Organic Reactions

VOLUME 68

A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey

Library of Congress Catalog Card Number: 42-20265
ISBN 978-0-470-09898-1

Printed in the United States of America

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry, the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Synthesis*, they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy, the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions*.

Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to contact the Editor-in-Chief.

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CHAPTER 1

COTRIMERIZATIONS OF ACETYLENIC COMPOUNDS

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Organic Reactions, Vol. 68, Edited by Larry E. Overman et al.

ACKNOWLEDGMENTS

We wish to thank Professor T. V. RajanBabu for helpful suggestions and Drs. Linda Press and Danielle Soenen for the editing of the manuscript.

INTRODUCTION

The cyclotrimerization of acetylenic compounds is a useful method for the construction of three new bonds in a one-step process. Although symmetry-allowed, there is a paucity of examples of purely thermal [2+2+2] cycloadditions. Berthelot reported the first example in 1866 which was the cyclization of acetylene to benzene.[1] High temperatures (ca. 400°) are required for this reaction and a mixture of products is formed. In 1948, Reppe discovered the first transition-metal-catalyzed version of this reaction in which nickel was used, leading to the formation of substituted benzenes.[2] Since then, catalysts based on no less than seventeen early to late transition metals (for representative examples see: Ti,[3,4] Zr,[5,6] V,[7] Nb,[8–10], Ta,[9] Cr,[11,12] Mo,[13] W,[12,14] Fe,[15] Ru,[16] Os,[17] Co,[18] Rh,[19–21] Ir,[22,23] Ni,[24] Pd,[25] Cu[26]), two lanthanides (Eu, Yb),[27] one actinide (U),[28] and aluminum[29] have been developed for the cycloaddition of substituted alkynes to benzene derivatives. Alkynes,[18,30–34] alkenes,[18,32] allenes,[34] aldehydes and ketones,[33] imines,[32] isocyanates,[32] isothiocyanates,[35] carbon monoxide,[32] carbon dioxide,[32] carbon disulfide,[35] and carbenes and carbynes[32] can take part in related cyclization reactions to give products with four-, five-, six-, or eight-membered rings. It is well known that nitriles can also be used as alkyne replacements in [2+2+2] cyclotrimerizations to afford pyridines.[18,32,36,37] Many of these reactions proceed with good chemo-, regio-, and stereoselectivities and have found many applications in organic synthesis.

During the last three decades this reaction has been extensively investigated and the topic has been thoroughly reviewed.[18,30–32,37–44] Because of the large number of publications in this area, it is impossible to present more than a limited set of examples, and several very interesting topics will have to be excluded from this chapter. Among them are: cyclizations of acetylenic compounds on low-index metal surfaces, kinetic studies of cyclotrimerizations, cyclizations mediated by metal ions introduced into zeolites, cyclotrimerization of nitriles to triazines, and cocyclization of transient strained cycloalkynes. The latter is mentioned in the "Comparison with Other Methods" section.

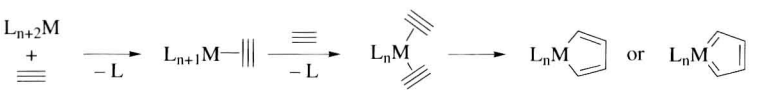
This chapter is devoted to early to late transition metal-mediated cotrimerization of acetylenic compounds directed towards organic synthesis. It addresses the scope and the generality of the reaction as well as the current state of the art with regard to regio- and stereoselectivities. In the context of selectivity, a mechanistic overview is provided. Inter- and intramolecular versions of the cyclizations are presented with an emphasis on applications in synthesis. The literature from 1980 up to the middle of 2004 is covered.

MECHANISM AND STEREOCHEMISTRY

The cotrimerization of alkynes in the presence of transition metals to produce arenes is probably the most general reaction of these compounds. It is possible to cyclotrimerize acetylene as well as mono- and disubstituted acetylenic compounds. In addition, selective intermolecular cyclizations involving more than one type of alkyne are also possible. A wide variety of homogeneous and heterogeneous catalysts are available for such cyclizations. Therefore, several mechanistic pathways have been proposed, which are mainly dependent on the nature of the catalyst. It seems obvious that the metal may act as a template for the formation of the arenes, by sequentially binding the alkynes and acting as a channel through which electrons flow between the ligands. However, debate about the cyclotrimerization mechanism continues. The emphasis here will be on the most common mechanism involving the intermediacy of metallacyclopentadienes. This mechanism is applicable to most of the metals (for representative examples see: Ti,[3] Zr,[6] Ta,[45] Mo,[46,47] Co,[48,49] Rh,[19] Ir,[22,23] Ru,[50] Ni,[51] and Pd[52]). It also provides a useful model for an understanding of the selectivities. Other types of mechanisms which do not involve the intermediacy of a metallacyclopentadiene will also be mentioned, particularly the Pd(II)-triggered cascade carbometallation route and the Ru(IV) metathesis route.

Metallacyclopentadiene Route

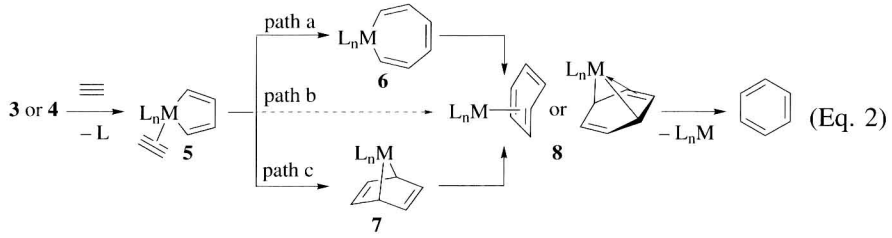
Initially, one and then two alkyne moieties sequentially displace two ligands of the metal to form alkyne complex **1** and then **2** (Eq. 1). Oxidative coupling may occur to give the coordinatively unsaturated complexes **3** or **4** which have oxidation states of two or four units higher than their precursor **2**.



1 **2** **3** **4** (Eq. 1)

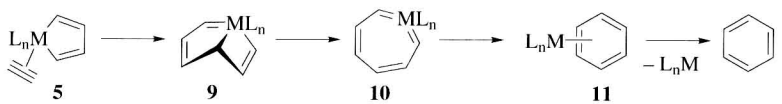
Several pieces of evidence supporting the intermediacy of these metallacycles including calculations and isolation of structurally characterizable molecules have been provided.[50,53–57] Upon opening a vacant coordination site by ligand dissociation, intermediates **3** and **4** may readily complex a third alkyne unit to give the metallacyclopentadiene(alkyne) complex **5** (Eq. 2). Compelling evidence for the accumulation of intermediate **5** in the catalytic cycle has been reported. It

has been observed that blocking the empty coordination site in **3** (M = Rh, Ir) with an ancillary ligand (L = Cl, PR_3) inhibits the arene formation or in some cases slows down the rate.[49] In addition, isolated examples of structural motifs such as **5** (M = Co) have been described.[58]



(Eq. 2)

Complex **5** may undergo insertion of the ligated alkyne into a metal-carbon bond to give metallacycloheptatriene **6** (path a). Reductive elimination may occur to provide the complex **8**, which has been isolated occasionally.[23,58–61] Lastly, decomplexation of the arene generates the benzene ring. The intermediacy of the metallacycloheptatriene **6**, which is frequently proposed, is questionable, because the reductive elimination converting **6** to **8** is symmetry forbidden.[62,63] This reaction path is thus expected to be kinetically difficult. Therefore, alternative processes for the formation of the η^4-benzene complex **8** have been proposed. In path c, a [4+2] approach is shown to give an intermediate 7-metallanorbornadiene complex **7** that subsequently leads to **8**. Although kinetic studies support the intermediacy of complex **7**,[49] it appears from more recent studies that the reductive elimination giving the arene formation is also symmetry forbidden.[50,62] For CpCo complexes, calculations support a direct [4+2] cycloaddition pathway (path b) with no intermediate for the conversion of **5** to **8**. This transformation requires a very small activation energy of 0.5 kcal/mol reflecting an extraordinarily large driving force of −81.4 kcal/mol.[62] A fourth suggestion has been made for ruthenium.[50,56,57] A bicyclic ring system **9** is formed from complex **5**. This metallabicyclo[3.2.0]heptatriene rearranges into a metallacycloheptatetraene complex **10**, which gives the η^2-cyclohexatriene complex **11** after reductive elimination (Eq. 3). Recently, a relevant iridabicyclo[3.2.0]heptatriene has been isolated and characterized by X-ray crystallography.[64]



(Eq. 3)

It is noteworthy that the metallacyclopentadiene **3** can lead to η^4-cyclobutadiene complex **12**,[63] as illustrated in Eq. 4. For some specific metals such as cobalt, rhodium, and iridium, the mechanism of this transformation has been probed by means of Density Functional Theory (DFT)/B3LYP calculations.[65] A multi-step reaction including a cyclopropylcarbene and a tetrahedrane-type intermediate was computed, supporting the initial proposal made by Vollhardt

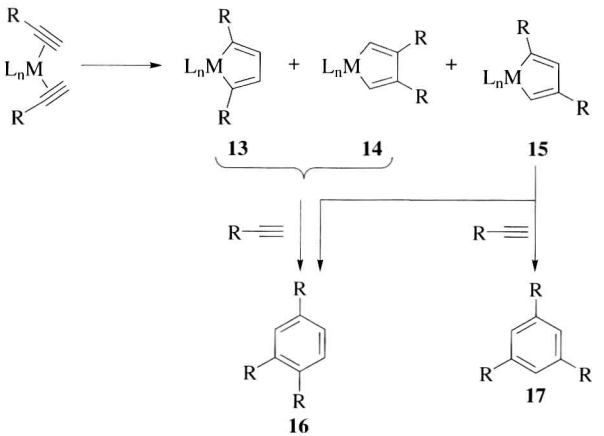
and co-workers.[66] It was shown that, as the substituents on the alkyne get larger, the cyclodimerization reaction becomes easier.[65]

3 **12** (Eq. 4)

For many years, cyclobutadiene complexes were proposed to be reactive intermediates in the formation of the arenes,[67] despite the high stability of such complexes. Experiments using a number of main group and transition metal catalysts have since provided strong evidence that the cyclotrimerization of alkynes does not take place through cyclobutadiene intermediates.[48] These results support the assertion that complex **12** is an inert byproduct leading to catalyst deactivation, due to the thermodynamic stability of the metal-cyclobutadiene bond.[68,69]

Although not fully clarified, the pyridine syntheses from alkynes and nitriles is thought to proceed according to the same kind of mechanism. The first step would be the formation of a metallacyclopentadiene from two alkyne units, followed by nitrile insertion.[70]

Regioselectivity. Whatever the mechanism, the major regiochemical consequence is that the trimerization of unsymmetrically substituted alkynes leads to arenes which display exclusively 1,2,4- or 1,3,5-substitution patterns. In the proposed mechanism, regioselection occurs at two stages: in the formation of the metallacyclopentadiene and in its subsequent reaction with a third alkyne equivalent. The preference for formation of the metallacyclopentadienes **13**–**15** clearly depends on the catalyst, the substitution pattern on the alkyne, and the reaction conditions (Eq. 5).

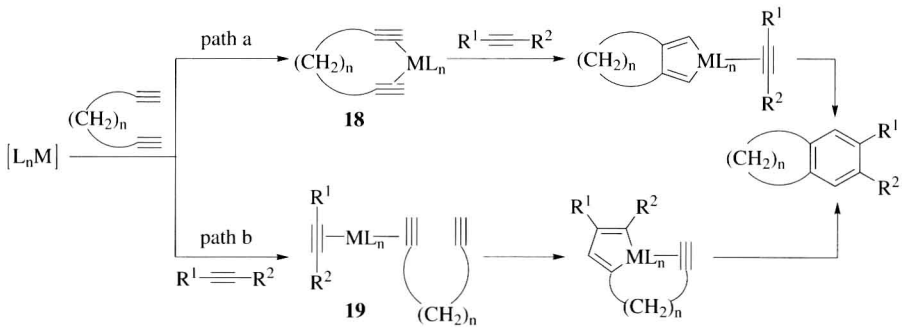


(Eq. 5)

Complexes **13** and **14** must lead exclusively to the 1,2,4-product **16**, independent of the orientation of the final insertion. The formation of the 1,3,5-compound **17** requires the intermediacy of the metallacycle **15**. However, complexes of type

15 can also give rise to 1,2,4-products.[55] Although products of type **17** seem statistically disfavored, many reports dealing with the selective formation of these compounds can be found (see Scope and Limitations).

Bimolecular and Intramolecular Cotrimerizations. The bimolecular cyclizations combine a diyne and a monoalkyne. Depending on the substrates, the initial bis-alkyne species is a complex of both alkyne units of the diyne (path a, complex **18**) or a complex of the monoalkyne together with one free alkyne unit (path b, complex **19**) as described in Eq. 6. Either pathway would afford the same arene products. Chemoselectivity is also a potential problem because the cyclizations could involve exclusively the diyne, or exclusively the monoalkyne, or one diyne unit and two monoalkynes. Those could compete with the desired process. In practice, chemoselectivity is readily achieved by employing sterically hindered monoalkynes, for instance, *bis*-trimethylsilylethyne, which is reluctant to undergo autocyclotrimerization.



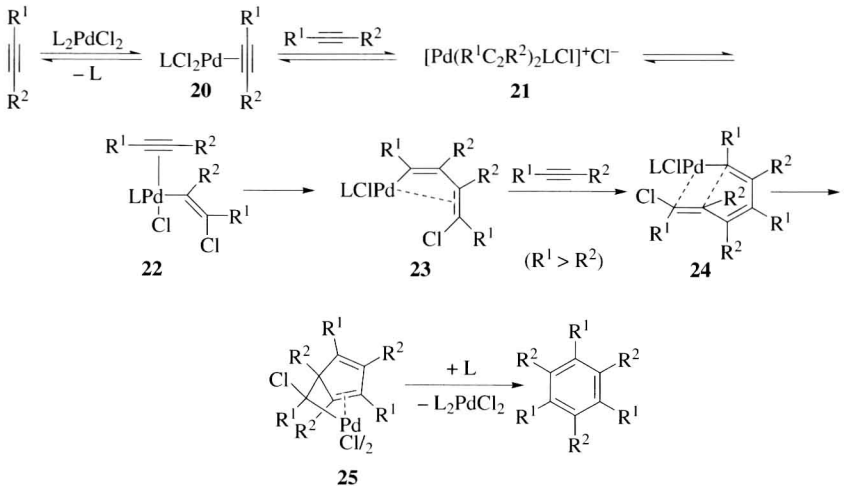
(Eq. 6)

Cascade Carbometallation Route

A cascade carbopalladation often occurs with Pd(II) complexes.[71,72]

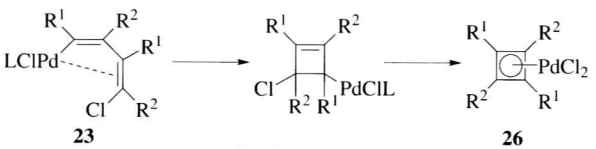
Intermolecular Cascade Reactions. Many palladium(II) complexes are reactive towards alkynes. In intermolecular versions, these Pd-catalyzed cyclizations are complex processes and appear to operate differently from those described above, even though the formation of the arenes is the end result in some of these processes.[38,73] Different intermediates are possible depending on the size of the alkyne substituents or even on the polarity of the solvent in which the reaction is carried out. Metallacyclopentadiene intermediates are not necessarily involved in these sequences. The proposed mechanism presented in Eq. 7 is based on several isolated intermediates.[74] The first step is the formation of the π-acetylene complex **20** after ligand exchange. A second ligand exchange with another alkyne unit provides the transient complex **21**, which is believed to be in equilibrium with the σ-alkenyl intermediate **22**. The irreversible insertion of the second coordinated acetylene into the Pd–C bond then occurs, giving the σ-butadienyl complex

23. With small R^2 groups, the next step is an anti-Markovnikov cis-insertion of another acetylene into the Pd–C bond giving a σ,π-hexatrienyl complex **24**. The terminal double bond coordinates the metal in such a way that internal cyclization leading to complex **25** becomes straightforward. Palladium in the complex **25** coordinates a cyclopentadiene double bond, which is sterically constrained. Ring expansion in complex **25** will be followed by its decomposition to give the expected arene product regenerating $PdCl_2$.



(Eq. 7)

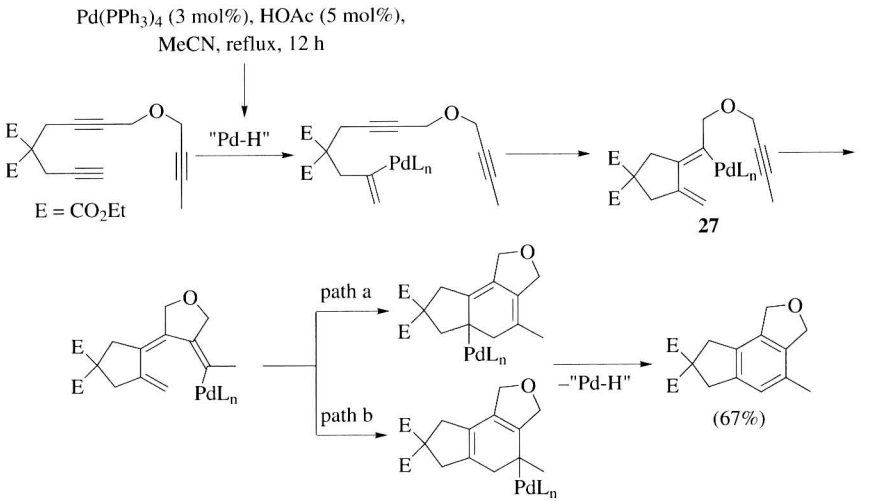
It is noteworthy that the cyclobutadiene complexes **26**, which are inert to further reaction with alkynes, can be obtained from the σ-(η^2-butadienyl)complexes **23** when alkynes are substituted by sterically demanding R^1 groups as shown in Eq. 8.[75]



(Eq. 8)

R^1, R^2 = various Ar, *t*-Bu

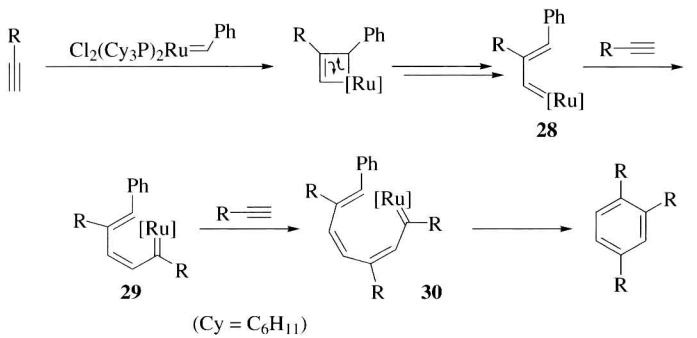
Intramolecular Cascade Reactions. The use of palladium(II)-mediated cyclotrimerizations had been scarce until the development of the intramolecular versions. Although the mechanism is not very clear, it is likely that **27** is a putative intermediate as shown in Eq. 9. It is generated by hydropalladation of the less-substituted alkyne function followed by two carbopalladations. The ring closure to the benzene derivatives might occur through a 6-endo-trig cyclization (path a) or an electrocyclic pathway (path b), both followed by a β-hydride elimination.[76,77]



(Eq. 9)

Metathesis Route

The Grubbs catalyst, $Cl_2((C_6H_{11})_3P)_2Ru{=}CHPh$, which has been widely used for the olefin metathesis reaction, is very efficient as a mediator for the cyclotrimerization of alkynes.[78,79] A cascade of four metathesis reactions has been proposed as a mechanistic rationale (Eq. 10).[78] The ruthenium benzylidene complex is proposed to add to the first alkyne to afford the vinylcarbene complex **28** which consecutively adds to two other alkyne units to produce the intermediate vinylcarbene complexes **29** and then **30**. Finally, the intramolecular ring-closing metathesis reaction from **30** gives the corresponding benzene derivative.



(Eq. 10)

SCOPE AND LIMITATIONS

Cotrimerization of acetylenic compounds can be performed under many different conditions, some mild, others quite harsh (see Experimental Procedures).