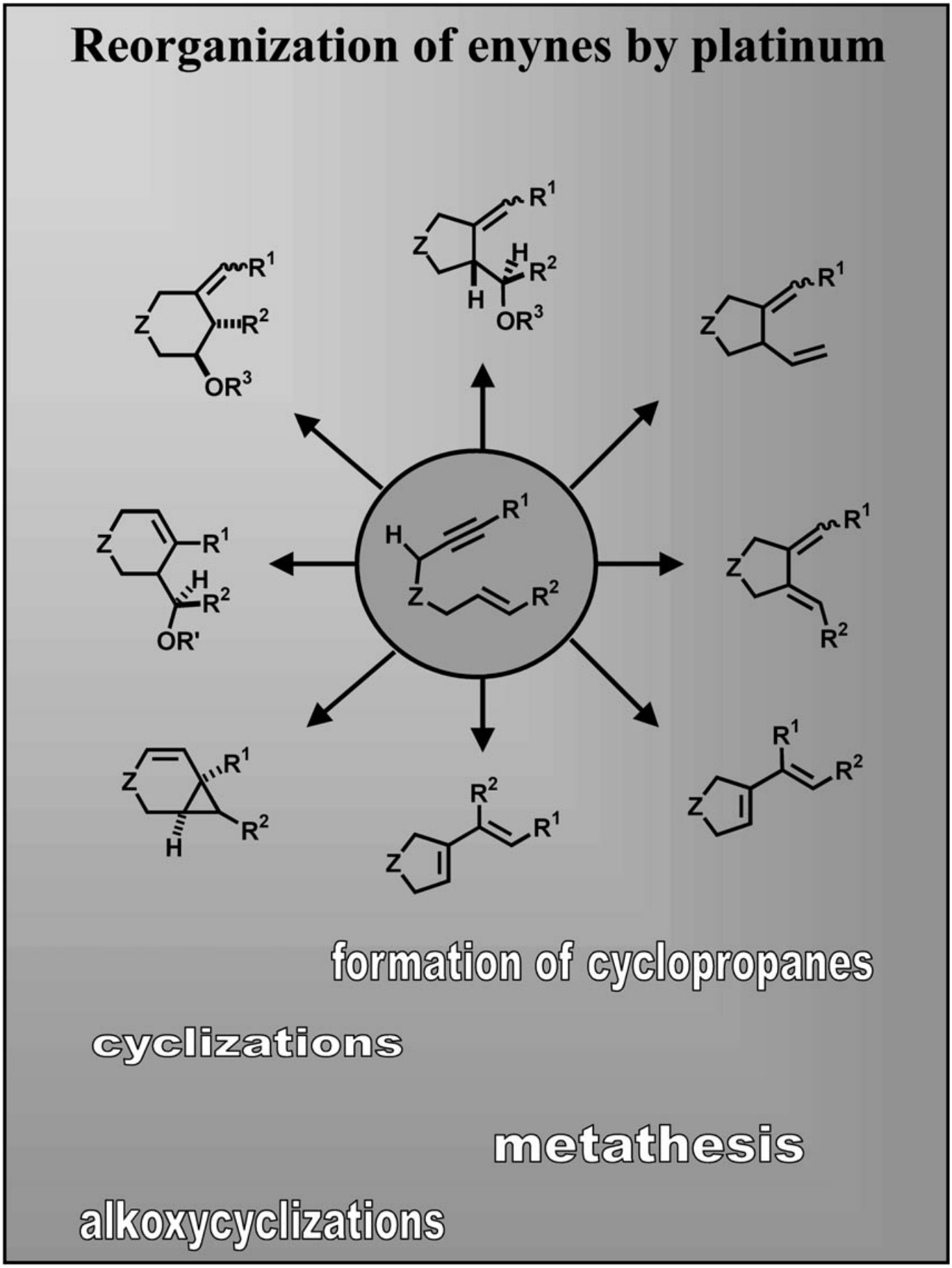
Reorganization of enynes by platinum



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Reorganization of Enynes Catalyzed by Platinum Salts

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Dedicated to Professor Jose Luis Soto Cámara on the occasion of his retirement

Abstract: Activation of alkynes with platinum salts allows their reaction with alkenes, giving rise to a myriad of interesting processes like cyclizations, formation of cyclopropanes, or metathesis. Weak nucleophiles can also participate in the processes leading to alkoxycyclizations. There are intriguing mechanistic aspects of these processes in which subtle variations of the reaction conditions and/or substrate structures can lead to completely different products.

Keywords: alkynes · cyclization · enynes · platinum · synthetic methods

Introduction

There is a growing interest in developing new strategies for the synthesis of highly functionalized polycyclic compounds in a stereocontroled manner. Transition-metal-catalyzed processes with unsaturated substrates, such as enynes, dienes, diynes, allenealkenes, or alkynyl- alkenyl-, and allenylarenes, are able to increase molecular complexity with high control. Some of these processes often involve the activation of alkynes that subsequently react with an olefin or an arene. Some complex transition-metal-based catalysts are able to mediate in these processes, but also simple salts of these metals are efficient. We would like to focus our attention in this paper on the reorganization of enynes by means of the activation of triple bonds with platinum halides and on interesting mechanistic aspects derived from this chemistry.

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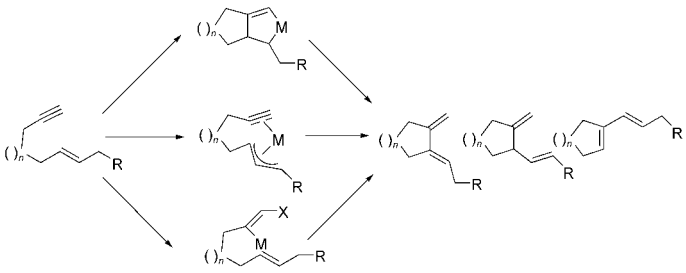
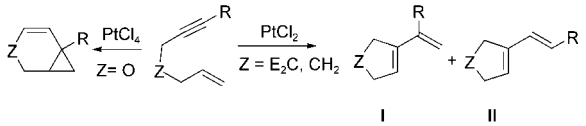
Cyclization of Enynes

There are a wide range of cyclization reactions of enynes catalyzed or mediated by transition-metal complexes.[1] Mostly the metal forms a complex either with the alkene, the alkyne, or both to follow a reaction pathway in which a metallacycle, a π-allyl complex, or a vinyl–metal complex is formed (Scheme 1).



Scheme 1.

The use of simple transition-metal halides is attractive as they are commercially available, stable, and easy to handle. In the context of platinum salts, the pioneering studies were by Blum[2] and Murai,[3] who used $PtCl_4$ and $PtCl_2$ respectively to cyclize 1,6-enynes and some 1,7-enynes. Murai observed that skeletal reorganization of enynes gave two types of products (Scheme 2). The first, **I**, is the expected product



Scheme 2.

of a metathesis reaction; the second, **II**, which is the major product with unsubstituted substrates, or when electon-withdrawing groups are present, involved an anomalous carbon–carbon bond formation. On the other hand, Blum was able to isolate bicyclic compounds, such as those depicted in Scheme 2, mostly with moderate yields, from parent allyl

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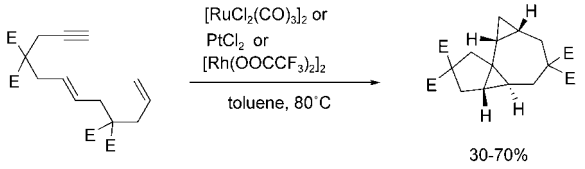
propargyl ethers. These early results pointed out to a possible common initial pathway for both processes, in which a heteroatom present in the tether could be responsible for the difference in the final product.

Murai used, soon afterwards, ene-ene-ynes to effect a cycloisomerization that gave complex polycycles, suggesting the intervention of a carbenoid intermediate in the process. In these cases he obtained better results with rhodium salts and ruthenium carbonyls (Scheme 3).[4]

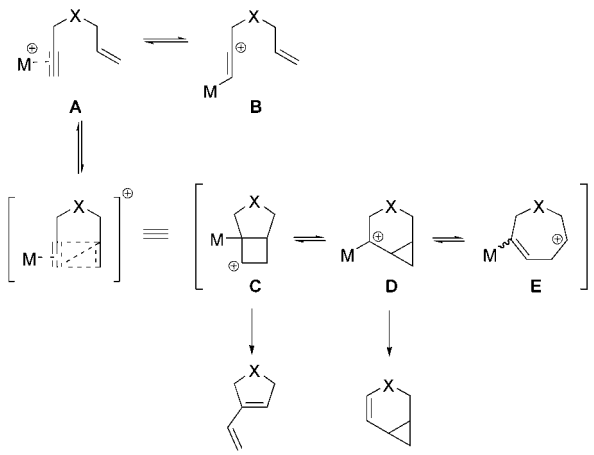


Scheme 3.

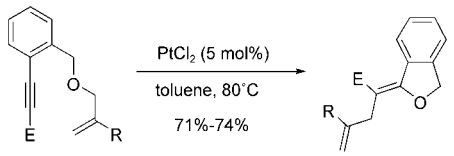
In 1998, and after his mechanistic studies and syntheses of some prodiginine antibiotics, Fürstner suggested a new reaction pathway involving the formation of a nonclassical carbocation as the reactive intermediate; this explained the formation of the different reaction products and even of some minor byproducts detected when scaling up the reaction to several grams of starting material (vide infra).[5] Following this approach he used several 1,6-enynes to observe the influence of the substitution pattern in the result of the reaction. The results can be explained by a cationic manifold. The attack of the platinum would render a cation that can be delocalized and represented by several structures. While the cyclobutyl structure **C** evolves to give typical metathesis compounds, carbenoid structure **D** would suffer a hydrogen shift to give a bicyclo[4.1.0]derivative. This latter product is favored when a heteroatom is present in the enyne, thus constituting an enamide or vinylether (Scheme 4).[6]

Due to the cationic nature of the intermediate, the presence of other nucleophiles in the substrate structure or in the media can give rise to new products. Thus, with appropriate ether derivatives, a cascade process takes places giving a new allyl shift (Scheme 5).

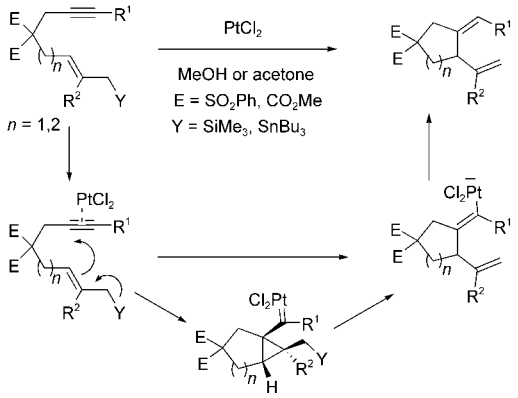
Echavarren used milder nucleophilic agents, such as allylstannanes and allylsilanes, to attack the carbocationic intermediate.[7] In this case no metathesis type products are formed and the carbocyclic products reach high yields (Scheme 6). The reaction is proposed to consist of coordination of the metal to the alkyne, followed by the *anti* attack of the allyl moiety, and proceeds generally with *anti* stereo-



Scheme 4.



Scheme 5.

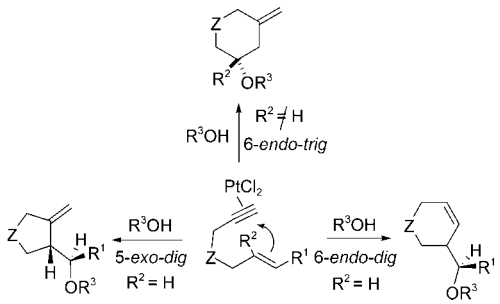


Scheme 6.

selectivity. Among the salts used, $PtCl_2$ in methanol or acetone usually gives best results.

Other nucleophiles used by this group soon afterwards were alcohols and water, which are able to trap the transient carbocation resulting from the attack of the alkene to the complexed alkyne. In this case the alkene is able to react with the complexed alkyne fragment, without the detection of any addition products derived from the reaction of the alkene with the alcohol. Although the process can be carried out with other metal salts like those of ruthenium, silver, or gold, best results are obtained with $PtCl_2$. In a couple of cases the authors detected an *endo* cyclization product. The alkoxycyclization process competes favorably with cycloisomerization unless the triple bond is disubstituted, in which case a mixture of products is obtained. Formation of cyclopropanes is only observed when an heteroatom is placed at the tether (Scheme 7).[8]

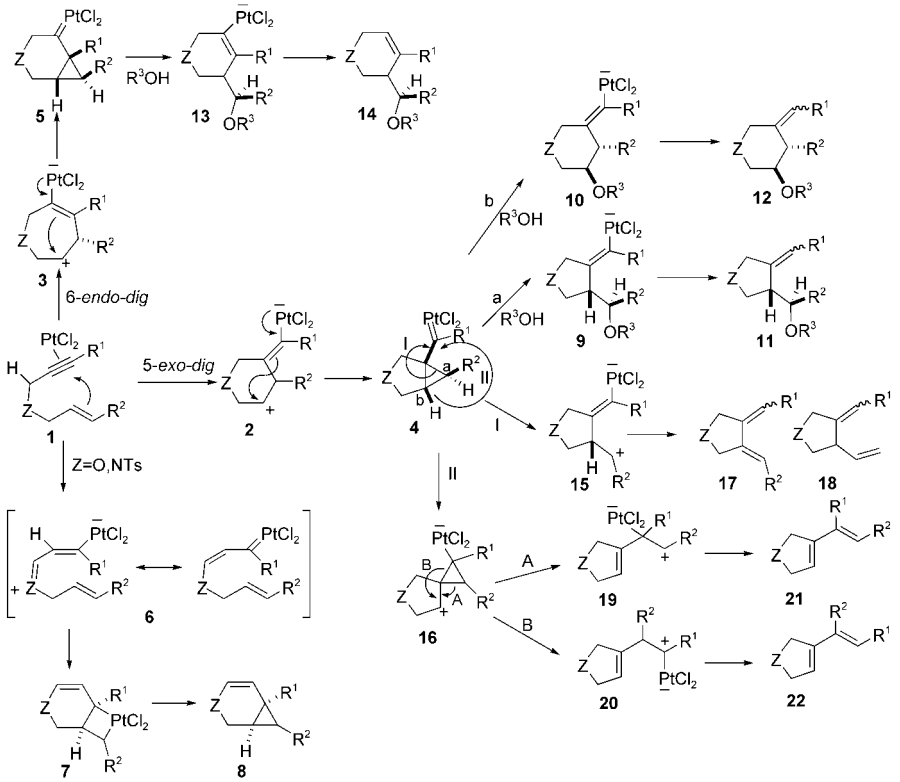
Abstract in Spanish: *Las sales de platino activan los triples enlaces dando lugar a varias transformaciones interesantes como ciclaciones, formación de ciclopropanos o metátesis. Ciertos nucleófilos débiles pueden participar en las reacciones conduciendo a alcoxiciclaciones. Hay aspectos mecanísticos fascinantes en estas reacciones, en las que pequeños cambios en las condiciones de reacción y/o en la estructura del sustrato, conducen a productos completamente diferentes.*



Scheme 7.

This group has recently addressed the cyclization reactions of enol ethers with alkynes in methanol using Pt^{II}, Pt^{IV}, and Au^{III} chlorides.[9] In this case some 6-*endo-dig* products are obtained with certain enynes.

Summarizing the reaction course (Scheme 8), after coordination of the metal with the triple bond, the alkene effects an intramolecular attack; this can give, either thorugh an *exo* or an *endo* attack, cyclopropyl carbenes **4** or **5** via intermediates **2** or **3**, respectively. The selection of either pathway depends on the substituents at the alkene and/or the tether, but the *exo* pathway is mostly preferred. The carbenic intermediate **4**, which has been proposed by virtually all groups involved in this chemistry, undergoes attack of the nucleophile to give the observed products. When a heteroatom is present in the tether, 1,2-hydrogen migration may take place forming an alkenyl carbene **6**, stabilized by the heteroatom. This complex would give a [2+2] cycloaddition reaction and, upon reductive elimination from **7**, form the cyclopropanes **8**.



Scheme 8.

Going back to **4**, the nucleophile can attack the carbon atoms a or b, giving rise to intermediates **9** or **10**, which in turn lead to final products **11** or **12**, respectively. The less frequent path via carbene **5** leads, through nucleophilic attack, to **14**.

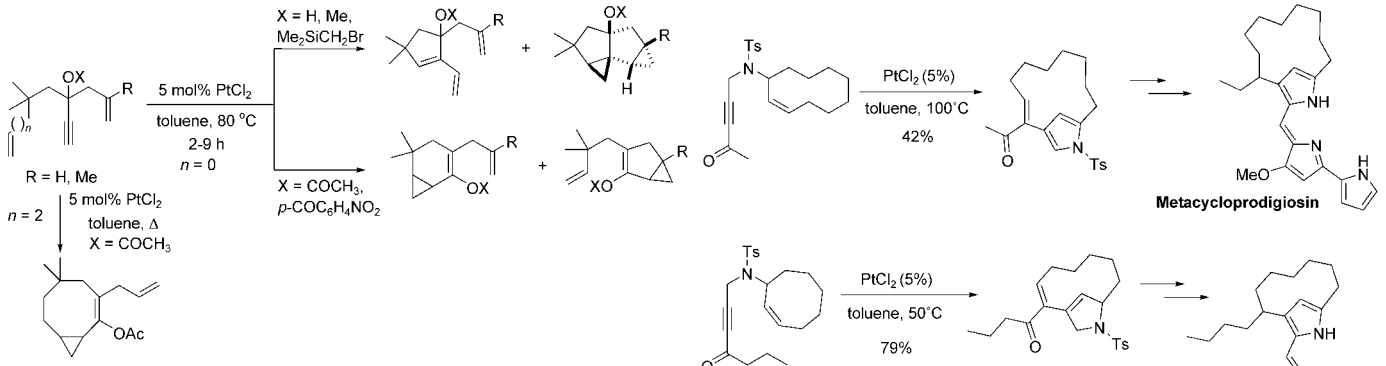
In the absence of a nucleophile in the medium, the cycloisomerization reaction takes place, although monosubstituted alkenes give poor results. In this case, as formulated by Oi,[10] both external bonds of the cyclopropane in **4** may cleave (paths I or II), giving intermediates **15** or **16**. While **15** leads to **17** and/or **18** by means of β-elimination, **16** may suffer two possible cleavages of its new cyclopropane (paths A or B). Cleavage following path A leads to typical metathesis product **21**, whereas path B gives the "anomalous" compound **22**.

Finally, we note that these kind of skeletal reorganizations can be effected by using other metal salts like those of Ru^{II}, Au^{III}, Pd^{II}, or Rh^{I} as commented before. Very recently Murai has used $GaCl_3$ to effect enyne reorganizations and announces mechanistic studies that will show the differences between this process and those catalyzed by late transition-metal salts.[11]

Related Systems

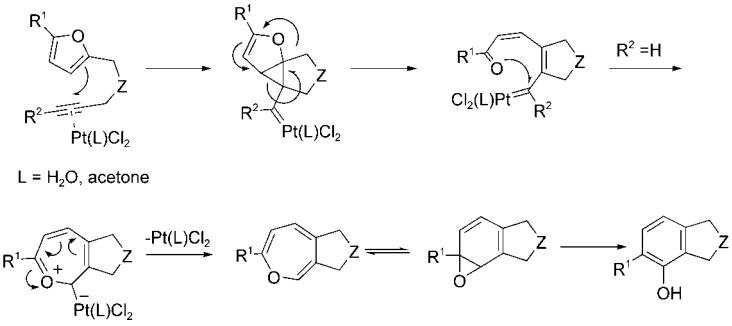
One extension of this chemistry to dienynes was reported recently.[12] The cascade cyclization of these systems is controlled by a hydroxy group situated at the propargylic position, or by its protecting group. Thus, depending on the nature or absence of this protecting group, tetracyclic compounds or cyclic enolesters were obtained. They also describe the synthesis of some cyclooctenes fused with a cyclopropane when elongating the tether in the staring material (Scheme 9).

Additionally furans can act as the alkene part in the reorganization of enynes. Echavarren has used furans with alkynyl or propargyl substituents to effect reorganization processes.[13] Assuming a related reaction pathway, the furan ring attacks the platinum–alkyne complex to form a cyclopropyl platinum carbene. The involvement of this carbene is supported by some reactions carried out in water that give products compatible with this intermediate. From this carbene, the authors propose an



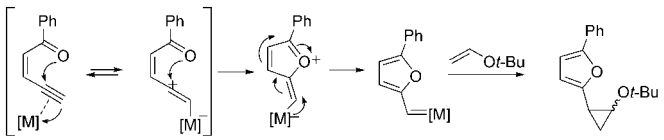
Scheme 9.

evolution to form a carbonyl compound, which reacts with the carbene forming an oxepine and finally an arene oxyde (Scheme 10). The last part of the mechanism is supported by DFT calculations.



Scheme 10.

Uemura reported recently a 5-*exo-dig* cyclization reaction of ene-yne-ketones to give 2-furfurilidene carbenes. This process follows path related to those described above and is catalyzed by several metal carbonyls and by Pd^{II} and Pt^{II} chloride. The carbene intermediate is cyclopropanated intermolecularly to give the final product (Scheme 11).[14]



Scheme 11.

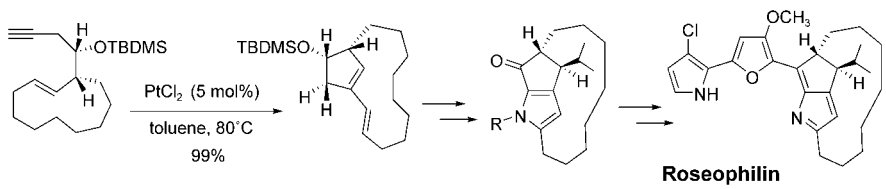
Synthetic applications

Despite how recent this chemistry is, some syntheses of natural products have used enyne reorganizations catalyzed by platinum salts as key steps. Fürstner reported a synthesis of Metacycloprodigiosin and Streptorubin B, in which the *meta*-bridged pyrrole core structures of these products are achieved by an enyne reorganization catalyzed by platinum chloride (Scheme 12). The metathesis was scaled up to several grams which allowed the isolation of several byproducts that support some of the mechanistic considerations made by the authors.[5]

Scheme 12.

Trost achieved an asymmetric synthesis of the tricyclic core of Roseophilin. The key step was a metathesis type reaction catalyzed by platinum chloride (Scheme 13).[15]

In summary, the activation of triple bonds by means of platinum salts leads to several transformations, which, in addition to set fascinating mechanistic issues, lead to interesting products with potential synthetic applications. Different structural reorganizations of enynes can take place. They probably share a carbenic intermediate. In the near future we can expect an increase in the range of these transformations, in the understanding of the mechanisms, and we will see new synthetic applications of this chemistry.



Scheme 13.

Acknowledgments

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