies that protodeauration can become the rate-determining step of certain gold-catalyzed processes; moreover, *gem*-diaurated off-cycle intermediates must be avoided for optimal turnover of the loaded catalyst.[29] These conclusions inspired others to perform very detailed kinetic analyses of gold-catalyzed hydroalkoxylation reactions, which will be highly valuable for the optimization of noble-metal-catalyzed transformations in the future.[31]

Several attempts were necessary to gain a concise picture of the bonding situation of gold carbenoids as the proposed key intermediates. In a first attempt, we relied on the rearrangement of cyclopropene derivatives such as **3** (Scheme 3).[32,33] To our surprise, the resulting gold complex **4** showed only marginal Au–C double bond character; rather, it must be viewed as an ordinary alkenylgold species bearing a positively charged ligand. Since the vinylogous heteroelements might not be innocent but intrinsically favor such a cationic character,[34] we attempted to prepare gold carbenoids devoid of stabilizing substituents. To this end, suitable chromium carbene precursors were subjected to transmetalation (Scheme 4).[35] Although gold-for-chromium exchange is known to work exceptionally well with Fischer-type carbenes,[36] it failed with complex **5** (Ar = Ph). Rather, coordination of the gold fragment to the Cr=C unit was observed, which deprives this entity of electron density such that the primary adduct **6** has to abandon one of the electron-withdrawing CO ligands even at low temperature. Nevertheless, the resulting bimetallic species **7** (X = H) does not break down but uses one of the neighboring phenyl rings as a steric guard (rather than as an electron provider). This



Scheme 3. Preparation of gold carbenoid **4** bearing vinylogous oxygen substituents by a cyclopropene rearrangement; the NMR spectrum shows that this reactive intermediate is best interpreted as an ordinary alkenylgold complex with a charged organic ligand. Since the rotational barrier about the Au–C bond is very small (≤ 30 kJ mol^{-1}), the contribution of the carbene resonance structure to the ground-state structure of this species is marginal. L = PPh_3.



Scheme 4. Experimental data relevant for a discussion of the structure and bonding of gold carbenoids; structures of complexes **7** and **9** in the solid state (only the complex cations are shown for clarity); color code: Au = green, Cr = blue, O = red, P = orange.

highly unorthodox situation is obviously still better than the release of the putative "unstabilized" gold carbenoid **8**.[35] When allowed to reach ambient temperature, the bimetallic complex **7** (X = H) simply decomposed.

From these observations it was concluded that neither $d_\pi \rightarrow p_\pi$ back donation nor two unsubstituted phenyl rings suffice to endow a gold carbenoid with a finite lifetime. To test this interpretation, we started to explore the borderline where gold carbenoids change over from fleeting to discrete intermediates by variation of the electronic properties of the flanking arene rings. Two remote methoxy substituents proved to be more than sufficient: while **8** could never be observed as a discrete species in solution, its substituted congener **9** was obtained in crystalline form and found to be stable for some time even at ambient temperature.[37] As anticipated from the results outlined above, the structure of this complex in the solid state (Scheme 4) shows that the arene rings carry much of the electronic burden whereas electron back-donation from the gold center into the empty singlet carbene orbital, though operative,[38] must be small; in any case, the Au–C bond order is very close to one.[37] This result corroborated our original interpretation of π-acid catalysis that had invoked "carbenoid" intermediates bearing considerable positive charge density on the organic ligand.[14,15] Even though it may be a semantic question whether one prefers the term "gold carbenoid" over "gold carbene" or "gold-stabilized cation", we emphasize that the popular notion of gold–carbon "double bonds" is currently not supported by structural or spectral evidence and should therefore be avoided when one refers to such species as distinct intermediates in condensed phase.[37]

The growing insight into the mechanistic background of π-acid catalysis in general spurred our efforts to take strategic advantage of the acquired knowledge in advanced organic synthesis. To show our confidence, we deliberately implement π-acid-catalyzed transformations into the late stages of multistep endeavors, where the compounds are obviously highly precious to those who had to make them. Since this aspect of our work has recently been summarized,[39] only a few of the conquered target structures are compiled in Figure 2. Suffice it to say, we would not have been able to find a solution for the gold-catalyzed formation of 2-pyrones developed en route to neurymenolide A, an exceptionally fragile compound of marine origin, without knowledge about the competition between *gem*-diauration and proto-demetalation.[40] Likewise, the late-stage transannular reactions that enabled the syntheses of spirastrellolide A,[41] amphidinolide F,[42] and polycavernoside A[43] have greatly benefitted from the now fairly detailed mechanistic understanding of alkyne hydroalkoxylation in general. Finally, the total syntheses of cubebene and related cyclopropane derivatives, though much less complex in structural terms, feature the carbenoid character of the reactive intermediates and illustrate that alkynes can serve as valuable *vic*-dicarbene synthons.[44–47] Enantioselective variants are also emerging, even though asymmetric gold catalysis remains a challenging task because of the one-point binding situation.[48] To this end, we proposed a novel phosphoramidite ligand scaffold which crafts an effective C_3-symmetric ligand environment about the gold catalyst in the first place. These readily prepared ligands led to excellent enantioselectivities in a host of gold-catalyzed transformations.[49–51]

Iron catalysis, a base metal for a noble task: The promise of high chemoselectivity is arguably one of the major reasons why a very significant proportion of catalysis, as applied to advanced synthesis, still relies on the favorable properties of the noble metals; the previous vignette on our own work on Pt and Au catalysis illustrates this aspect. Even though cost considerations are meaningless at the fundamental level of discovery that our work tries to address, we certainly

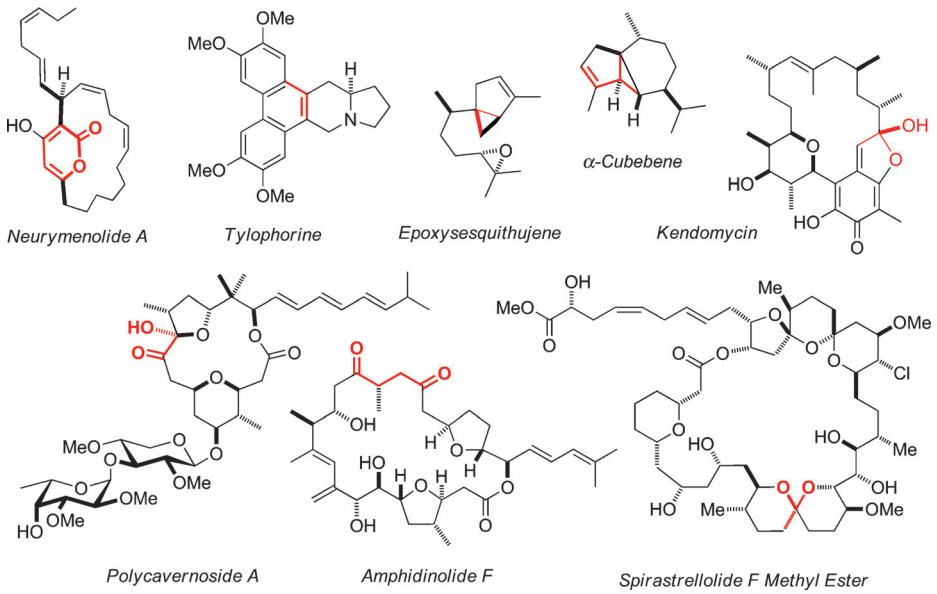


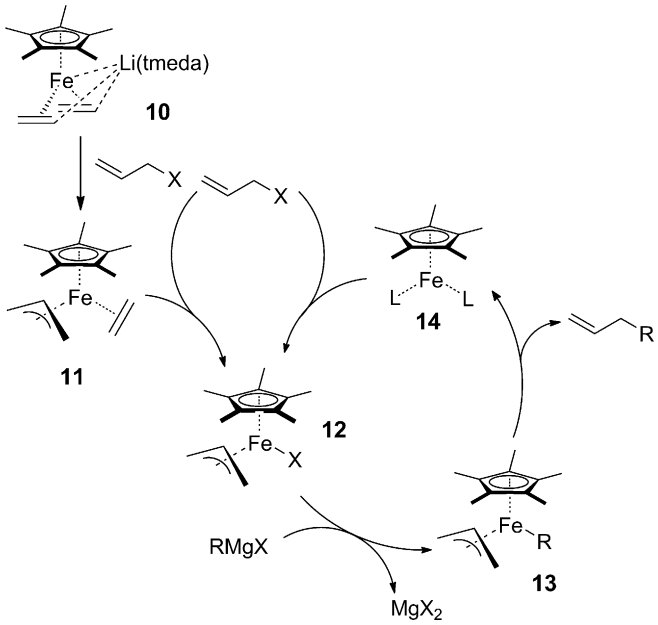
Figure 2. Selected total syntheses based on platinum- or gold-catalyzed transformations; the substructures formed by this chemistry are highlighted in red.

appreciate that one of the big challenges of catalysis research is the need to emulate the exquisite selectivity of noble metals with cheap, benign, and readily accessible base-metal substitutes. Iron is an obvious candidate.[52,53] Despite its many advantageous attributes, iron catalysis has not been a focal point until fairly recently. Arguably, however, the potential is tremendous and the gradient of activity in the field is skyrocketing.[52–57]

We launched our program at a time when iron catalysis was still largely centered on the Lewis acidic properties of Fe^{3+}. Inspired by truly pioneering work of Kochi et al., who had shown that iron salts catalyze the cross-coupling of Grignard reagents with alkenyl halides,[58] we became interested in investigating the then largely unexplored scope of this transformation. Although aryl halides are arguable more important substrates, it was basically unknown at the outset of our project whether they would be amenable to iron-catalyzed C–C bond formation. Gratifyingly, we could show that aryl and heteroaryl chlorides and sulfonates react well and are better suited than the corresponding bromides and iodides.[59] The reactions with alkylmagnesium halides as the preferred nucleophiles usually proceed under exceptionally mild conditions at low temperature and tolerate a reasonable number of functional groups. Moreover, this chemistry scales well and was successfully applied in synthesis by us and other groups.[57] Aryl Grignard reagents were found to be more problematic and required activated heteroaryl chloride partners;[59] more recent results, however, are encouraging in that they show that such donors can also be encompassed, at least in certain cases.[60]

Conceptually more rewarding is the fact that iron-catalyzed C–C bond formation extends to substrates that are nonprivileged coupling partners otherwise.[53–57] In this context, the ease with which alkyl halides are amenable to cross-coupling is particularly noteworthy.[61–63] Moreover, a formal ring-opening/cross-coupling reaction of 2-pyrones with formation of stereodefined dienyl carboxylate derivatives was found, which has very little precedent.[64] An iron-catalyzed transformation of propargyl epoxides into allenol derivatives turned out to be stereo-complementary to established copper chemistry.[65] This transformation was instrumental for the total synthesis of amphidinolides X and Y and a series of analogues of these bioactive macrolides.[66–68]

A qualitative analysis of the observed reactivity patterns let us speculate early on that iron-catalyzed cross-coupling reactions might not follow a uniform mechanism.[69] Rather, it was proposed that different pathways can be operative depending on the particular combination of nucleophile and electrophilic partner. In fact, we could demonstrate that methyl donors afford iron ate-complexes in the first place, which are moderately nucleophilic and react only with sufficiently activated electrophiles (alkenyl triflates, acid chlorides, 2-pyrones, etc.).[70] In contrast, higher alkylmagnesium halides reduce the chosen iron precatalyst to low-valent species, the exact nature of which is still a matter of debate.[71] In any case, we were able to emulate for the very first time all of the elementary steps of a possible catalytic cycle (Scheme 5),[72] starting from well-defined low-valent iron complexes such as **10** which had previously been prepared



Scheme 5. Possible catalytic cycle of iron-catalyzed cross-coupling reactions for which crystallographic evidence could be obtained (see Figure 3); note that an Fe^0 complex was used as the entry point but the actual cross-coupling shuttles between Fe^+ and Fe^{3+}; the mechanisms by which iron catalysts generated in situ are operative, however, may be different and/or considerably more complex.

in Mülheim by Jonas et al.;[73] all proposed organoiron intermediates of the chosen model cross-coupling reaction were obtained in crystalline form, despite their exceptional sensitivity (Figure 3).[72] Despite this success, it became apparent that different redox manifolds must be considered. Therefore we express a caveat that generalizations about the operative mechanism in iron-catalyzed reactions under differ-

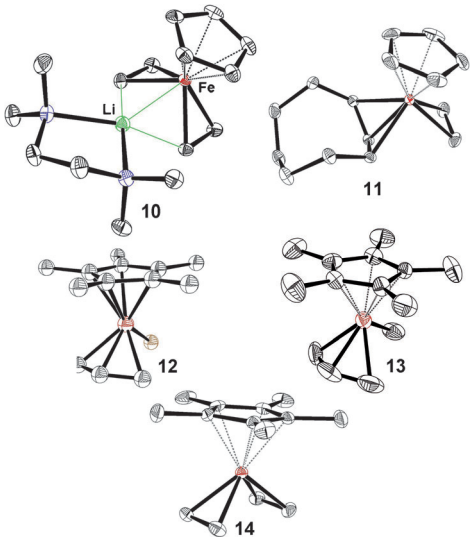
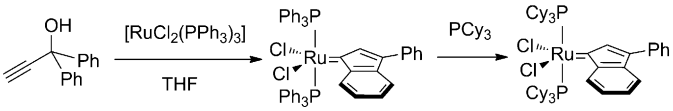


Figure 3. A series of fully characterized iron complexes which emulate the intermediates of the putative cycle shown in Scheme 5; color code: Fe = red, Li = green, N = blue, Cl = orange. The formula numbers of the specific compounds refer to the types of intermediates shown in Scheme 5.

ent experimental conditions must be made very cautiously at the present stage of development.[72] This uncertainty notwithstanding, we could also show that low-valent iron complexes qualify as catalysts for other C–C bond formations, including the ring opening of vinyl cyclopropanes,[74] as well as intramolecular Alder–ene reactions and [4+2], [5+2], and [2+2+2] cycloadditions.[75]

Olefin metathesis for synthesis: I was extremely lucky to start my independent career in Mülheim at the time when olefin metathesis was about to revolutionize organic synthesis. In the early 1990s, the now classical catalysts became available that combine high activity with a splendid functional-group tolerance.[76,77] The subsequent avalanche of interest has profoundly changed the way organic chemistry is practiced now and in the future.[78–82] Some of our early work, in particular on the formation of medium-sized[11,12] and macrocyclic rings by ring-closing olefin metathesis (RCM),[83–85] may have helped to make this method popular and to reveal its logic, which is—in part—complementary to that of traditional organic synthesis.[86] The conquest of glycolipids such as tricolorin, woodrosin, putative gobienine A, and the ipomoeassins is instructive: the macrocyclic rings were forged in the middles of the aliphatic tether, far remote from any functionality (Figure 4).[87–91] Suffice it to say that such a site would not be a serious option if conventional retrosynthetic logic were applied. Similarly counterintuitive may be the formation of the very cytotoxic agent iejimalide which was ultimately prepared on gram scale by an RCM reaction in which two out of ten double bonds present in the cyclization precursor had to be selectively activated.[92,93]

Once the awesome power of olefin metathesis became apparent to us, we also tried to contribute to the advancement of this imporant field by finding alternative and/or better catalysts,[94–96] by improving the handling of the known catalysts,[97] by proposing more-benign reaction conditions,[98] and by finding safer routes to carbene complexes. Specifically, the use of propargylic alcohols as a carbene source and the derived indenylidene complexes became quite popular and are now produced on (industrial) scale (Scheme 6).[99]



Scheme 6. The use of a propargyl alcohol as a safe and convenient carbene source: preparation of ruthenium indenylidene complexes for olefin metathesis.

The evolution of selective molybdenum alkylidynes: Yet another base metal for a noble task: In the course of our work in the olefin metathesis area, we soon encountered a serious limitation in that the classical catalysts would not allow kinetic control over the configuration of the newly formed double bond to be exerted.[100] In response to this challenge,[101] we explored ring-closing alkyne metathesis (RCAM) as a possible alternative.[102,103] Initially, we had to use either catalysts formed in situ from $[Mo(CO)_6]$ and substituted phenols (Mortreux-type catalysts)[104] or the Schrock alkylidyne $[(t\mathrm{BuO})_3\mathrm{W}\equiv\mathrm{CCMe}_3]$.[105,106] However, it soon turned out that the Mortreux-type systems were hardly adequate for our purposes, not least because of the forcing reaction conditions that endanger sensitive and/or highly functionalized substrates.[107] $[(t\mathrm{BuO})_3\mathrm{W}\equiv\mathrm{CCMe}_3]$ was better

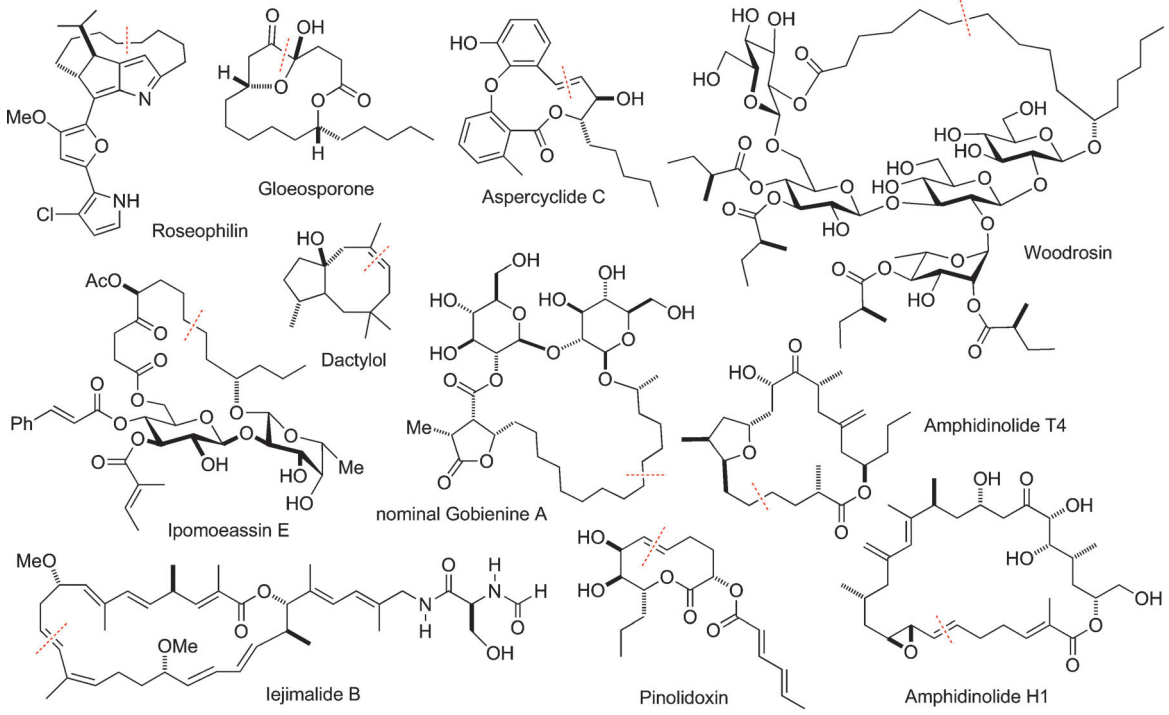


Figure 4. Selection of natural products of different ring sizes made by RCM in our laboratory; the site of ring closure is indicated in red.

suited and allowed a number of promising RCAM reactions to be carried out, although the scope of this catalyst is seriously limited owing to its fairly high Lewis acidity.[107] Yet, a series of early applications to the syntheses of natural products, though relatively simple in structural terms, convinced us of the potential of RCAM, which could be fully harnessed only if more appropriate catalysts would become available.[103,108]

To accomplish this goal, we reasoned that molybdenum (rather than tungsten) alkylidyne complexes might be an inherently better starting point, even though the parent complex $[(t\mathrm{BuO})_3\mathrm{Mo}\equiv\mathrm{CCMe}_3]$ itself was known to be inactive.[109] Provided this lack of reactivity could be overcome, the lower intrinsic Lewis acidity of molybdenum might translate into a higher functional-group tolerance and practicality. This expectation was corroborated when we managed to activate $[\mathrm{Mo}[(\mathrm{N}(t\mathrm{Bu})\mathrm{Ar}]_3]$ (**15**; Ar = 3,5-dimethylphenyl) with the help of CH_2Cl_2 or related halogen sources (Figure 5).[110] Under these conditions, a catalytically competent mixture of a molybdenum methylidyne and a molybdenum chloride was generated in situ, which showed a remarkable tolerance vis-à-vis a number of sensitive functional groups.[111] Consequently, this catalyst system allowed several natural products to be made by RCAM, which are reasonably complex and biologically relevant. Epothilone C, the latrunculins, prostaglandin E_2 1,15-lactone, cruentaren A, amphidinolide V, and leiodermatolide fall into this category.[103,112]

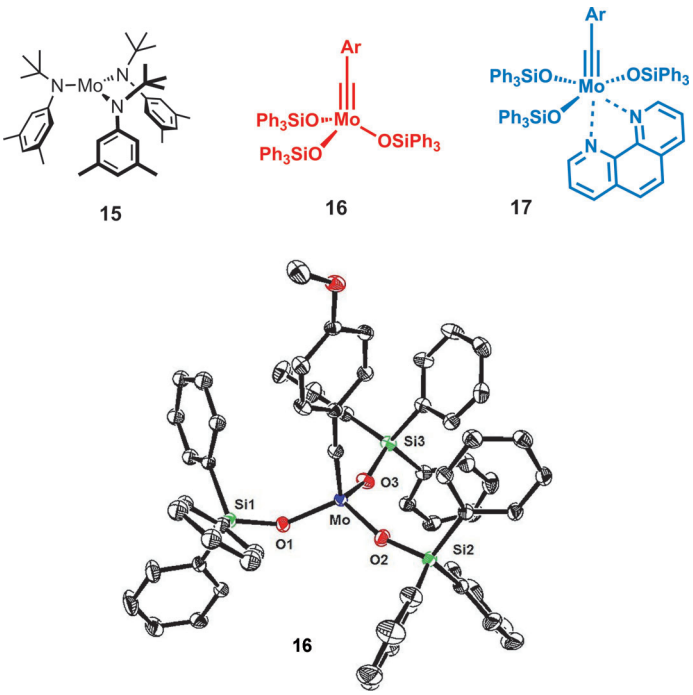


Figure 5. Evolution of molybdenum-based alkyne metathesis catalysts: the very sensitive complex **15** has to be activated in situ by treatment with CH_2Cl_2, whereas the alkylidyne complex **16** is highly active and shows outstanding functional-group tolerance; complex **17** is a bench-stable variant thereof. The ORTEP plot shows the structure of **16**, Ar: *p*-$MeOC_6H_4$.

In practical terms, however, the use of **15**/CH_2Cl_2 brought no improvement, because **15** is exceptionally sensitive to oxidants and moisture, and even capable of activating N_2 at ambient temperature.[113] To achieve wider acceptance of alkyne metathesis, it was mandatory to find a more user-friendly alternative without jeopardizing the advantageous chemical attributes. This strategic task was achieved with the development of molybdenum alkylidyne complexes endowed with triarylsilanolate ligands, which can even be rendered bench-stable upon reversible complexation to phenanthroline; in form of such adducts, the catalysts are simple, safe, and convenient to use (Figure 5).[114,115]

Complex **16** and relatives outperform $[(t\mathrm{BuO})_3\mathrm{W}\equiv\mathrm{CCMe}_3]$ in terms of activity, which is the benchmark in the field (Figure 6). Most notably, however, **16** excels in terms of compatibility with substrates having polar and apolar substituents; its tolerance is reminiscent of the chemoselectivity one may expect from noble-metal catalysts. Moreover, the ability of **16** to distinguish between triple bonds and double bonds renders alkyne metathesis strictly orthogonal to alkene metathesis and hence particularly well suited for the synthesis of polyunsaturated targets. In terms of substrate scope, **16** accepts alkyne derivatives that were problematic previously, including propargylic alcohol derivatives, electron-deficient and electron-rich alkynes of various kinds, and even terminal acetylenes.[116–119] Limitations are encountered with very bulky substrates that do not bind to the operative alkylidyne unit surrounded by a somewhat crowded silanolate ligand sphere.

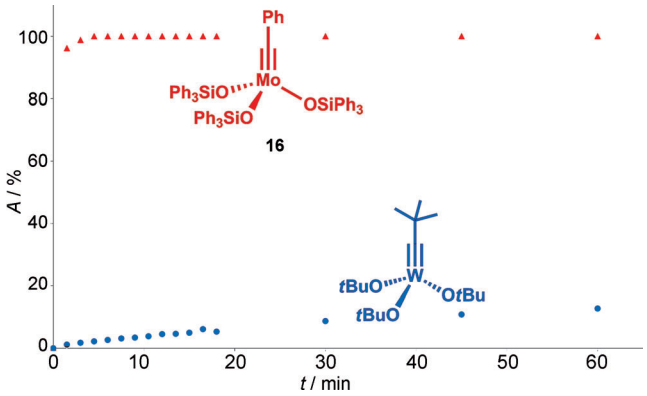


Figure 6. Comparison of the activity *A* of the classical tungsten alkylidyne complex $[(t\mathrm{BuO})_3\mathrm{W}\equiv\mathrm{CCMe}_3]$ with that of the molybdenum alkylidyne complex **16** (Ar = Ph), which is endowed with triarylsilanolate ligands, in the conversion of 1-phenyl-1-propyne into tolane at ambient temperature; other reactions show that **16** is not only far more active but also much more functional-group-tolerant.

The reasons for the excellent match between the formally high-valent molybdenum center in **16** and the ancillary silanolate ligands were studied in some detail; the adaptable electronic features of silanolates seem to be the key to success.[115] Moreover, a flexible synthesis route was developed that delivers complexes **16** and the stabilized variant **17** on multigram scale (they are now also commercially available). The major decomposition pathways of such catalysts

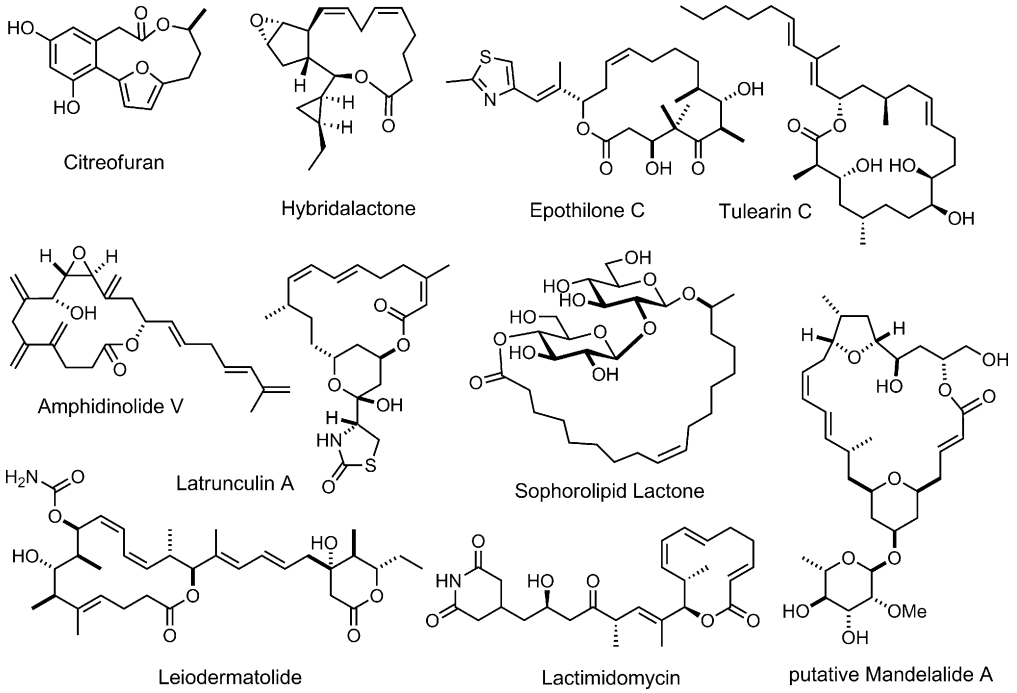


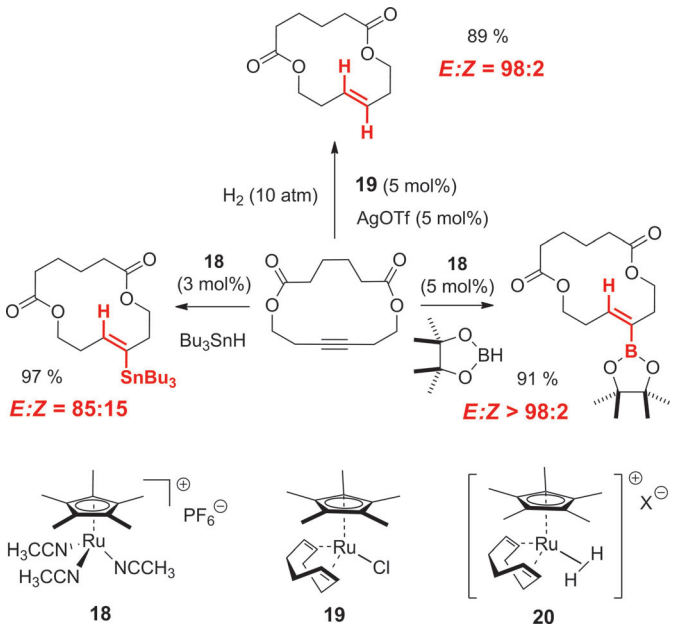
Figure 7. Selection of bioactive natural products made by RCAM; for additional examples, see spirastrellolide F, kendomycin, polycavernoside A and amphidinolide F displayed in Figure 2.

were also elucidated in order to guide future design.[115] Applications to increasingly complex targets illustrate the performance of these tools (Figure 7). It is perhaps unnecessary to mention that the resulting alkyne products can not only be reduced to either *Z*- or *E*-alkenes, as one desires (see neurymenolide shown in Figure 2,[40] hybridalactone,[120] tulearine C,[121] and lactimidomycin);[122] they can also be subjected to a host of other postmetathesis transformations, which brings many additional structural motifs into reach. In this context, the use of alkynophilic π-acids is attractive. For example, we have used a sequence of RCAM followed by gold or platinum catalysis as the key strategic maneuver en route to spirastrellolide F,[41] amphidinolide F,[42] polycavernoside A,[43] and kendomycin (see Figure 2).[123] Because the structural span is deemed significant, alkyne metathesis deserves consideration in retrosynthetic planning.

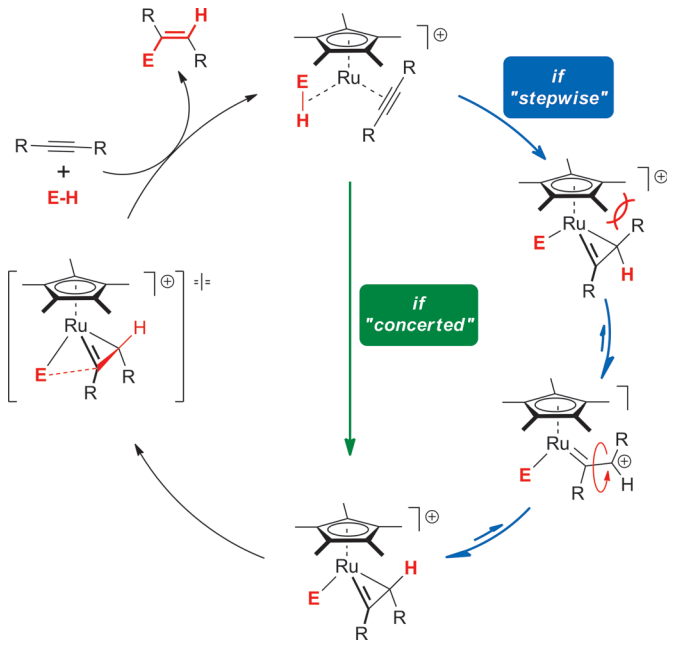
***trans*-Hydrometalation and *trans*-hydrogenation**: As mentioned above, alkyne metathesis in combination with a Birch-type reduction opens a stereoselective entry into *E*-alkenes. With the advent of powerful and, at the same time, convenient alkyne metathesis catalysts such as **16**, it became increasingly clear that the weak point of this tactics is actually the semi-reduction step, which, in its classical format, requires strongly reducing conditions that preclude many functional groups.[124] The best current alternative is the *trans*-hydrosilylation chemistry developed by Trost and co-workers, followed by proto-desilylation of the resulting alkenylsilanes.[125,126]

We have taken advantage of this chemistry on several occasions,[127,128] not least during an extensive program directed toward the putative cell migration inhibitor lactimidomycin and a host of synthetic analogues of this lead compound.[122] Nevertheless, it seemed rewarding to generalize the underlying principle, because the isolobal relationship[129] between R_3Si^+ and H^+ suggests that $R_3Si{-}H$ might be replaced by H–H. The envisaged *trans*-hydrogenation of acetylene derivatives, however, violates the fundamental rule of *syn*-delivery of the two H atoms of H_2 to the π-system of the substrate to be reduced, which has been the governing principle in hydrogenation chemistry since the beginning. Therefore it is deemed remarkable that cationic ruthenium complexes do in fact allow a broadly applicable, reasonably functional-group-tolerant and—most importantly—highly *trans*-selective hydrogenation of internal alkynes to be realized (Scheme 7).[130] Although over-reduction and/or isomerization of the olefin interfere in certain cases, this unusual stereochemical outcome denotes a certain paradigm change.

It is too early to draw a detailed mechanistic picture, but the available evidence suggests that the cationic σ-dihydrogen complex **20** might be the relevant species (or a close relative of it) accountable for this unconventional reaction mode.[130] Likewise, computational studies invoked σ-silane complexes into the *trans*-hydrosilylation chemistry referred to above.[131] Therefore we are tempted to believe that these reactions are nothing but different incarnations of a more general mechanism (Scheme 8); if so, reagents other than H_2 or R_3SiH might also be amenable to *trans*-addition across triple bonds. In fact, pinacolborane was recently shown to undergo a ruthenium catalyzed *trans*-hydroboration, which disobeys the fundamental *cis*-addition mode of traditional hydroboration (Scheme 7).[132] Similarly, Bu_3SnH is smoothly added *trans* to alkynes in the presence of [Cp*Ru]-based catalysts (Cp* = pentamethylcyclopentadienyl).[133,134] Whereas the

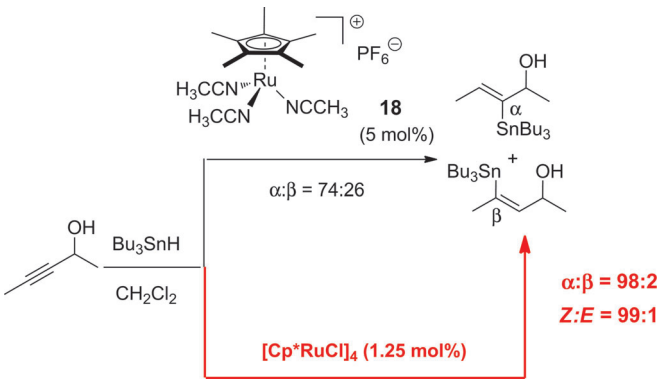


Scheme 7. Examples of *trans*-addition reactions to a model compound; the σ-dihydrogen complex **20** is likely related to the active catalyst generated in situ from **19**/AgOTf under H_2 atmosphere.



Scheme 8. Putative mechanism that can manifest itself as *trans*-hydrogenation, *trans*-hydroboration, *trans*-hydrosilylation, *trans*-hydrogermylation, or *trans*-hydrostannation of alkynes; E = H, $(RO)_2B$, R_3Si, R_3Ge, R_3Sn.

trans-hydrogenation as well as the *trans*-hydroboration are currently limited to internal alkynes, the *trans*-hydrostannation has a larger substrate scope, in that internal, terminal, silylated, and chlorinated alkynes have already been successfully employed.[133] The high functional-group tolerance includes substituents that would not subsist under free-radical conditions or in the presence of strong Lewis acids.[135]



Scheme 9. Representative example for the regioselective hydrostannation of an unsymmetrical alkyne, which is thought to originate from synergy between a neutral catalyst and the protic functionality in the substrate.

Moreover, it was found that neutral (rather than cationic) ruthenium complexes are also able to promote *trans*-hydrostannation; actually, they impose excellent levels of regioselectivity onto reactions of unsymmetrical alkynes bearing protic functionalities (Scheme 9).[133] The generality of this observation is currently under investigation.

The ruthenium-catalyzed *trans*-addition reactions described above commenced as a spin-off of our natural product synthesis program. Although our focus is currently still on the fundamental aspects, we are confident that this chemistry will lend itself to target-oriented synthesis in the future. In this case, it will be another example for the cross-fertilization of total synthesis and catalysis research.

Summary and outlook: In this Essay, which was written on the occasion of the 100th anniversary of the Max-Planck-Institut für Kohlenforschung, I took the liberty of focusing on the research pursued by my own group in Mülheim. From the cited examples, however, the more general notion might become apparent that the interface between basic research into organometallic catalysis and natural product total synthesis is a fertile ground for innovation. In our case, it led us from pyrrole alkaloid chemistry to a detailed study of the structure and bonding of gold carbenoids, from cross-coupling to the preparation of exceptionally sensitive low-valent organoiron complexes, from macrolide synthesis to the design of bench-stable and highly tolerant alkyne metathesis catalysts, and from the pursuit of a presumed anti-metastatic agent to the investigation of σ-bond complexes and their unusual *trans*-addition chemistry. Further examples could be cited, such as the proof that Nozaki–Hiyama–Kishi reactions can be rendered catalytic in chromium,[136] the first examples of carbonyl coupling reactions catalytic in titanium,[137] and the development of the now quite popular 9-MeO-9-BBN variant of the Suzuki coupling.[138–140]

It was a fantastic experience to work in areas which had either just began to flourish when I started my career (metathesis), or which were largely nonexistent (platinum/gold catalysis) or ignored (iron-catalyzed cross-coupling) at the time; eventually, these fields developed into very topical subjects. The fact that I experienced more than once how rapidly a seeming niche area can become mainstream busi-

ness makes me confident about the bright future of our science. Those who think of organic and organometallic chemistry as mature fields underestimate the capability of fellow chemists to innovate.[141] We have every reason to be optimistic. Emil Fischer's verdict from a century ago at the inauguration of the Max-Planck-Institut für Kohlenforschung still holds true:[1] *This chapter of catalysis is virtually unlimited, and thorough investigations in this area promise considerable success.*

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