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From Understanding to Prediction: Gold- and Platinum-Based π-Acid Catalysis for Target Oriented Synthesis

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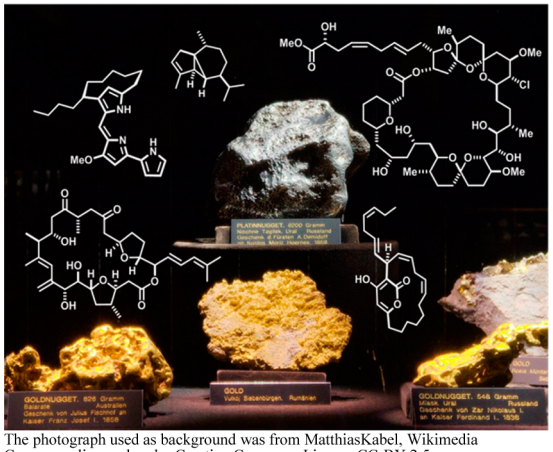
CONSPECTUS

During the last century, conceptual advances in organometallic chemistry were often rapidly embraced by target oriented synthesis. Feedback provided by such preparative scrutiny has greatly benefitted method development; particularly prominent are examples from the entire cross coupling arena, as well as olefin metathesis.

Seen against this backdrop, it is somewhat surprising that the explosive growth of research into π-acid catalysis has not yet yielded a matching number of implementations into the synthesis of structurally complex targets of biological significance. In contrast to the massive output of methodological and mechanistic investigations, few studies illustrate the strategic use of gold, silver, or platinum catalysis in late stages of such multistep endeavors. These elaborate and highly precious compounds demand utmost confidence in the reliability and robustness of the method to be applied.



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In this Account, we analyze the possible reasons for this imbalance, after a short summary of the conceptual basis of carbophilic activation of π-bonds with the aid of soft transition metal cations or complexes. We pinpoint mechanistic subtleties, which, at least in part, produce a great deal of structural diversity but can jeopardize predictive power. With the advances in the understanding of π-acid catalyzed processes in general, however, this uncertainty is gradually vanishing and the entire field is transitioning from comprehension to prediction. This is expected to foster advanced applications, while recent progress in asymmetric gold catalysis further improves the preparative significance.

The presented work in this Account illustrates our own commitment to the field as well as our growing confidence in the maturity of platinum and gold catalysis. The carbophilic activation of π-bonds, particularly of alkynes, provides a method to manipulate functional groups that is orthogonal to traditional carbonyl chemistry. We illustrate this notion by presenting a new approach to hydroxypyrone derivatives that has enabled the total synthesis of the fragile polyunsaturated cyclophane derivative neurymenolide A. The synthesis of the pyrrole alkaloid streptorubin by an enyne cycloisomerization is equally instructive. In addition, different manifestations of transannular hydroxyl addition reactions across alkyne partners mark the late stages of our conquests of amphidinolide F, polycavernoside A, and spirastrellolide F. Together with a few model studies and a personal selection of recent highlights from other groups, these examples augur well for future applications of π-acid catalysts in the realm of target oriented synthesis.

Introduction

Although the use of soft and polarizable late (transition) metal cations for the activation of π-bonds in homogeneous phase has a long history, it was only shortly before the turn of the millennium that this chemistry entered a new era of exponential growth. At about that time, the somewhat paradoxical notion started to catch the imagination of the preparative chemists that some of the most noble metals may give rise to the most active and selective catalysts, rather than being fairly inert as their "noble character" might suggest. Platinum took the lead, closely followed by gold, which soon became particularly popular.[1−6]

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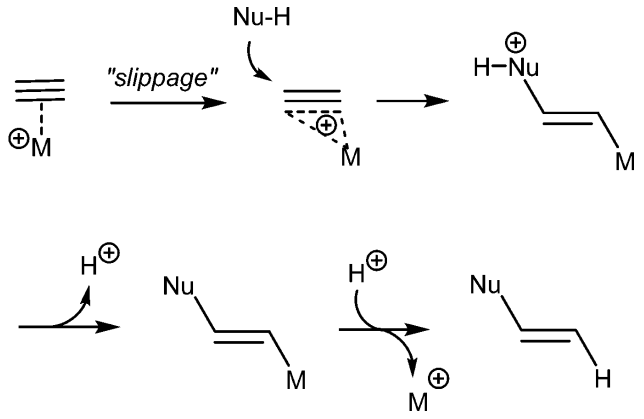
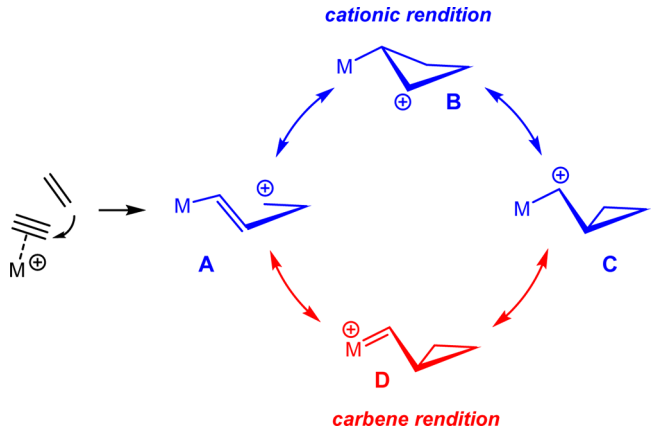
SCHEME 1. Basic Mechanism of π-Acid Catalysis Exemplified by the Net Trans Addition of a Protic Nucleophile across an Alkyne



SCHEME 2. Noble Metal Carbenoids Generated by Reaction of an Ene–Yne Pair



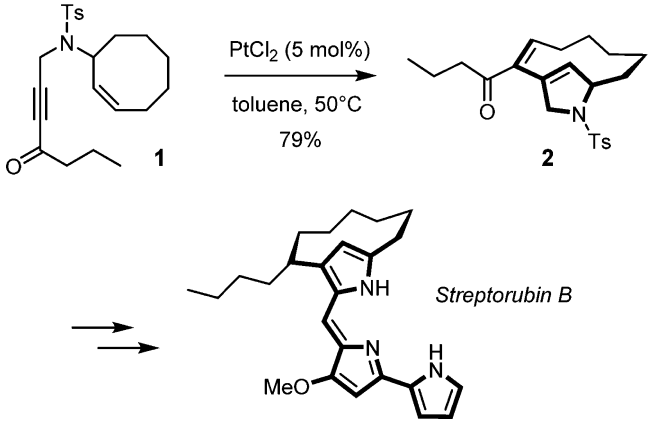
Reactions catalyzed by such π-acidic catalysts cover an impressively large structural space. Yet, it is possible to navigate the almost countless number of applications with the help of a rationale of beautiful simplicity (Scheme 1). In essence, coordination of a carbophilic catalyst to a polarizable π-bond deprives the organic ligand of electron density to the extent that it becomes susceptible to an outer-sphere attack by an adequate (protic) nucleophile. Once the new bond is formed, the resulting intermediate is subject to proto-demetalation with release of the final product and regeneration of the active species. Under aprotic conditions, suitable electrophiles other than protons can be used to close the catalytic cycle. The net outcome is the formal *trans* addition of the chosen carbon- or heteroelement-based nucleophile across the original π-system. This mechanism was originally spelled out for platinum catalysis[7,8] but has become the consensus scheme for "carbophilic activation" of π-bonds in general.[1−6]

Although this basic mechanism of "carbophilic activation" is certainly oversimplified and exceptions do exist,[9] it captures the crux in that it illustrates that no metal-based redox steps are involved in the turn over. This explains why noble metal cations, which are, by definition, adverse to oxidation, form particularly adequate catalysts, and why many such reactions are simple, safe, and convenient to perform. Furthermore, the affinity of the catalyst to soft π-bonds ensures compatibility with a large variety of polar functional groups or heterocyclic motifs and makes product inhibition unlikely, which is a common threat when working with hard oxophilic Lewis acids. Overall, π-acid catalysis is largely complementary and, in part, orthogonal to traditional carbonyl-based chemistry.

The arguably most striking aspect, however, is the "structural diversity" that carbophilic catalysts allow to be harnessed. Although it may be counterintuitive, the basic scenario outlined above also allows this aspect to be rationalized. Imagine, for example, that an olefin is used as the nucleophile to attack an alkyne substrate coordinated to a π-acidic metal fragment (Scheme 2). Once the new C–C-bond is set, the formally resulting species **A** is only one of several resonance extremes needed for an adequate description; forms **C** and **D**, in which the C atom bound to the metal formally carries positive charge, visualize the carbenoid character of the reactive intermediate. Such subtleties readily explain the many mechanistic studies and computational investigations published during the past decade. Furthermore, it becomes clear why the outcome of gold- or platinum-catalyzed reactions is not always easy to predict. It is neither intuitive which resonance extreme gains most "weight" under the chosen reaction conditions nor always trivial to compute the conceivable pathways with the necessary level of accuracy, given the highly relativistic nature of the involved noble metal cations.[3]

Structural diversity can be a blessing for discovery[10] but is detrimental in case it equals a lack of predictive power. The willingness to subject highly precious compounds to a certain method is a rigorous, if not the ultimate, proof of confidence in its reliability and robustness. In this context, it has been diagnosed earlier that the number of applications of homogeneous gold and platinum catalysis to target-oriented synthesis is disproportionally small relative to the massive number of methodological and mechanistic studies.[11] If one solely counts completed syntheses of structurally nontrivial targets that rely on π-acid catalysis as one of the key steps, the number of successful cases

SCHEME 3. Key Step en Route to a Prodigiosin Alkaloid



reported during the past decade remains in fact fairly small.[12,13]

After a decade of rampant growth and mechanistic scrutiny, more testimony of this kind can be expected from the field. A survey of the recent literature, however, makes me confident that the gradient is right. In any case, the selected projects described below are meant to showcase our own commitment, emanating from the conviction that gold and platinum catalysis starts reaching a level of maturity where it gradually transitions from understanding to prediction.

Our "Initiation"

In view of the foregoing, it is perhaps ironic that my group entered this research area early on during an ambitious natural product synthesis project.[7] Although all prior reports on platinum or gold catalysis had basically been confined to the transformation of simple substrates, we felt nevertheless encouraged by a model study published by Murai, Chatani, and co-workers[14] to pursue a $PtCl_2$-catalyzed cycloisomerization of an enyne as a possible gateway to the challenging tripyrrole alkaloid streptorubin B (Scheme 3).[7,15]

To this end, enyne **1** was exposed to catalytic amounts of either $PtCl_2$ or $PtCl_4$ in toluene to furnish diene **2** in high yield. This "low tech" reaction turned out to be nicely scalable, providing access to multigram amounts of product as needed en route to the target. While pleasing in preparative terms, it was by no means clear at the outset why and how the highly strained bicyclic array **2** is formed from substrate **1** solely under the influence of bare $PtCl_x$ ($x = 2, 4$) as the catalyst: note that **2** comprises a *meta*-bridging 10-membered cycle as well as a bridgehead olefin.

It was the analysis of an ensemble of byproducts, formed in minute amounts, together with a set of control experiments using catalysts other than $PtCl_x$ ($x = 2, 4$) that gave us the confidence to propose the mechanistic scheme invoking "carbenoid" intermediates sketched in Scheme 2, not without emphasizing that such species can also be interpreted as nonclassical cations in the coordination sphere of a transition metal catalyst.[7,8] We used the symbol of the "Janus head" to portray this peculiar situation.[1,6,16]

Since then, the entire field basically evolved within this conceptual framework.[1−6] Importantly, this rationale embraces the structural diversity aspect alluded to above and explains why late transition metals such as platinum or gold are particularly effective, but by no means unique, in their behavior. Moreover, the proposition that only one of the π-bonds of the originally used enyne **1** is activated by the carbophilic metal fragment, whereas the other one merely serves as nucleophile, implies that substrates other than enynes and nucleophiles other than alkenes should also be amenable to π-acid catalysis. Finally, the conception of high levels of delocalized charge density on the organic ligands is manifest in a host of later reactivity data[17] and was independently confirmed by spectroscopic means.[18,19]

Interlude

Next, our group tried to use the mechanistic hypothesis (Scheme 2) deduced from the streptorubin project as a search tool in the quest for new reactivity. Since this part of our program has already been reviewed,[1,6] it may suffice to mention our major findings: thus, we showed that enynes can be converted into cyclopropane and cyclobutene derivatives as predicted by the mechanism;[8,20] the proposed nonclassical behavior was unveiled in the rearrangement of alkylidenecyclopropanes;[21] unconventional nucleophiles such as ethers,[8] acetals,[22,29] dienes,[23] and (hetero)arenes[24] were found suitable to attack tethered alkynes in the presence of a carbophilic catalyst; reactions benefitting from anchimeric assistance of a propargylic ester were also reduced to practice.[25,26] Finally, soft main group metal cations such as Ga(+3) or In(+3) were shown to obey the same mechanistic logic as platinum or gold, and their use was found beneficial in certain applications.[24,30]

In parallel, these new reactivity patterns were implemented into a first series of total syntheses of natural products of moderate but steadily increasing complexity (Scheme 4). A notable case is a stereoselective approach to α-cubebene based upon the $PtCl_2$-catalyzed rearrangement of substrate **3**;[31,27] this and related studies showed that a propargyl ester entity constitutes a convenient and safe synthetic equivalent

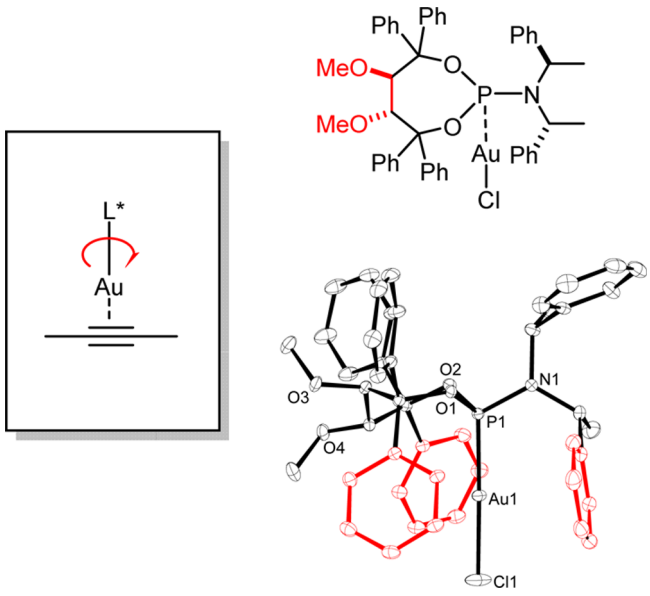
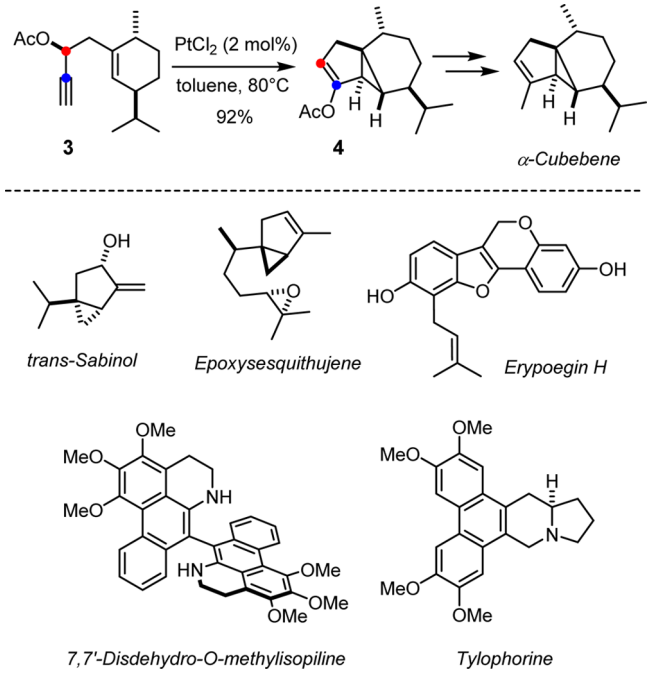


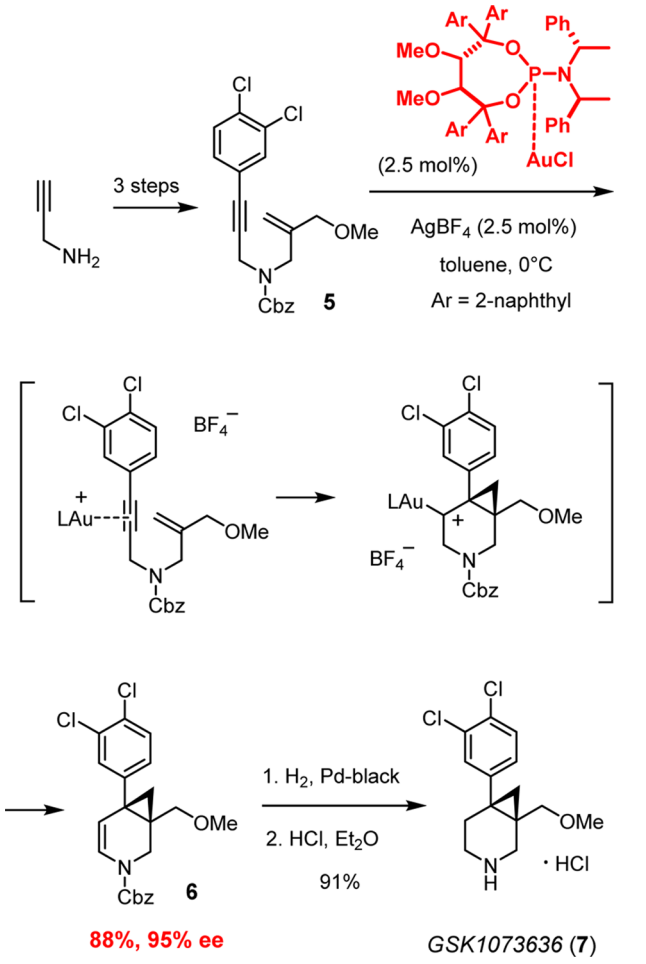
FIGURE 1. Asymmetric gold catalysis: Structure of a prototype gold–phosphoramidite complex developed by our group.

SCHEME 4. Early Applications of π-Acid Catalysis to Natural Product Synthesis Pursued by Our Group[29−33]



to an α-diazoketone.[25,26] Equally useful are intramolecular hydroarylation reactions of arenes and heteroarenes,[24] which enabled the total synthesis of tylophorine and related alkaloids.[33,30] This transformation gained popularity in material science and was lately improved using platinum complexes endowed with polycationic phosphine ligands.[28]

SCHEME 5. Enantioselective Synthesis of an Antidepressive Drug Candidate



Asymmetric Gold Catalysis for Target Oriented Synthesis

It is inherently difficult to impose an enantioselective course upon an outer-sphere process triggered by a linear dicoordinate cation such as Au(+1). This particular bonding situation means that the metal can accommodate only a *nonchelating one-point-binding ligand* held at maximum distance from the substrate (Figure 1). Several creative solutions for this challenging problem have been proposed.[34] Our contribution consists in the design of a new type of phosphoramidite ligands comprising TADDOL-related diols with an *acyclic* dimethyl ether backbone (Figure 1).[35,36] Crystallographic data show that they are able to craft an effective C_3-symmetric chiral pocket about the metal that is largely invariant to rotation. Although DFT-calculations suggest that the binding site becomes C_1-symmetric upon coordination of the substrate, these readily available and reasonably small ligands allow remarkable levels of asymmetric induction to be attained in a variety of gold-catalyzed transformations.[36]

The synthesis of the antidepressive drug candidate GSK1073636 (**7**) in optically pure form was the first test for these new phosphoramidite ligands (Scheme 5).[37,38] Enyne **5** was subjected to cycloisomerization with formation of the cyclopropane derivative **6**, which occurred with excellent induction (95% ee). Subsequent saturation of the double bond over palladium black with concomitant hydrogenolysis of the N-Cbz group completed the synthesis of the drug candidate, which was isolated in the form of the crystalline hydrochloride salt in no more than five steps, starting from propargylamine, with an overall yield of 69%.

The gold-catalyzed key step (**5** → **6**) constitutes the asymmetric version of the racemic platinum-catalyzed cycloisomerization chemistry previously developed by our group.[8] As such, it shows that platinum and gold (and other carbophilic π-acids) may differ in their efficiency but qualitatively often engender the very same outcome; this notion is perfectly in line with the basic mechanistic rationale outlined above.

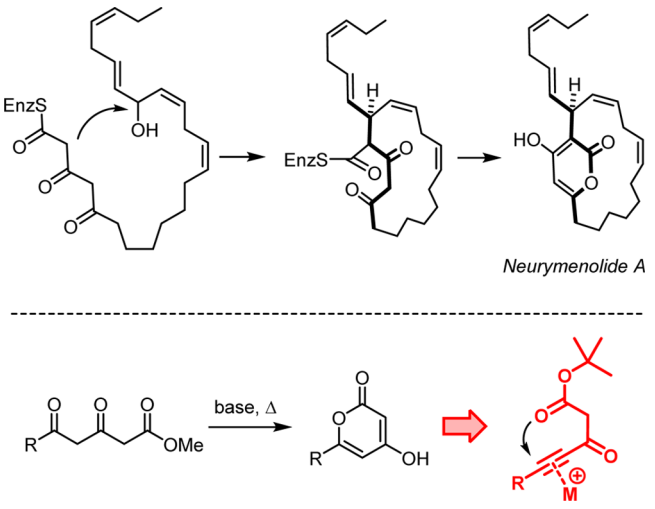
Neurymenolide A: Preparative Aspects and Mechanistic Implications

While asymmetric gold catalysis for target oriented synthesis is still in its childhood,[39] we strive to implement the use of carbophilic catalysts in general into the total synthesis of increasingly complex natural products of biological significance. In so doing, we deliberately *focus on the late stages* of multistep projects to scrutinize the performance of π-acidic catalysts to the highest possible extent and, at the same time, showcase our growing confidence in the robustness of the reactions they induce.

The total synthesis of neurymenolide A is representative.[40] Biosynthetically thought to derive from eicosatetraenoic acid via chain extension by two acetate units followed by two cyclization events (Scheme 6, top), this unusual cyclophane derivative shows an element of planar chirality in addition to a residual chiral center; however, the resulting atropisomers equilibrate over the course of hours.

Because neurymenolide had been reported to be exceptionally sensitive to isomerization of the skipped alkenes embedded into its frame, it seemed unreasonable to rely on a kind of "biomimetic" formation of the pyrone ring from a 1,3,5-tricarbonyl precursor, because such reactions usually requires base and gentle heating.[41] Rather, we conjectured that it might be advantageous to "mask" one of the carbonyl groups as an alkyne and to close the heterocyclic ring by a π-acid catalyzed intramolecular attack of the adjacent ester carbonyl (Scheme 6, bottom). Since many gold- or

SCHEME 6. Structure and Proposed Biosynthesis of Neurymenolide A: "Biomimetic" versus "Carbophilic" Approach to 4-Hydroxy-2-pyrones



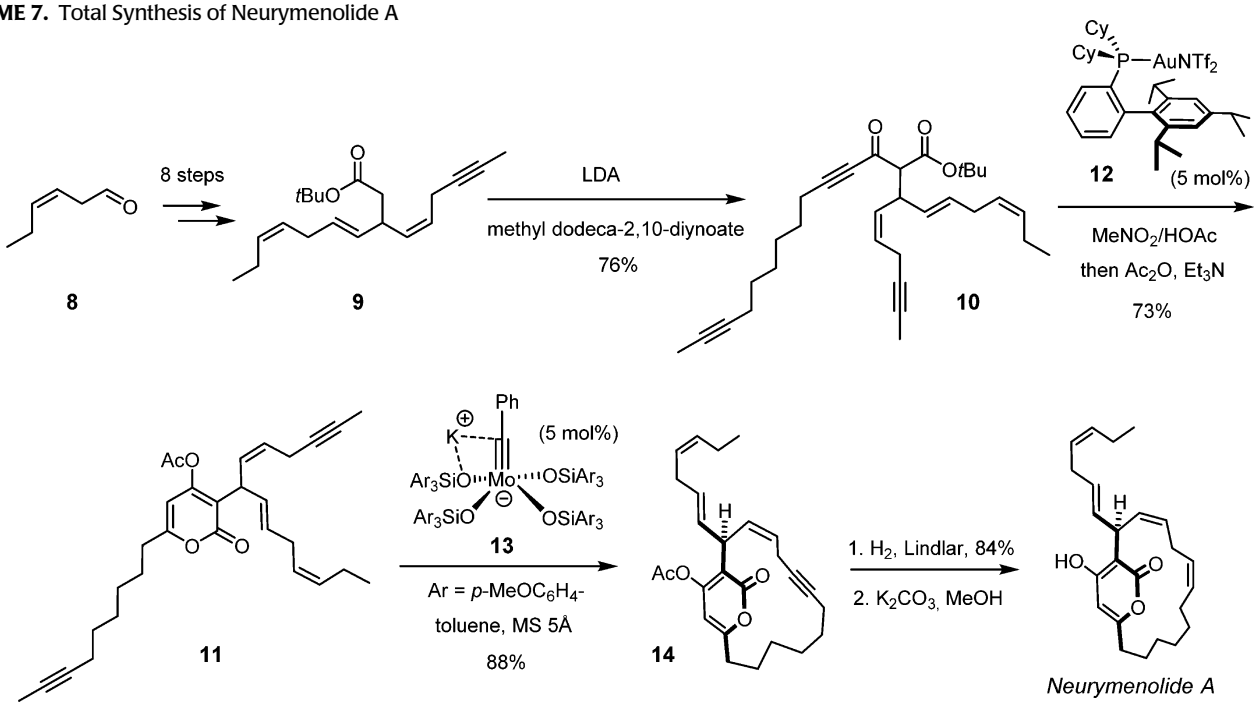
platinum-catalyzed reactions proceed under notably mild conditions, this tactic seemed more promising.

To this end, compound **9** was prepared in eight steps from the commercial aldehyde **8**, using an Ireland–Claisen reaction to set the skipped triene motif (Scheme 7). A subsequent Claisen condensation furnished the required cyclization precursor **10** that contains no less than six nonconjugated sites of unsaturation, not counting the highly enolized β-ketoester moiety. Although a carbophilic catalyst will, a priori, hardly discriminate between these sites, addition of catalytic amounts of the gold complex **12** to a solution of **10** in $MeNO_2$/HOAc resulted in fast and efficient α-pyrone formation, which was isolated as the chemically more robust acetate **11**.[40]

This outcome likely reflects a high level of kinetic selectivity. Although the reacting alkyne unit in **10** is actually the least electron-rich π-system and hence expected to have the lowest affinity to the electrophilic gold species, it outperforms all competitor binding sites; once the metal catalyst ligates this alkyne, the forward reaction with the suitably located nucleophilic partner is obviously very favorable. This interpretation implies that the gold–alkyne π-complex formation is fast and reversible.[42,43]

Another noteworthy aspect concerns the role of acetic acid used as cosolvent. Although model studies had shown that the pyrone formation also proceeds in aprotic media, the use of $MeNO_2$/HOAc (4:1) resulted in a considerable rate acceleration.[40] This aspect was critical for the successful formation of **11**, because prolonged reaction times led to significant or even complete loss of material. Control experiments demonstrated that it is the gold fragment rather than

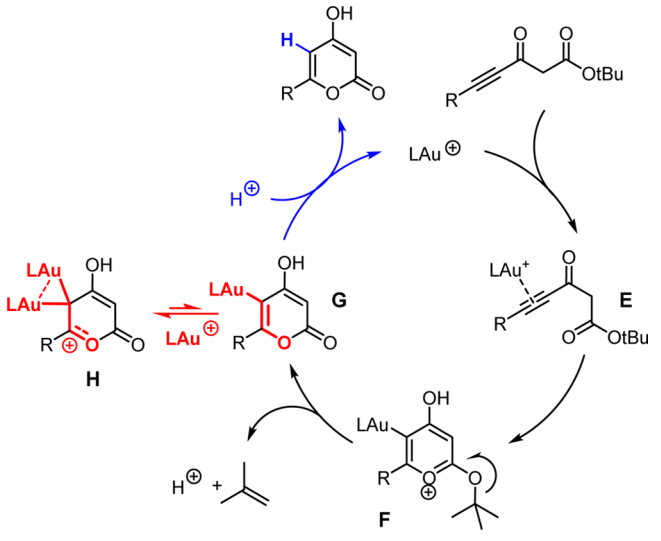
SCHEME 7. Total Synthesis of Neurymenolide A



the proton that accounts for the actual cyclization event. The significant effect of the added HOAc is therefore thought to emanate from the proto-deauration step terminating the catalytic cycle (Scheme 8). Earlier work from our laboratory had shown that alkenylgold complexes bearing an alkoxy substituent at the β-position are prone to bind a second [LAu$^+$] entity with formation of surprisingly stable *gem*-diaurated species.[44] Since the proposed intermediate **G** comprises such a substructure, proto-deauration and *gem*-diauration with formation of **H** are likely to compete, with the latter process benefitting from the high affinity of the soft metal cation to the equally "soft" enol ether substructure of **G**. Increasing the proton concentration is thought to counterbalance this off-cycle event and hence favors productive turnover.

Pyrone **11** thus formed was advanced to neurymenolide A via ring closing alkyne metathesis (RCAM) for the formation of the macrocyclic frame (Scheme 7).[45] This reaction took advantage of the excellent reactivity and chemoselectivity of the latest generation of molybdenum alkylidyne complexes endowed with triarylsilanolate ligands.[46,47] The key enabling feature is their ability to discriminate between the olefins that remain intact, independent of their configuration and positioning, and the acetylenic π-bonds that are activated with remarkable ease. A Lindlar reduction of product **14** thus formed completed the first total synthesis of neurymenolide A.[40]

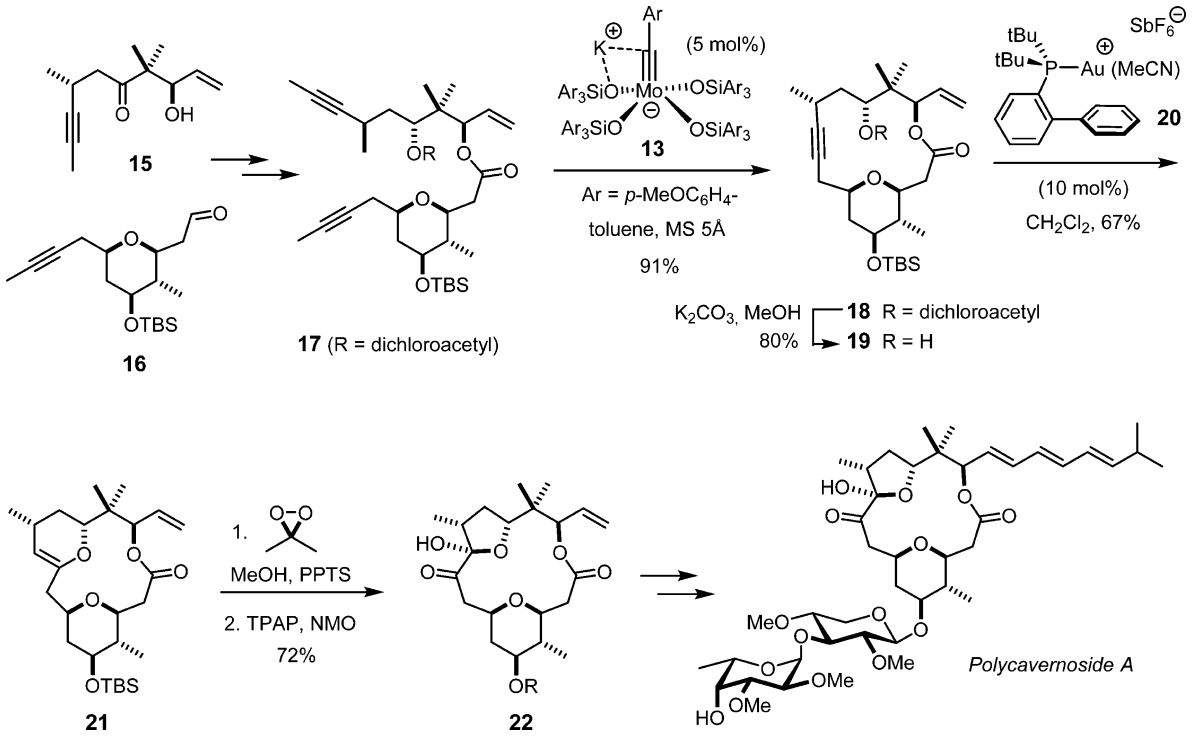
SCHEME 8. Proposed Mechanism and Possible Interference of *gem*-Diauration as an Off-Cycle Event



Polycavernoside A

The interplay between alkyne metathesis and alkyne functionalization with the aid of a π-acidic catalyst also formed the conceptual basis of a recent synthesis of polycavernoside A, the causative agent of a series of lethal foodborne intoxications incurred in Southeast Asia.[48] We conjectured that the signature 1,2-diketone substructure of this target, partly masked in the form of a transannular hemiketal, lends itself to an RCAM/gold-catalysis maneuver.

SCHEME 9. Formal Total Synthesis of Polycavernoside A



As shown in Scheme 9, an Evans–Tishchenko reaction of the two building blocks **15** and **16** set the required 1,3-*anti* diol motif while forging the ester bond. Traditionally, this redox-esterification process mandates the use of a large excess of the aldehyde partner.[49] Because this is not practical for a valuable component such as **16**, the conditions were optimized to reduce the excess of the aldehyde to workable 1.3 equiv. Because the resulting product was prone to intramolecular transesterification, which corrupts the site of attachment, the secondary hydroxyl group was temporarily protected as a dichloroacetate **17** before RCAM was used to close the macrocyclic ring. Once again, this reaction proceeded with remarkable ease when catalyzed by a silyloxy-bearing molybdenum alkylidyne complex.

Cleavage of the dichloroacetate set the stage for a transannular addition of the released hydroxyl group in **19** across the alkyne. Following a literature precedent,[50] we first opted for $[PtCl_2(C_2H_4)]_2$, which effected the desired transformation but also caused a concomitant Overman-type rearrangement of the allylic ester subunit.[51] Gratifyingly though, the bulky gold complex **20** allowed this undesired side reaction to be suppressed and enol ether **21** to be isolated in high yield. This compound can be oxidatively rearranged to hemiketal **22**, which intercepts a previous total synthesis of polycavernoside A.[50]

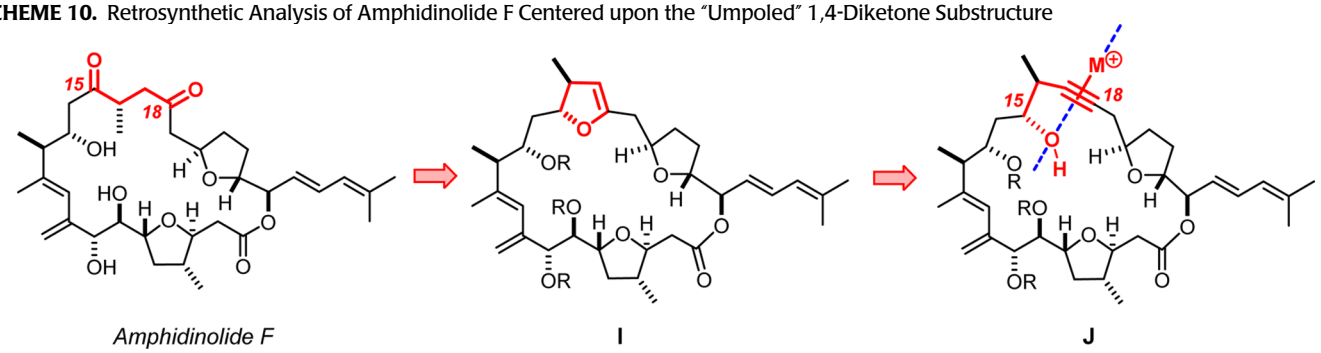
Amphidinolide F

Conceptually related yet even more ambitious were the key steps pursued en route to amphidinolide F, one of the most complex members of this family of structurally unusual marine natural products.[52] This peculiar polyketide derivative is distinguished by an odd-numbered macrolide frame comprising a rare "umpoled" 1,4-diketone unit, which raises questions as to its biosynthesis.

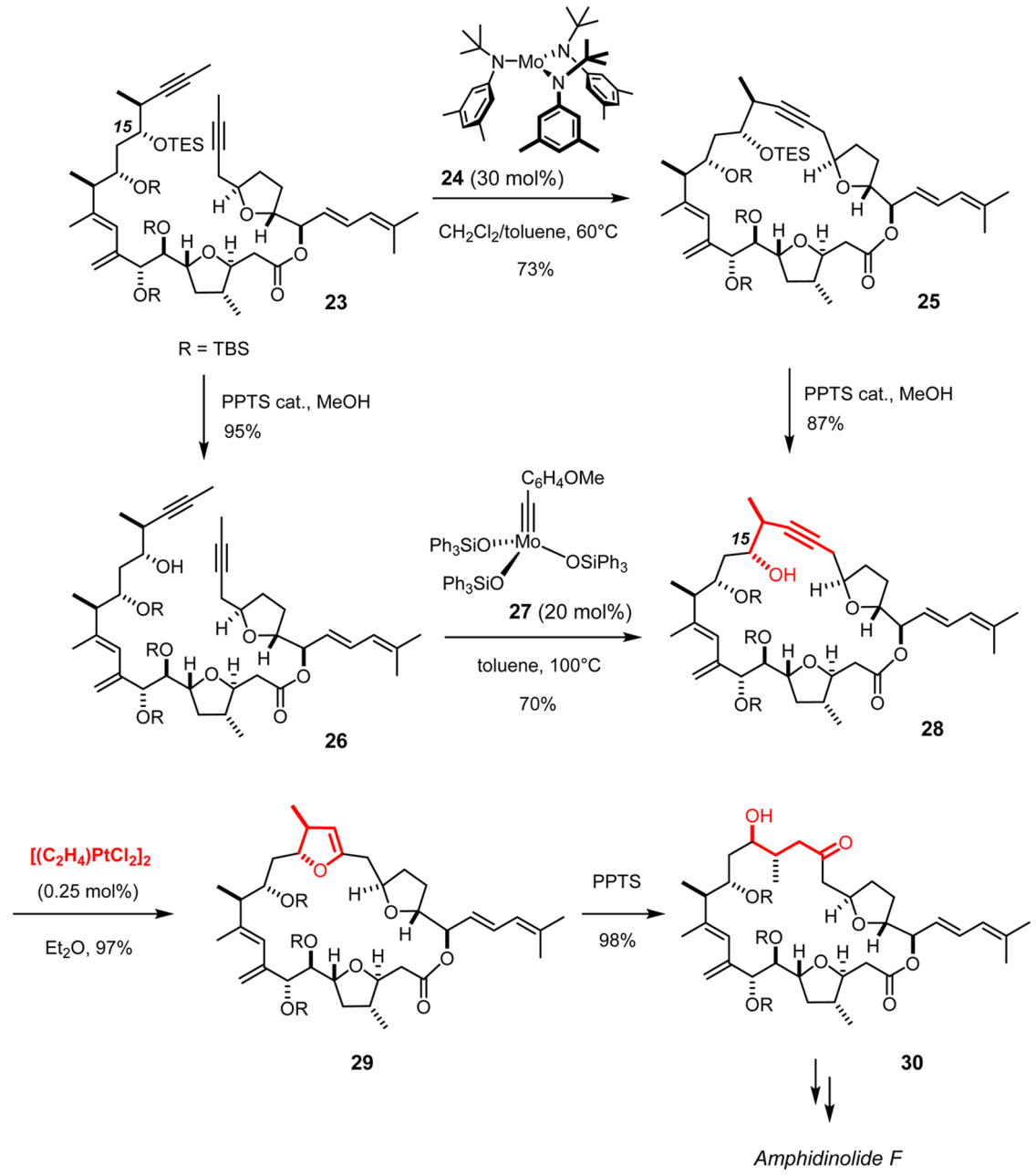
It was this very substructure that caught our attention and became the cornerstone of our synthesis blueprint (Scheme 10).[53] Specifically, it was envisaged that a directed transannular alkyne hydration might open access to this motif. Provided that the conformational peculiarities of the highly decorated macrocyclic ring allow the unprotected hydroxyl group in **J** to align in such a way that it reaches the alkyne *trans* to an activating π-acid entity, a highly regioselective 5-*endo* cyclization must ensue, because a 4-*exo* pathway would give rise to a much more strained intermediate. Hydrolysis of the resulting dihydrofuran **I** and adjustment of the oxidation state would unmask the signature 1,4-oxygenation pattern.

Gratifyingly, this plan worked out exceedingly well (Scheme 11). After optimization of the routes leading to the polyfunctionalized diyne **23**, cyclization by RCAM required the use of complex **24** as the catalyst, activated in situ

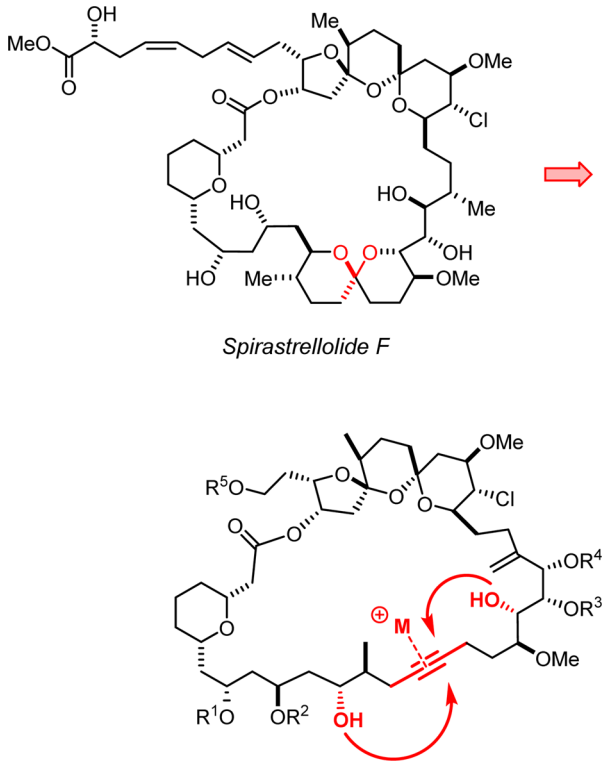
SCHEME 10. Retrosynthetic Analysis of Amphidinolide F Centered upon the "Umpoled" 1,4-Diketone Substructure



SCHEME 11. Total Synthesis of Amphidinolide F



SCHEME 12. Retrosynthetic Analysis of Spirastrellolide F



with CH_2Cl_2 as previously described by our group,[54] whereas alkylidyne **27** endowed with bulkier triarylsilanolate ligands gave appreciable amounts of an acyclic dimer as a by-product. Importantly, however, the more functional group-tolerant complex **27** excelled when the TES-ether group at C.15 flanking the reacting alkyne unit was removed prior to ring closure (**23** → **26** → **28**).

Cycloalkyne **28** underwent a surprisingly rapid and essentially quantitative transannular hydration to give enol ether **29** on treatment with as little as 0.25 mol % of $[PtCl_2(C_2H_4)]_2$ in Et_2O as the preferred solvent. Exploratory studies had shown this convenient platinum catalyst to be superior to a host of other carbophilic Lewis acids based on gold, palladium, or mercury. As expected, none of the regioisomeric ketone derived from a competing 4-*exo-dig* pathway was detected in the crude material after a brief hydrolytic work-up. Oxidation of the resulting product **30** followed by global deprotection furnished amphidinolide F in respectable overall yield over the 21 steps of the longest linear sequence.[53] Equally important is the message conveyed by this exigent project that alkyne metathesis and π-acid catalysis are both reaching a level of maturity where they meet the rigorous criteria of contemporary total synthesis and can be safely applied to intricate compounds in advanced stages of elaboration.

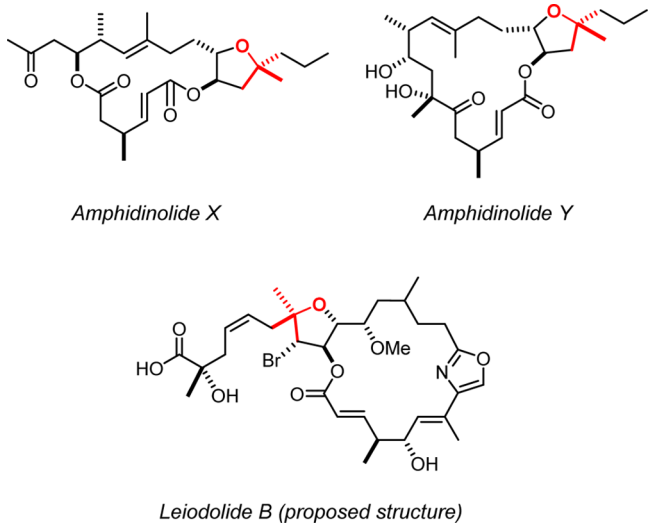


FIGURE 2. Targets prepared via silver-mediated cyclization reactions.

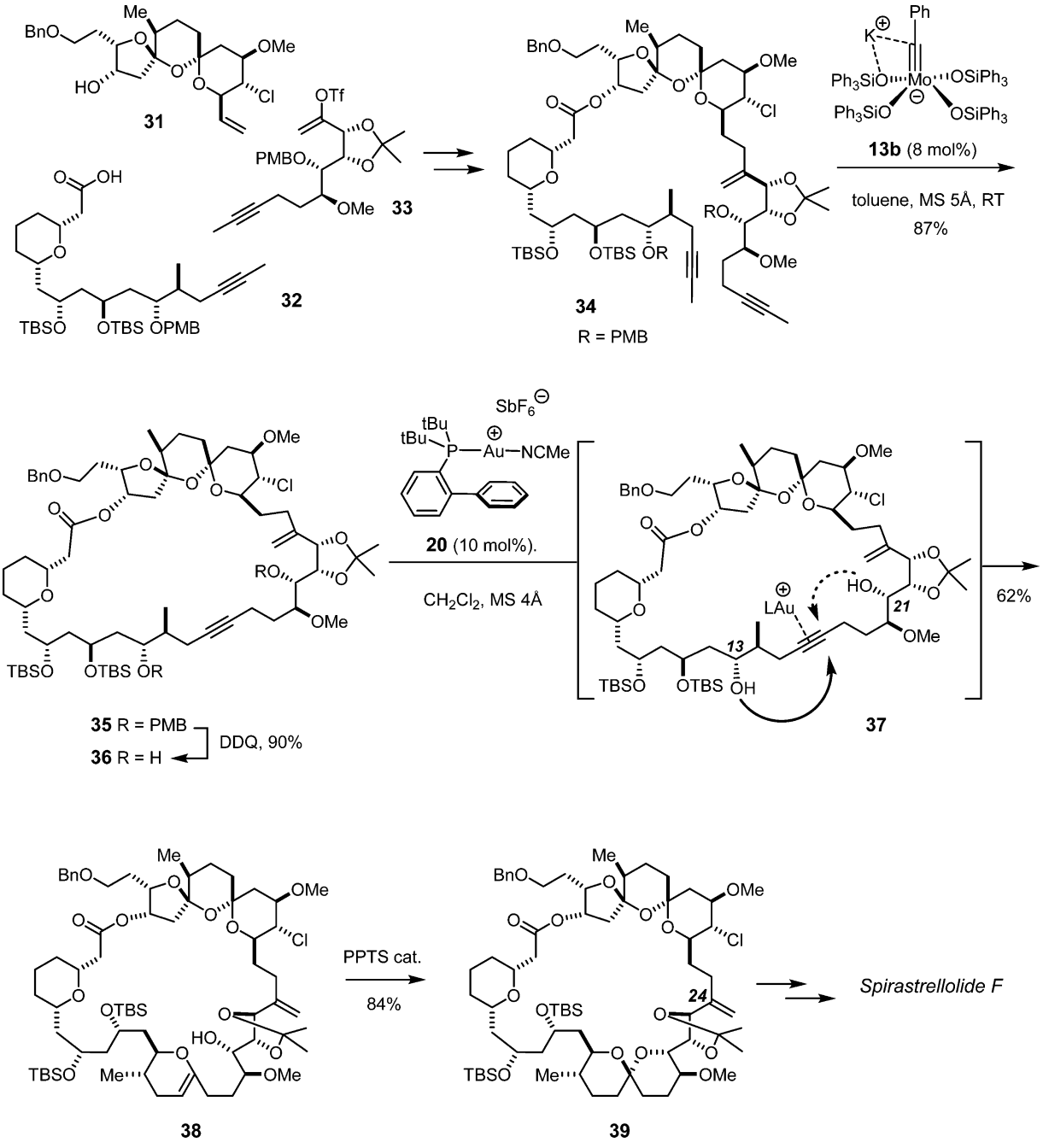
Spirastrellolide F

Yet another way of using an alkyne as a carbonyl surrogate is manifest in a total synthesis of the potent phosphatase inhibitor spirastellolide F, whose backbone is decorated with no less than 21 chiral centers and a fragile skipped 1,4-diene motif.[55] It is the B,C-spiroketal forming the "southern" sector of this enticing macrolide that was selected as the strategic site of disconnection (Scheme 12).

The synthesis commenced with the convergent assembly of the cyclization precursor **34** from building blocks **31**–**33** by an alkyl-Suzuki coupling and subsequent esterification (Scheme 13). Diyne **34** underwent a high yielding ring closure when exposed to complex **13**, which further illustrates the excellent performance of this latest generation of molybdenum-based alkyne metathesis catalysts.[46,47]

Cycloalkyne **35** thus obtained was elaborated into the core structure **39** by cleavage of the PMB-ethers at C.13 and C.21 followed by a transannular spiroacetalization. This transformation was accomplished in a stepwise fashion, starting with a 6-*endo-dig* hydroalkoxylation induced by the bulky gold complex **20** as the catalyst of choice. More simple gold sources furnished the incorrect regioisomer via an undesirable 5-*exo-dig* addition process; gratifyingly though, complex **20** allowed this inherent bias to be overridden (*exo*/*endo* ≈ 1:5) and the desired product **38** to be isolated in 62% yield. Simultaneous attack of the more crowded hydroxyl group at C.21 could not be enforced under these conditions. Importantly, however, the required spiroketal was formed as a single isomer in 81% yield on treatment of enol ether **38** with catalytic amounts of pyridinium *p*-toluenesulfonate in toluene at 80 °C. With this

SCHEME 13. Key Steps of a Total Synthesis of Spirastrellolide F

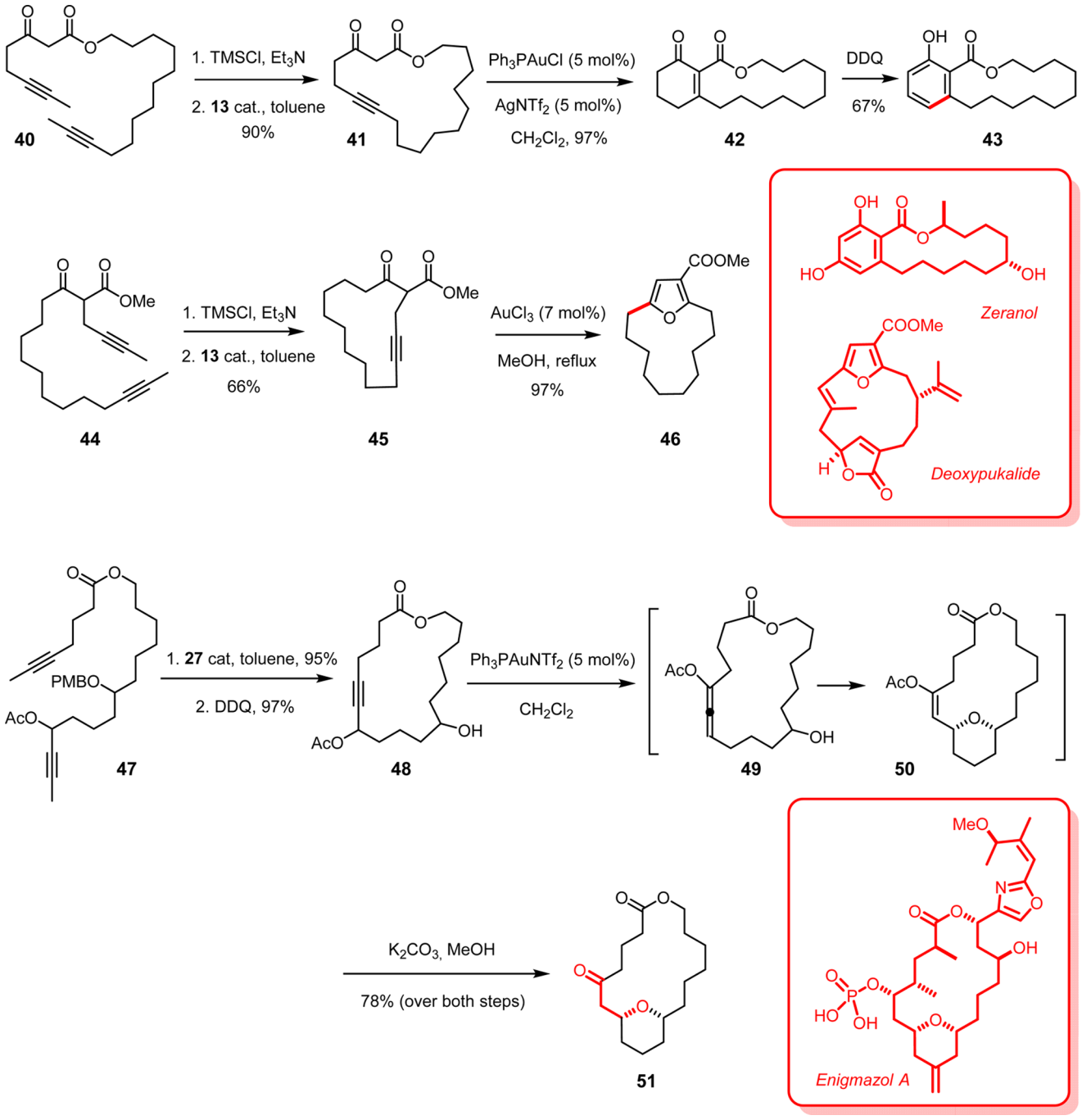


crucial building block in hand, the total synthesis of spirastrellolide F was completed by a fully diastereoselective, substrate controlled hydrogenation of the *exo*-methylene group at C.24 followed by attachment of the target's lateral chain via a Julia–Kocienski olefination as the key steps.[55−57]

Prospects

Implementations of π-acid catalysis are not discussed in this Account in any great detail if they have not left the stadium of model studies. Yet the possibilities seem countless and the examples in Scheme 14 showcase just a few promising outlooks.[58] Specifically, a gold-catalyzed transannular Conia-ene type reaction constricts substrate **41** with ease, thus forging the bicyclic edifice characteristic for many resorcylide macrolide antibiotics. Likewise, a gold-catalyzed reaction of the isomeric macrocyclic β-ketoester **45** furnishes the bare skeleton of several furanocembranoids.

SCHEME 14. Model Studies



Another feasibility study showed that access to the cytotoxic macrolide enigmazole A might be gained by RCAM. The model diyne **47** was subjected to ring closure, followed by cleavage of the PMB-ether and elaboration of the resulting propargylic ester derivative **48**. Specifically, a gold-catalyzed Meyer–Schuster rearrangement[59] generates the corresponding allenyl acetate **49**, which is subsequently activated by the very same catalyst toward addition of the transannular hydroxyl group. The ultimate product of this cascade, after hydrolytic work up of the mixture, is compound **51**, which maps onto the framework of enigmazole A.[58]

Another cursory remark concerns the use of silver as a carbophilic Lewis acid, which has a fairly long tradition.[60] It served our group exceedingly well in the total syntheses of amphidinolide X and Y,[61] as well as in an approach toward the proposed structure of leiodolide B[62] (Figure 2).

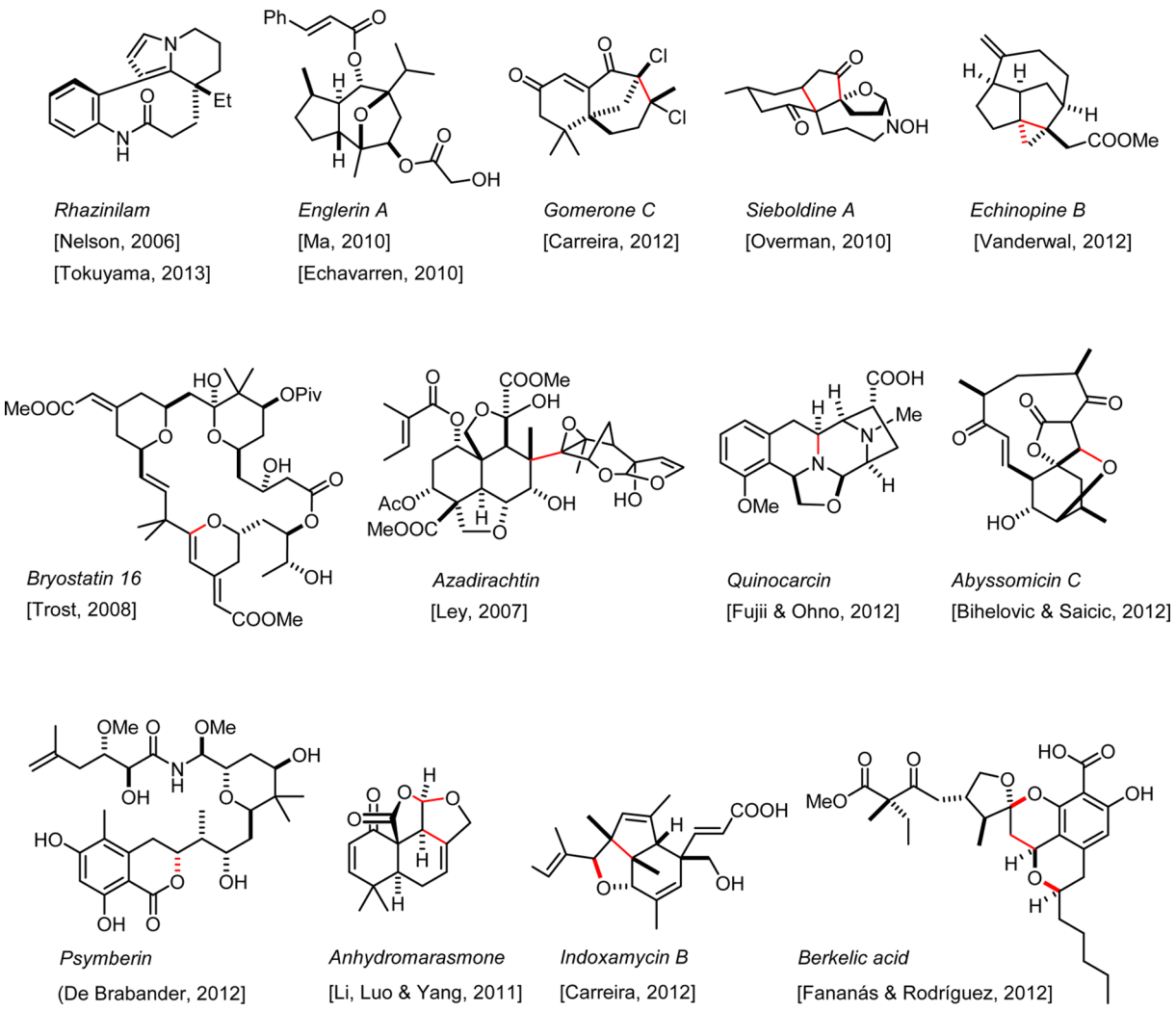


FIGURE 3. Selection of recent total syntheses of structurally complex natural products from other groups comprising late-stage π-acid (Pt, Au, or Ag) catalyzed key steps.[63−75]

Although these particular applications were stoichiometric in nature, an increasing number of examples from the recent literature indicate that the outlook for using silver as π-acidic catalyst in the context of natural product synthesis is bright (an instructive case is contained in Figure 3).[60]

Context

This Account is basically confined to total syntheses of architecturally challenging targets completed by our group that invoke the strategic use of carbophilic catalysts. It is gratifying to see, however, that other groups also increasingly commit themselves to such endeavors.

This fact is illustrated by the examples compiled in Figure 3, which are nothing but a personal selection of recent highlights. They manifest noteworthy triumphs, stand out of the avalanche of publications, and convey the increasing maturity of π-acid catalysis in general. It is my conviction that more such testimony is needed to foster the growth of this fascinating field of research.

I sincerely thank my co-workers and collaborators involved in our π-acid catalysis project, whose names appear in the references. Generous financial support by the MPG and the Fonds der Chemischen Industrie is gratefully acknowledged. We thank Umicore AG & Co KG, Hanau, for a gift of noble metal salts.

BIOGRAPHICAL INFORMATION

Alois Fürstner obtained his doctoral degree in 1987 at the Technical University of Graz, Austria. After a postdoctoral stint with the late Prof. Oppolzer and a Habilitation in Graz, he joined the Max-Planck-Institut für Kohlenforschung (1993), Germany, where he was promoted to the rank of Director in 1998. His research program is focused on organometallic catalysis and applications thereof to the synthesis of structurally challenging targets of biological significance.

FOOTNOTES

The author declares no competing financial interest.

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