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Zipper-mode cascade carbometallation for construction of polycyclic structures

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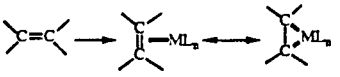
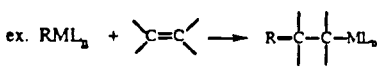
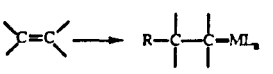
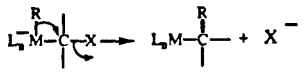
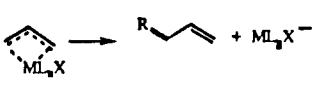
Abstract - A novel concept for the synthesis of polycyclic compounds via "zipper"-mode cyclic carbometallation reactions has been introduced. The Zr-promoted bicyclization-carbonylation of enynes can be highly diastereoselective, leading to the formation of stereoisomerically homogeneous bicyclic ketones. The reaction has been applied to a total synthesis of pentalenic acid with essentially complete control of stereo- and regiochemistry. In contrast to the $ZrCp_2$-promoted methodology, whose applicability is limited to bicyclization, cyclic carbopalladation can repeat itself to produce three or more rings in one step, provided that β-elimination or other decomposition paths are not available. Alkynes and 1,1-disubstituted alkenes can serve as relay functionalities. With 1,1-disubstituted alkenes, however, the regiochemistry of cyclization can be complicated by cyclopropanation. Efforts have been made to delineate the scope of cyclopropanation. Finally, cyclic acylpalladation followed by intramolecular trapping by *O*-enolates can give enol lactones via bicyclization. This bicyclization process has been applied to an expeditious synthesis of a tricyclic intermediate for a promising anti-ulcer agent U-68,215.

INTRODUCTION

Carbometallation[1] involves addition of a carbon-metal bond to an alkene or alkyne. As such, it represents both carbon-metal and carbon-carbon bond forming processes of fundamental importance (Table 1).

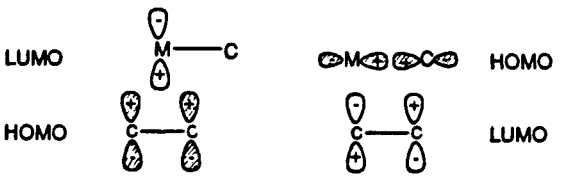
Many metals, main group and transition metals alike, are known to participate in the process. The only essential requirement for facile and stereoselective carbometallation appears to be the ready availability of a low-lying empty metal orbital, even though other factors, steric and electronic, undoubtedly play important roles. With an empty

TABLE 1. Some Fundamental Patterns for Transformations of Organotransition Metals

M-C Bond Formation	C-C Bond Formation
1. Oxidative addition ex. $ML_n + RX \longrightarrow R{-}ML_nX$	1. Reductive Elimination ex. $R^1R^2ML_n \longrightarrow R^1{-}R^2 + ML_n$
2. Complexation Oxidative Coupling ex. $ML_n +$ 	2. Carbometallation ex. $RML_n +$ 
3. Carbometallation ex. $RML_n +$ 	3. Migratory Insertion ex. 
4. Transmetallation ex. $RM^1 + M^2X \rightleftharpoons R{-}M^2 + M^1X$	4. Nucleophilic & Electrophilic Attack on Ligands ex. $R^- +$ 

metal orbital, a concerted HOMO-LUMO interaction scheme shown in Scheme 1 becomes available to the reactants.

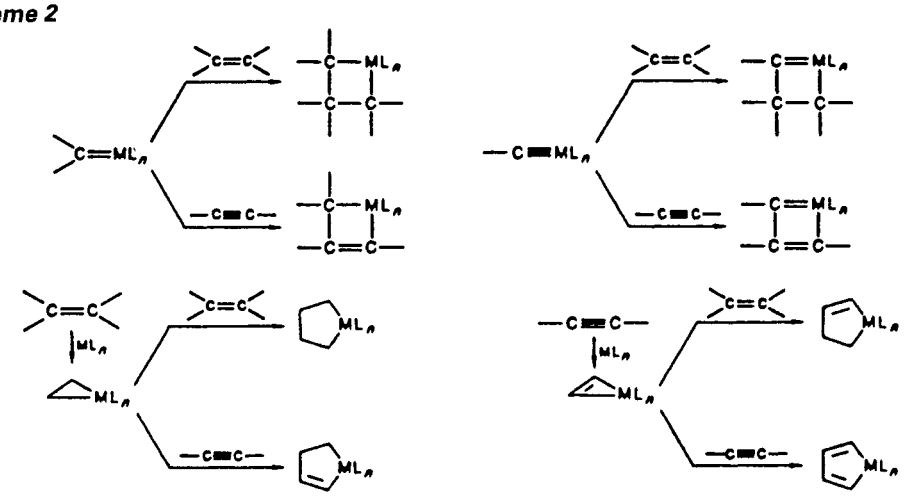
Scheme 1



The products of carbometallation reactions developed earlier, e.g., the Ziegler-Natta polymerization[2] and Wilke's cyclooligomerization of dienes,[3] were mostly simple and highly symmetrical. Over the past few decades, however, carbometallation reactions and procedures applicable to the synthesis of complex and unsymmetrical molecules, e.g., Zr-catalyzed carboalumination[1a] and carbocupration of alkynes[1b] and Pd-catalyzed substitution of alkenyl hydrogen with an aryl or alkenyl group,[4] have been developed.

Of particular interest here are those carbometallation processes that produce cyclic structures. Two fundamentally different types of processes may be considered for this purpose. One is to devise an intramolecular version of carbometallation, and the other is to make use of carbometallation reactions of metal-carbene and metal-carbyne complexes as well as those of three-membered metallacycles (Scheme 2). Indeed, most of the known cyclooligomerization reactions of dienes[3] and alkynes[5] may be explained in terms of carbometallation of metallacyclopropanes and metallacyclopropenes. In this review, attention will be focused on the development of the *"zipper-mode cascade cyclization* via carbometallation leading to cyclic products as a new concept for construction of polycyclic structures.

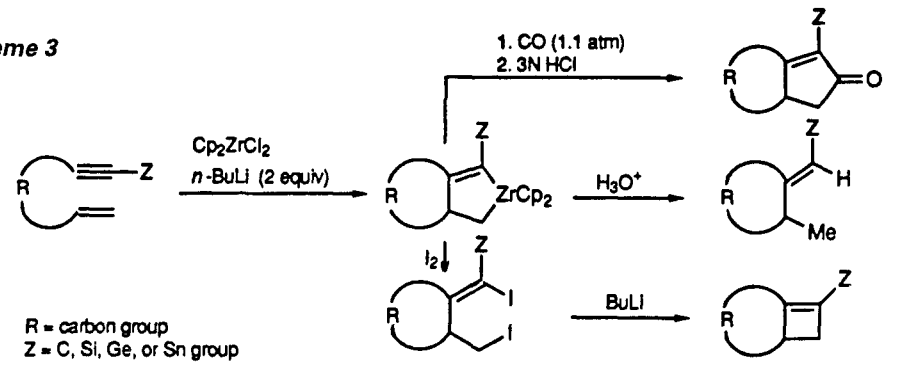
Scheme 2



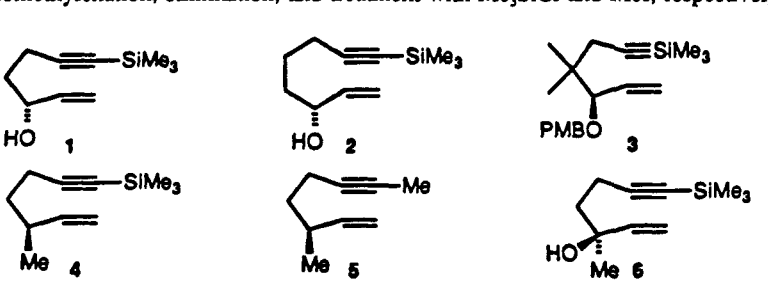
DIASTEREOSELECTIVE ZIRCONIUM-PROMOTED BICYCLIZATION OF ENYNES – APPLICATION TO A TOTAL SYNTHESIS OF PENTALENIC ACID

In pursuit of a "pair"-selective and regioselective process for generating metallacyclopropenes and converting them into metallacyclopentenes according to Scheme 2, we developed and reported in 1985 a Zr-promoted bicyclization of enynes[6] (Scheme 3). Some other transition metals, such as Co,[7] are also known to undergo similar cyclization predicted reactions. It may be safely predicted, however, that each will display its own unique scope and characteristics. For example, the Co-promoted bicyclization is currently useful only for a bicyclization-carbonylation sequence. On the other hand, the Zr-promoted reaction can produce organozirconium compounds which can be transformed into many different products. Subsequent studies by us[8,9] and others including Buchwald,[10] Nugent,[11] Taber,[11b,c] and Livinghouse[12] have revealed the broad synthetic applicability and some surprisingly high levels of "pair"-, regio-, and stereoselectivities.

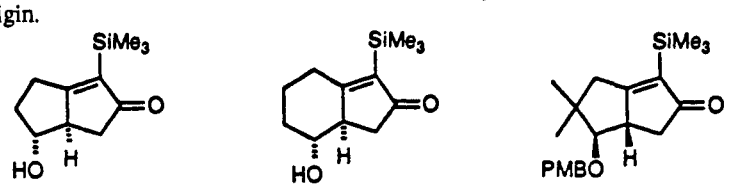
Scheme 3



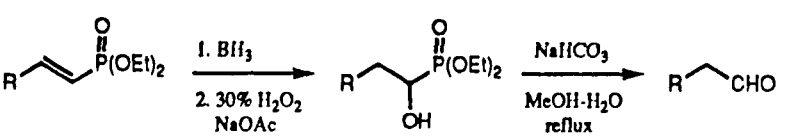
A couple of critically important pending items, as of a few years ago, were (i) to demonstrate the true synthetic utility of the methodology through its application to asymmetric synthesis, either diastereoselective or preferably enantioselective, of natural products[13] and (ii) to devise synthetically attractive catalytic processes. Following promising earlier leads,[8c,8g,10b] especially the case of allylically oxygenated enynes,[12c] we have investigated in detail the stereochemistry of the Zr-promoted bicyclization of enynes **1**-**6**. Although **3** and **6** were racemic mixtures, **1**, **2**, **4**, and **5** were >98% e.e. The Sharpless kinetic resolution[14] using (+)-diethyl tartrate, $Ti(OPr\text{-}i)_4$, *t*-BuOOH, and molecular sieve 3 or 4A provided **1** and **2**, even though our attempts to apply the same method to the resolution of the 4,4-dimethyl derivative of **1** were unsuccessful. (+)-β-Citronellene (Fluka) was converted to **4** and **5** via ozonolysis, dibromomethylenation, elimination, and treatment with Me_3SiCl and MeI, respectively.



The Zr-promoted bicyclization in all six cases proceeded in >90% diastereoselective manner, selectively producing the corresponding zirconabicycles in good to excellent yields. After carbonylation **7**-**12** were obtained in the yields indicated in parentheses based on **1**-**6**.[15] The high diastereoselectivity observed in the reaction of **4**-**6** appears to be largely steric in origin.



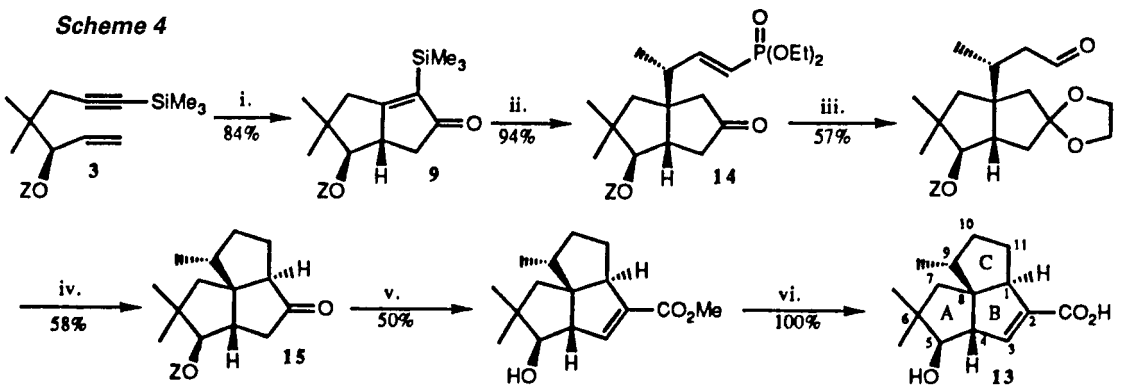
Comparison of **9** with pentalenic acid (**13**) indicated that selective conversion of **9** into **13** would require fusion of the C ring onto **9** with control of the relative stereochemistry at the C-9 center. A survey of the literature revealed that conjugate addition of the lithio derivative of crotylphosphonates[16] would convert **9** into **14** but that there was no established procedure for effecting the conversion of **14** into **15**. We have found that hydroboration of α,β-unsaturated phosphonates followed by oxidation with 30% H_2O_2 and NaOAc gives the corresponding α-hydroxyphosphonates which can be cleanly converted to free aldehydes by treatment with refluxing methanolic $NaHCO_3$ (Eq. 1).



(1)

Conversion of **15** into pentalenic acid was achieved as described previously. Throughout the synthesis essentially complete control of stereo- and regiochemistry was attained (Scheme 4).

Scheme 4



a : Z = Bn.

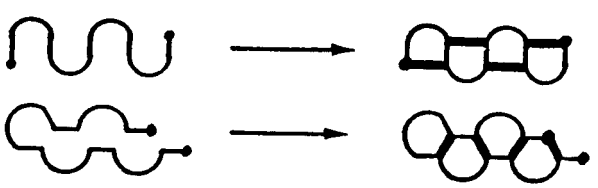
b : Z = MPM.

i. 1. *n*-BuLi (2.4equiv), Cl_2ZrCp_2 (1.2 equiv), THF, -78 to 20°C, ovemight. 2. CO (1.1 atm), 3h, -20°C. ii. 1. (Z)-$CH_3CH{=}CHCH_2PO(OEt)_2$, *n*-BuLi, THF, -78°C, 15min. 2. *n*-Bu_4F, THF, 0°C, 5min. iii. 1. $(CH_2OH)_2$, PPTS, benzene, 2.BH_3·THF, 20°C, ovemight then 30% H_2O_2, NaOAC, 50°C. 3. $NaHCO_3$, MeOH-H_2O, 50°C, 3h. iv. 1. PPTS (1 equiv), acetone, H_2O, reflux, 16h. 2. MsCl, NEt_3, CH_2Cl_2, 0°C, 10min. 3. DBU, benzene, reflux, 10min. 4. H_2,Pd/C, EtOAc, 20°C, 10h. v. LDA then Tf_2NPh, DME, -78 to 20°C, 26h. 2. CO, $Pd(OAc)_2$, PPh_3, NEt_3, DMF, MeOH, 20°C, 16h. 3. DDQ, CH_2Cl_2, H_2O, 20°C, 45 min. vi. KOH, MeOH-H_2O, 45°C, 3h.

"ZIPPER"-MODE CASCADE CARBOPALLADATION

The transition metal-catalyzed bicyclization reactions discussed above provide an attractive and efficient way of constructing not just one but two rings in one step. This mode of ring construction (*"zipper"-mode*) contrasts itself with a previously developed *"crochet"-mode* of ring construction of W. S. Johnson[17] and others (Scheme 5).

Scheme 5



"Crochet"-mode multiple cyclization

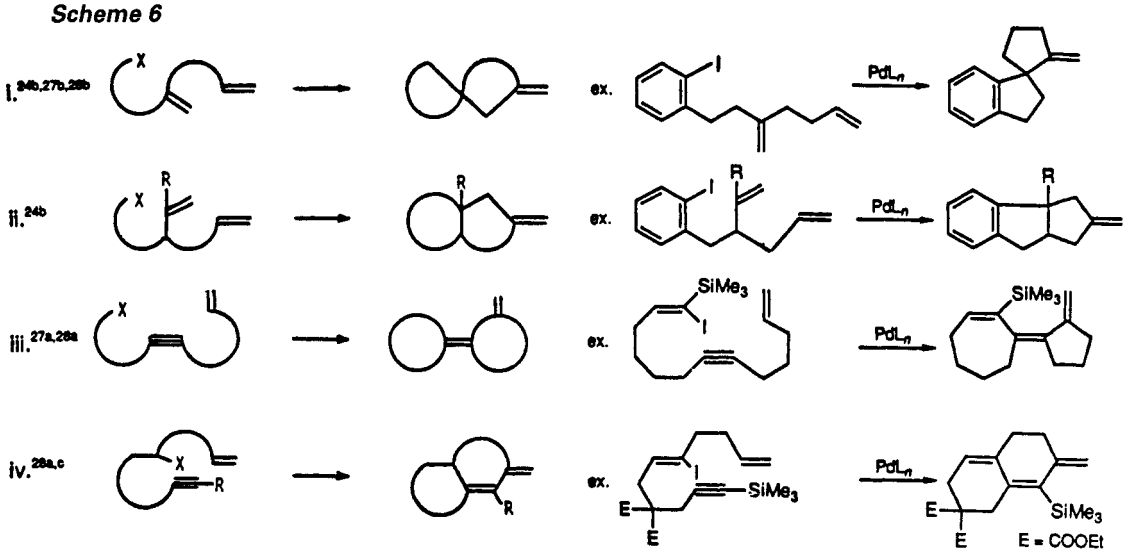
"Zipper"-mode multiple cyclization

Unfortunately, the bicyclization reaction of enynes, whether Co-promoted or Zr-promoted, is capable of producing only two rings in a step. With a notable exception of biogenetic polyketide cyclization,[18] the "zipper"-mode cascade cyclization to produce three or more rings in one step does not appear to have been developed, much less recognized as a viable synthetic methodology. Nonetheless, we noted that the ability of carbometallation to repeat itself (*vide supra*) would be well-suited for developing such a methodology. Cyclic carbopalladation appeared to be a prime candidate for this purpose. We were further attracted by the simplicity of its retrosynthetic analysis and the inherently limited and hence simple nature of the synthesis of acyclic precursors.

Prior to our study, carbopalladation has been implicated in various reactions, such as the Maitlis-type alkyne cyclooligomerization[19] and the Heck-type addition-elimination reaction.[4] During our investigation of the mechanism of acylpalladation (vide infra), we carried out a cyclic carbopalladation reaction to give a carbocycle[20] and noted that, whereas the Heck reaction had been extensively applied to the synthesis of heterocycles,[4] a very limited number of examples of the synthesis of carbocycles[21,22a] were known. By the end of 1988 several research groups besides our own,[23] notably those of Grigg,[22] Overman,[24] and Larock,[25] had reported on application of the Heck reaction to the synthesis of carbocycles. Although different, a series of papers by Trost[26] since 1985 have also dealt with the synthesis of carbocycles via cyclic carbopalladation.

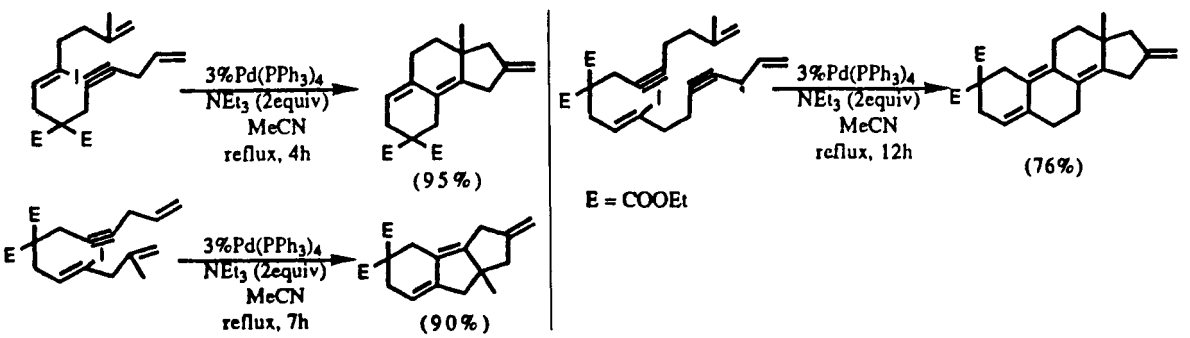
These early examples mostly dealt with monocyclization, and the concept of cascade carbopalladation, with the exception of cyclotrimerization mentioned above,[19] had not been developed until 1988. Since then several different types of cascade carbopalladation have been developed (Scheme 6). Although only bicyclization processes are shown, each process is, in principle, applicable to polycyclization.

Scheme 6

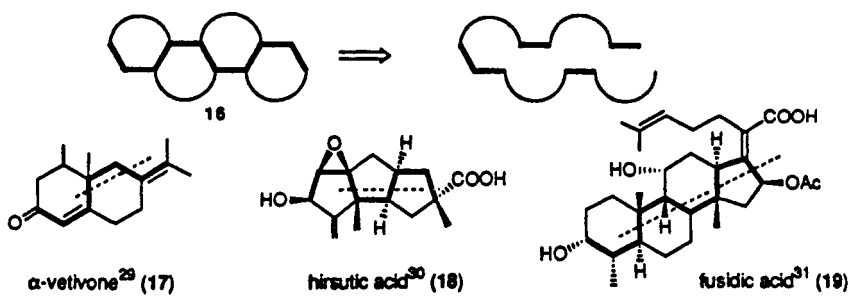


Of particular interest to us is the "zipper"-mode cascade (type iv), and the example shown in Scheme 6, for the first time, indicated its feasibility.[28a] We have subsequently demonstrated that this methodology is indeed applicable to tri- and tetracyclization.[28c] All three reactions shown in Scheme 7 are exceptionally clean and selective, producing virtually nothing but the indicated products. Although we have not yet performed, appropriately structured acyclic precursors into polyfused compounds containing more than four rings appears to be eminently feasible.

Scheme 7



One crucial structural requirement for the "zipper"-mode cascade cyclization is the presence in the product of a "zigzag" backbone shown in **16** (Eq. 2). Luckily, a large number of fused bicyclic and polycyclic natural products, such as **17-19**, do have a backbone of this type.

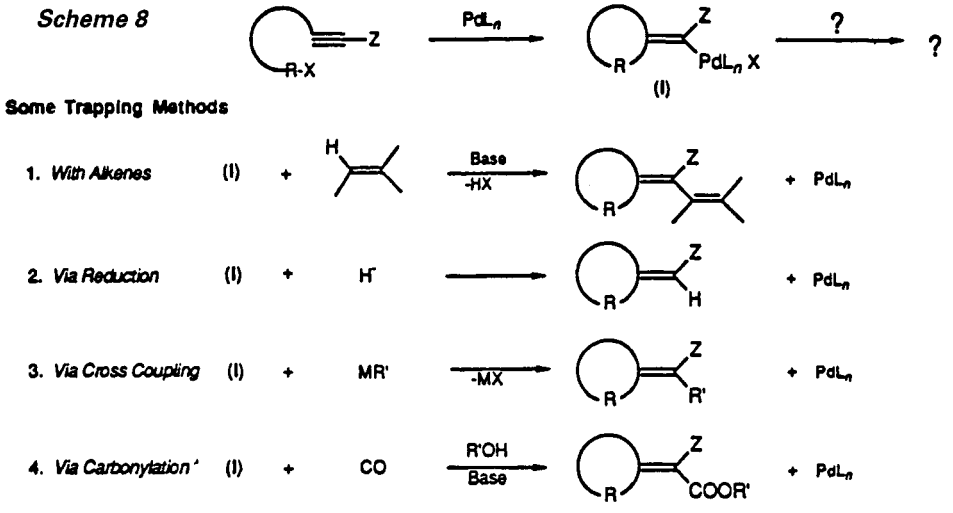


(2)

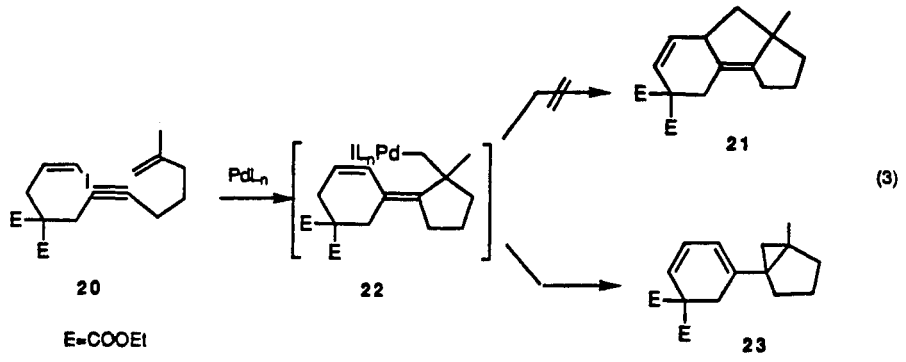
However clean and attractive the results shown in Scheme 7 might be, they merely indicate the feasibility of the "zipper"-mode cascade cyclization. Clearly, a number of obstacles must be overcome before this methodology becomes useful in the construction of complex natural products and related compounds, such as **17-19**.

The "zipper"-mode cascade carbopalladation requires (i) relay functional groups for propagation and (ii) a terminating functional group, which not only terminates a cascade but must also induce regeneration of the Pd catalyst. The relay functional groups must not induce undesirable side reactions, such as β elimination via dehydropalladation and cyclooligomerization to give benzene derivatives and other related byproducts. We have found that yet another potentially serious side reaction is cyclopropanation via cyclic carbopalladation, as discussed later. Alkynes and 1,1-disubstituted alkenes have so far been used as relay functionalities. The use of others, such as dienes, allenes, and trisubstituted alkenes, is currently under investigation. In the great majority of cases reported to date, alkenyl groups that can provide hydrogen β to Pd have been used as terminators. In principle, there are at least several other methods for terminating cascade carbopalladation. Some representative examples are shown in Scheme 8. These reactions have so far been used to trap organopalladium intermediates after just one cyclization. One generally encountered difficulty is to be able to control the timing or site of termination, avoiding any premature action. This point will be discussed later in some detail.

Scheme 8



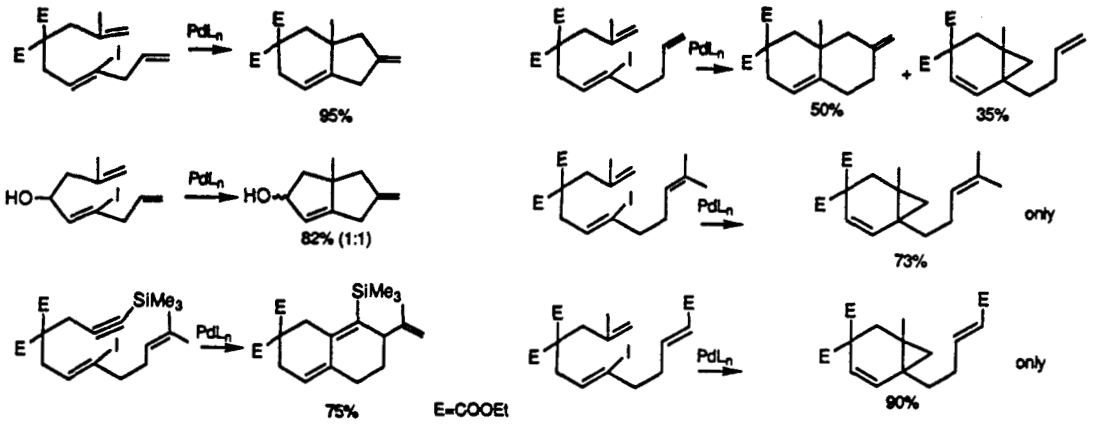
Cyclopropanation vs. Common Ring Formation. Cyclopropanation via cyclic carbopalladation was first observed unexpectedly in our attempt to convert **20** into **21**. Presumably, **22** formed as an intermediate cyclopropanated to give **23**[28a] (Eq. 3). Similar cyclopropanation and cyclobutanation reactions have since been reported.[24c,32]



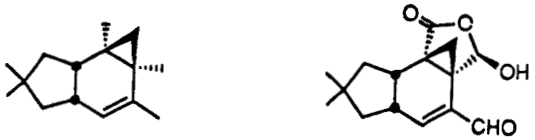
(3)

A systematic study has indicated that the extent to which cyclopropanation occurs is a function of several factors including (i) the size of the desired ring, (ii) the nature, steric and electronic, of the alkenes including the one that is to act as a terminator, and (iii) conformational and stereoelectronic constraints associated with all possible competing carbopalladation processes. The following generalizations may be made based on the currently available data. 1) Alkenylpalladium species do not give cyclopropenes. 2) Six-membered ring formation is more readily competed by cyclopropanation than five-membered ring formation. 3) Highly substituted electron-deficient terminating alkenes do not readily undergo cyclic carbopalladation and hence tend to induce cyclopropanation. Some representative results are shown in Scheme 9.[33]

Scheme 9

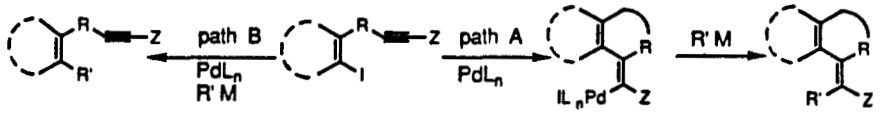


Although undesirable from the viewpoint of the "zipper"-mode cascade carbopalladation, the cyclopropanation reaction appears to offer some attractive synthetic possibilities. For example, vinylcyclopropane containing compounds, such as marasmane[34] (24) and marasmic acid[34] (25) may be prepared using this reaction.



24 25

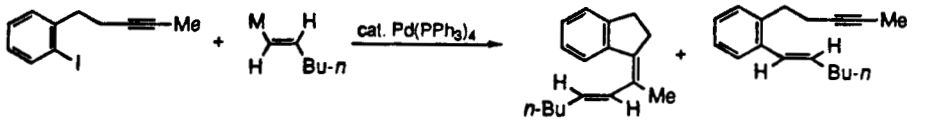
Cross Coupling as a Means of Termination. All of the cascade cyclization processes presented above involve cascade termination via carbopalladation-dehydropalladation, i.e., the Heck reaction. We have, for quite some time, been aware that Pd-mediated cross coupling[35] would convert alkenylpalladium intermediates into organic products (path A). However, our initial attempts using organozinc reagents as external trapping agents led mainly to a premature trapping (path B).[36]



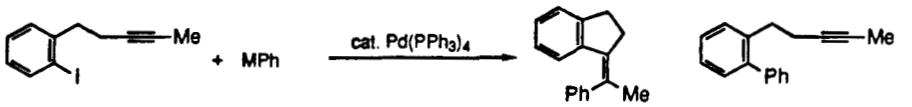
(4)

Our previous finding that organozincs undergo Pd-catalyzed cross coupling much faster than other organometals, such as those containing Al, B. Sn, and Zr, suggested to us that, perhaps for the very reason, organozincs might actually be unsuitable for trapping which must not compete with but follow cyclic carbopalladation. This indeed has been the case, and the use of arylaluminum, alkenylzirconium, and alkenyl- and alkynyltin derivatives has led to satisfactory results,[37] even though its application in the cascade carbopalladation has not yet been performed (Scheme 10).

Scheme 10

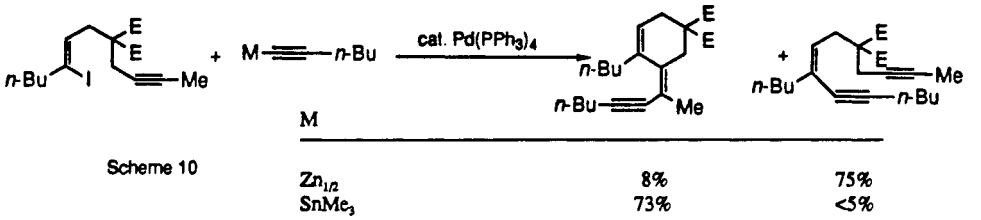


M		
ZnCl	19%	68%
$ZrCp_2Cl$	84%	≤3%
$SnMe_3$	69%	≤3%
$Al(Bu\text{-}i)_2$	57%	32%



M		
ZnCl	34%	57%
$AlPh_2$	93%	<2%
$Sn(Bu\text{-}n)_3$	trace	trace

Scheme 10 (cont.)

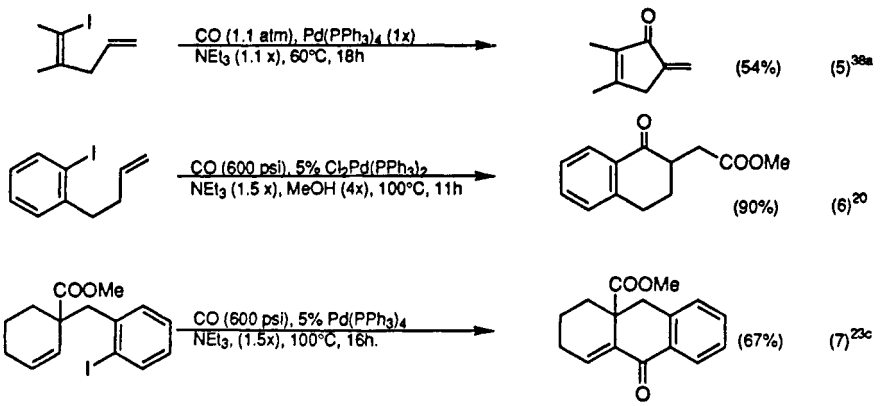


Scheme 10

M		
$Zn_{1/2}$	8%	75%
$SnMe_3$	73%	<5%

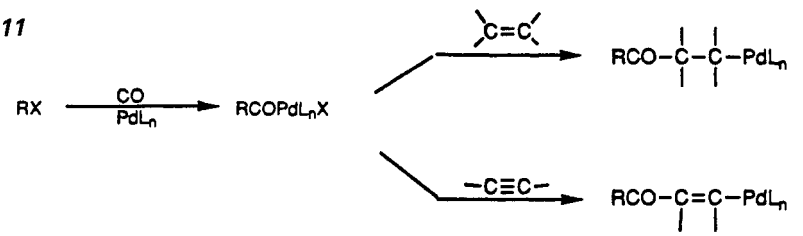
CYCLIC ACYLPALLADATION

We have previously reported that acylpalladium species generated in situ via carbonylation with CO can add intramolecularly to alkenes and alkynes to produce cyclic enones. Some representative early results are shown in Eqs. 5-7.[20,23c,38]

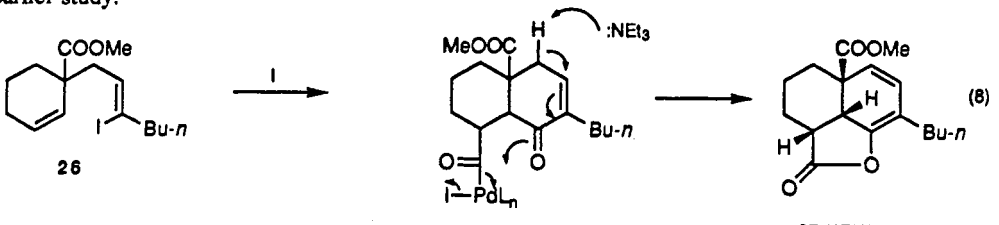


These reactions most probably proceed via acylpalladation (Scheme 11). Except for the presence of CO, the required reaction conditions are usually the same as those for carbopalladation. So, the use of CO in cyclic carbopalladation can, in principle, introduce interesting ramifications that may complicate the overall reaction scheme on the one hand, but may also broaden the synthetic scope of carbopalladation on the other, if the course of the reaction can be controlled in a predictable manner. Before making any predictions, however, observation of some facts must be made to increase our knowledge basis.

Scheme 11



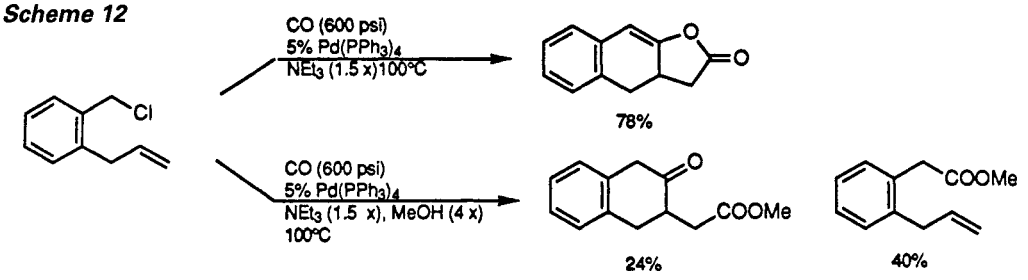
Trapping of Acylpalladium Species with *O*-Enolates. The carbonylation reaction of **26** under the conditions identical to those for the reaction shown in Eq. 7 gave a totally different type of product, which has been identified as **27**.[39] Although not yet fully clarified, the reaction must have taken the course outlined in Eq. 8. Three C-C and two C-O bonds are formed in one step in a highly selective manner. A similar *O*-enolate trapping was also observed by us in an earlier study.[38b]



I = CO (600 psi), 5% $Pd(PPh_3)_4$, NEt_3 (1.5 x),100°C

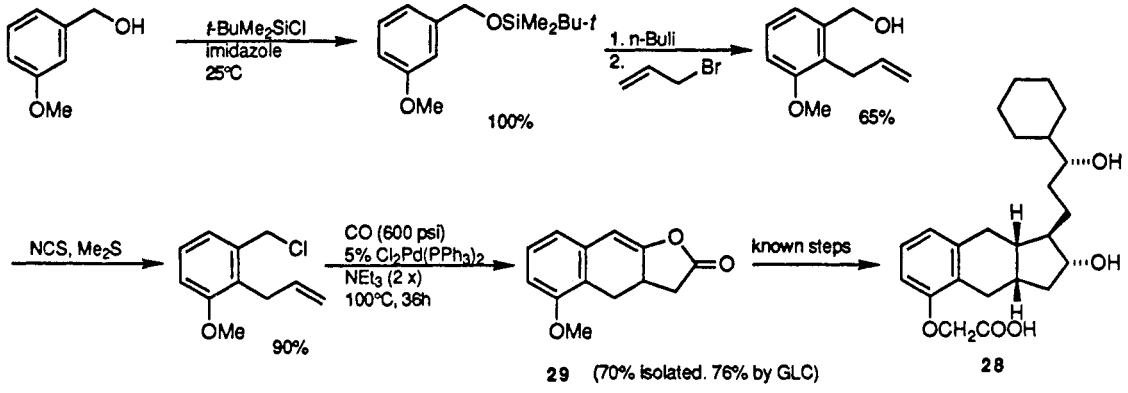
Our more recent study[40] has shown that the *O*-enolate trapping reaction can provide, in some cases, an attractive alternative (Scheme 12) to the procedure involving trapping with MeOH (Eq. 6). Methanolysis of the *O*-enolate trapping product readily gives the MeOH trapping product.

Scheme 12



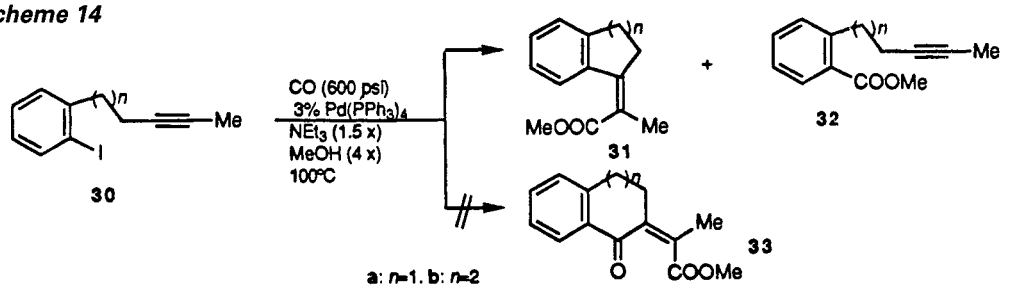
A literature survey has indicated that U-68,215 (**28**) is a promising anti-ulcer agent which has been synthesized via **29**. This intermediate, in turn, was previously synthesized in 7 steps from a naphthalene derivative. As summarized in Scheme 13, **29** can now be prepared in 4 steps from commercially available *m*-methoxybenzyl alcohol via acylpalladation-trapping with *O*-enolate.[41]

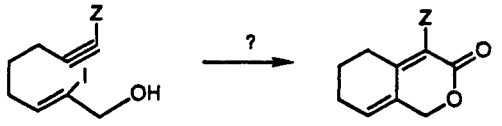
Scheme 13



Trapping of Acylpalladium Species with Internal Alcohols. In general, migratory insertion of CO appears to be faster than carbopalladation or acylpalladation. However, this does not necessarily shut out carbopalladation, since CO insertion is thought to be reversible. This is a crucially important point, if we are to use carbonylation as a means of terminating cascade carbopalladation. We have recently observed that treatment of **30a** and **30b** with 3 mol % of $Pd(PPh_3)_4$, CO (600 psi), NEt_3 (1.5 equiv), and MeOH (4 equiv) gives mixtures of the corresponding **31** and **32** in 60-70% combined yields, the ratios of **31** to **32** being 60/40 for **31a/32b** and 30/70 for **32a/32b**.[28a] Significantly, neither **33a** nor **33b** was formed (Scheme 14). These results indicate that cyclic acylpalladation of alkynes must be unfavorable relative to cyclic carbopalladation. These results prompted us to develop a potentially

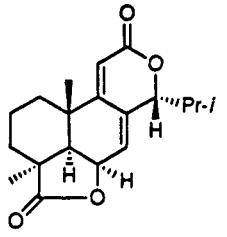
Scheme 14



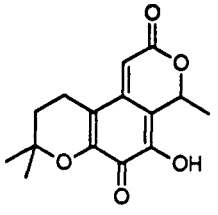


(9)

attractive procedure for the transformation outlined in Eq. 9. Its attractiveness lies, in part, in the fact that a number of natural products, such as **34**[42] and **35**[43], possess the same structural component as the product in Eq. 9.

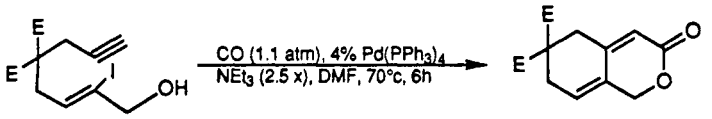


34 (nagilactone F)



35 (fuscin)

With the goal outlined above in mind, we recently carried out the transformation shown in Eq. 10.[44] This reaction is surprisingly clean, and no other processes seem to be competing with it.



(10)

80%

CONCLUSION

The results presented above indicate that the "zipper"-mode cascade carbometallation promoises to provide a novel and attractive methodology for the synthesis of polyfused compounds. Cyclic carbopalladation appears to be particularly well suited for this purpose. Its usefulness may be further reinforced by cyclic acylpalladation. A number of obstacles must still be overcome before this methodology may become truly useful, and a considerable amount of efforts are being expended toward that goal. Although our efforts to induce either diastereo- or enantioselective cyclic carbopalladation have been disappointing, it still remains as a worthy challenge. A few recent efforts by others[45] toward this goal are noteworthy.

Acknowledgements

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