

New Synthetic Methods Vol. 6

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Cyclometalation
 α -Metalated Isocyanides
Phosphacumulene
and Phosphaallene Ylides
Flash Thermolysis
Phase-Transfer Catalysis
Titanium Tetrachloride
in Organic Synthesis

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**New
Synthetic
Methods
Vol. 6**



New Synthetic Methods

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- Vol. 2** CC Bond Formation with Organometallic Reagents · α -Metalated Isocyanides · Umpolung of Amine Reactivity · Halomalondialdehydes · Phosphorylcarbenes
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- Vol. 6** [4 + 2] and [3 + 2] Cycloadditions · Cyclometalation · α -Metalated Isocyanides · Phosphacumulene and Phosphaallene Ylides · Flash Thermolysis · Phase-Transfer Catalysis · Titanium Tetrachloride in Organic Synthesis

About this book

To synthesize new compounds and to improve the routes leading to known substances have always been and will probably continue to be the major objectives of chemistry. Scientific craftsmanship may be a term suitable to describe the approach that is required in order to ensure success. As in any other craft, then, it is important, if not crucial, to be familiar with the arsenal of available methods and to be able to select from it that method which is most suitable for the task at hand. It is the purpose of this book to aid the chemist in his search for and selection of this method.

The papers collected here describe modern methods of synthetic chemistry in such a way that their advantages, applicability, requirements and limitations become obvious. They do not enumerate each and every publication relevant to the subject matter. Rather, their contents have been critically compiled so as to highlight important recent developments, but all contributions contain adequate references providing the reader with easy access to comprehensive details.

All papers have previously appeared in the International Edition of "Angewandte Chemie". It is the unusual interest which they have aroused among the readers of this journal that has led to their presentation in the form of this book. Divested, as it were, of the material that accompanied them in the pages of the journal they will be more convenient to use. Moreover, the authors have updated their reports such that they reflect the latest state of the art, thus adding considerably to the value of the book.

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Intramolecular [4 + 2] and [3 + 2] Cycloadditions in Organic Synthesis

By Wolfgang Oppolzer^[*]

Dedicated to Professor Vladimir Prelog on the occasion of his 70th Birthday

Numerous examples of intramolecular cycloaddition of 1,3-dienes, nitrones, and azomethine imines attest the preparative value of this variant for regioselective and stereoselective synthesis of annelated and bridged ring systems. The common features, differences, and limitations of these types of reaction are systematically reviewed.

1. Introduction

Thermally induced additions of 1,3-dienes and of 1,3-dipoles to multiple bonds clearly lead to six- or five-membered rings with the simultaneous formation of two σ -bonds, *via* a highly ordered aromatic transition state^[1-3]. The stereochemical consequences of a reaction course of this type are paralleled by reactivity and orientation phenomena ascribed to frontier orbital interactions^[4]. The great preparative importance of these features of the mechanistically related reactions is shown, *inter alia*, by a multitude of fascinating applications of the bimolecular Diels-Alder reaction to the synthesis of complex molecules^[2].

From investigations carried out in recent years it follows that the synthetic potential of such cycloadditions is decisively increased by the principle of intramolecularity. Intramolecular additions of this type result not only in the simultaneous formation of *two* rings, but also in certain consequences which

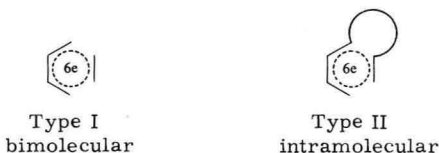
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are superimposed on those of the classical bimolecular variants.

The aim of the present review is to collect the common characteristics of intramolecular additions of 1,3-dienes, nitrones, and azomethine imines and to indicate the possibilities and limitations of these processes. Entropy factors and problems of kinetically controlled regio- and stereoselectivity deserve special attention which justifies their detailed discussion. An attempt is made, with the aid of selected examples, to demonstrate the scope and utility of these reactions in the synthesis and biogenesis of structurally complex natural products.

2. Intramolecular Diels-Alder Reactions

Bimolecular $[4+2]$ cycloadditions (type I), whose general applicability was recognized by *Diels* and *Alder* nearly 50



Scheme 1. $[4+2]$ -cycloaddition of dienes.

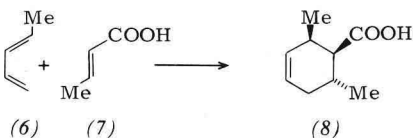
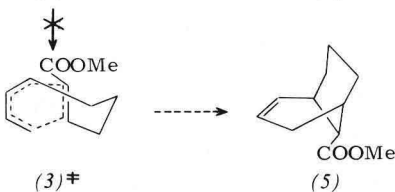
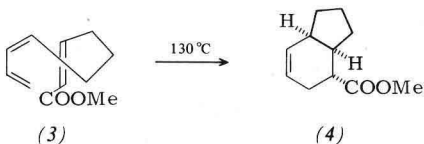
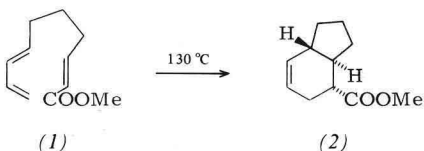
years ago^[5], are today one of the most important types of reaction used in organic synthesis^[2]. Although *Alder* had already indicated the possibility of intramolecular $[4+2]$ additions (type II) as early as 1953^[6], and other authors later found occasional examples^[7], it was not until the last decade that the general utility of this reaction became apparent^[8].

2.1. Acyclic Dienes

2.1.1. Construction of 5,6- and 6,6-Ring Systems

The first systematic investigation of this type of reaction, described by *H. O. House* in 1965^[9], suffices to bring certain characteristic features to light. When heated to 130°C, the

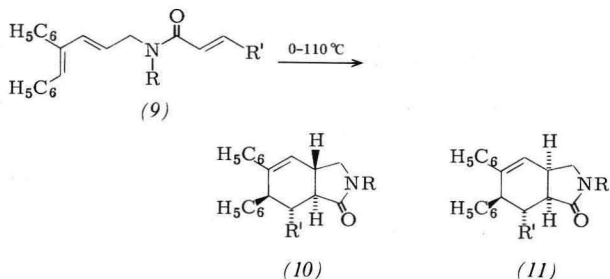
trans-diene unit in the triene (1) adds smoothly to the double bond of the acrylic ester linked to the diene by a bridge of three carbon atoms leading to the *trans*-annulated hydriindane derivative (2). Surprisingly, under the same conditions the *cis*-substituted diene (3) reacts in a similar manner, but with exclusive formation of the *cis*-annulated product (4). In view of the fact that *cis*-substituted open-chain 1,3-dienes usually undergo bimolecular Diels-Alder reactions only with difficulty, we are forced to the conclusion that the reaction (3)→(4) profits from entropy factors due to the spatial proximity of the reaction partners. (Examples given below show that nonactivated dienophiles smoothly undergo intramolecular cycloaddition for the same reason.)



A further notable feature of intramolecular [4+2] additions is the influence of orienting factors promoting the formation of annulated products. For example, the reaction of the *cis*-

diene (3) gave no trace of the bridged positional isomer (5); in this connection it should be remembered that the addition in the intramolecular reactions (1)→(2) and (3)→(4) takes place in the opposite direction to that strongly favored in the bimolecular reaction (6)+(7)→(8)^[10].

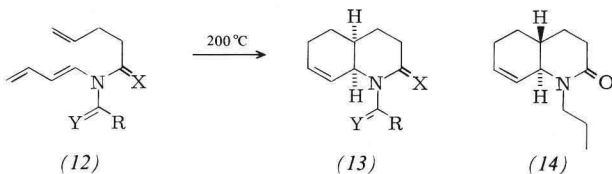
Consideration of models (see Section 2.6.2) shows that the formation of a bridged adduct from (1) is blocked by strain, whereas the formation of the transition state (3)[‡] from (3) does not require any deformation of the bond angles; thus, the absence of (5) after thermolysis of (3) is due to other causes, presumably the (entropically favored) easier closure of a five-membered ring than that of a six-membered ring. The pronounced stereoselectivity of the conversion (3)→(4), on the other hand, appears to be due to a strongly strained transition state, which would have to be overcome in the alternative reaction (3)→(2) (see Section 2.6.3). The *endo*-position of the ester group appears to be decisive for favoring the reaction (1)→(2) over the reaction (1)→(4).



The results of kinetic and stereochemical studies^[11] of the thermal reaction (9)→(10)+(11) are in accord with the above conclusions. For example, an activation entropy of $\Delta S^\ddagger = -14.4 \text{ cal K}^{-1} \text{ mol}^{-1}$ is found for the intramolecular addition of the acrylamides (9), R = *tert*-butyl, R' = H, whereas bimolecular Diels-Alder reactions have considerably more negative ΔS^\ddagger values (between -30 and $-40 \text{ cal K}^{-1} \text{ mol}^{-1}$). Furthermore, the reaction (9)→(10)+(11) becomes increasingly slower as the size of the nitrogen substituent R decreases (probably for conformational reasons). The stereochemistry of these kinetically controlled additions reflects again the pref-

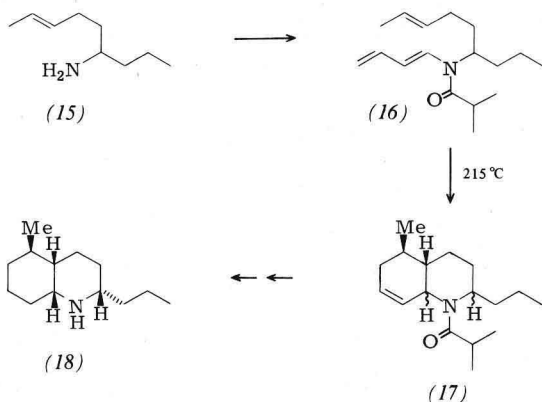
erential *endo*-orientation of terminal π -substituents R' , *i.e.* the *trans*-fused adducts (10) are formed selectively from the amides (9), $R' = \text{COOEt}$ or C_6H_5 . This opens a simple route to polysubstituted perhydroisoindoles with stereochemical control of up to five chiral centers.

A close connection between systematic study and direct application of intramolecular Diels-Alder reactions to the synthesis of natural products is shown in the following example. Attempts to synthesize the physiologically active (but almost inaccessible) alkaloid pumiliotoxin C (18) in a stereoselective manner led to a study of the intramolecular additions of dienamides (12), X or $Y = \text{O}^{[12]}$. It transpired that the amide (12), $X = \text{H}_2$, $Y = \text{O}$, $R = \text{CH}_3$, is converted at 200°C into the very nearly pure *cis*-fused octahydroquinoline (13), whereas the amide (12), $X = \text{O}$, $Y = \text{H}_2$, $R = \text{C}_2\text{H}_5$, affords, with lower but reversed selectivity, the *trans*-lactam (14) and its *cis*-isomer (13) in the ratio of 3:2. The different courses of the reaction can be due to a preferred coplanar arrangement of the amide and diene units in the corresponding transition states. Incidentally, this investigation provided the impetus for the development of a productive general synthesis of the then unknown *N*-butadieny lamides^[13].

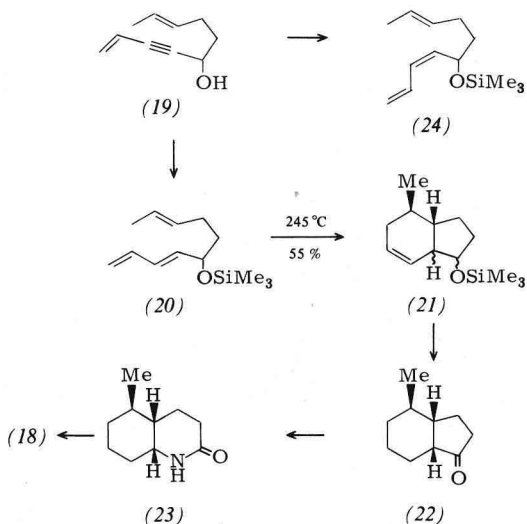


Using this process the readily available amine (15) could be converted in two stages into the dienamide (16). When heated in toluene for 24 h at 215°C in a sealed, silylated glass tube, (16) undergoes efficient intramolecular cycloaddition^[14a, 14b]; the adducts (17) (isolated in 60 to 90 % yield), when hydrogenated and hydrolyzed, finally afforded the racemic alkaloid (18) in 60% yield together with three stereoisomers (in yields of 17, 15, and 2%). The remarkable feature of this synthesis is the simultaneous control over all four chiral centers in the key step (16) \rightarrow (17), dictated by the

trans-configuration of the dienophile and, presumably, by the double-bond character of the amide group.

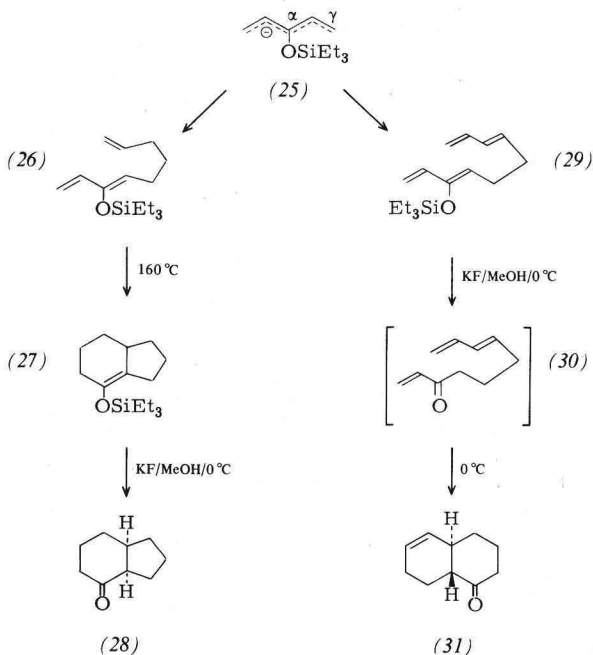


Another route to pumiliotoxin C^[14c] is also based on an intramolecular [4 + 2] addition [(20) \rightarrow (21)], which favors an *endo*-orientation of the three-carbon bridge; hydrogenation and oxidation of the adduct (21) lead thus to an easily separable 2:1 mixture of the *cis*-hydrindanone (22) and its *trans*-



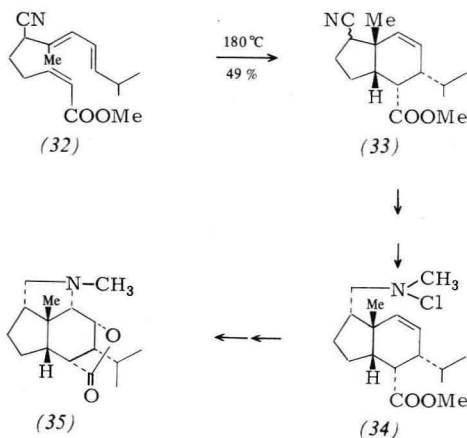
annelated isomer. After Beckmann rearrangement of the main product the carbonyl group of the perhydroquinolone (23) serves for simple and stereoselective introduction of the propyl group. For the preparation of *cis*-2,3,3a,6,7,7a-hexahydro-7a-methyl-1-indenone by thermolysis of *trans*-2-methyl-1,6,8-nonatrien-3-one, see Ref.^[15].

In the synthesis of carbocyclic systems by intramolecular Diels-Alder reactions there occasionally arose the problem of how to prepare the necessary polyene substrates by a rational route. In this connection the (triethylsilyloxy)pentadienyl anion (25) recently became available as a convenient building block for the construction and attachment of functionalized diene and dienophile units because of its reactivity toward electrophiles^[16]. Thus, γ -alkylation of (25) led stereoselectively to (*Z*)-silyloxydienes, for example (26) or (29). The triene (26) underwent an intramolecular cycloaddition at 160°C and after ether cleavage afforded the hydrindanone

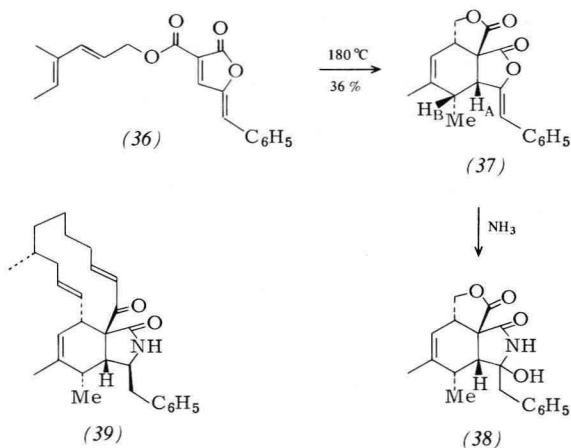


(28) in an overall yield of 55 %. When, however, the tetraene (29) was treated at 0°C with potassium fluoride, the *trans*-octalone (31) was produced directly (in 62 % yield) in an astonishingly smooth (kinetically controlled) *exo*-addition of the unisolable vinyl ketone (30).

A recent attempt to synthesize the alkaloid dendrobine yielded its 8-*epi*-isomer (35)^[17]. The *endo*-oriented addition (32) → (33) occurred with stereochemical control of all chiral centers except the center next to the nitrile group. It is assumed that (32) is formed by thermal isomerization from its (*Z*)-isomer (central double bond) prior to its conversion into (33). In subsequent steps the newly formed double bond of the adduct (33) served as a bifunctional site to close the pyrrolidine and the lactone rings of (35).

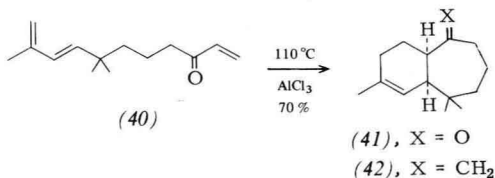


An elegant solution of stereochemical problems is also encountered in the thermal conversion of (36) into (37), which was conceived as the key step for construction of the microbial metabolic product proxiphomine (39)^[18]. The sole adduct obtained, (37), apparently (concluded from the NMR coupling $J_{AB} = 7$ Hz) contains the correct relative configuration of the natural product (39) with respect to all four chiral centers. Treatment of (37) with ammonia led to the isoindole system (38).



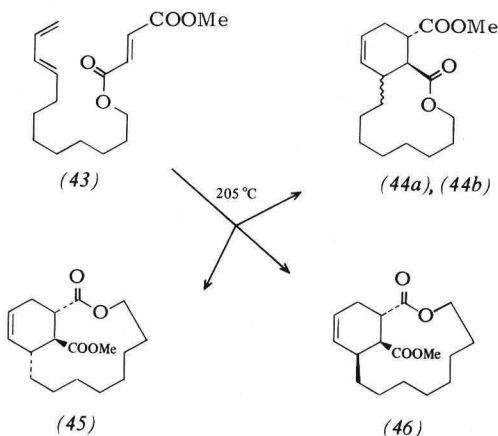
2.1.2. Construction of 6,7- and 6,12-Ring Systems

It can be assumed that bicyclic systems containing seven- or more-membered rings may be constructed by intramolecular addition if the distance between the diene and dienophile units is increased.



The validity of this assumption is demonstrated by the Lewis acid-catalyzed conversion of the triene (40) into the annulated cycloheptanone (41) (70%), which was transformed by methylenation into the sesquiterpene α -himachalene (42)^[19].

The fact that 12- and 13-membered rings can also be closed by intramolecular cycloaddition to *activated* dienophiles is exemplified by the thermolysis of (43)^[20]. When low steady state concentrations are used (to suppress the undesired bimolecular addition), a 7:3:4:1 mixture of the stereo- and position-isomeric products (44a), (44b), (45), and (46) is obtained



in 80 % yield. This (kinetically and/or partially thermodynamically controlled) product ratio reflects the loss of the control over regio- and stereochemistry that characterizes the previously discussed construction of 5,6- and 6,6-ring systems.

2.2. Endocyclic Dienes

Intramolecular cycloadditions of 1,3-dienes which are partly or wholly incorporated in a ring may provide complicated ring systems which are accessible by other routes only with difficulty.

2.2.1. 1-Vinylcycloalkenes

This is illustrated, *inter alia*, by a model study on the synthesis of gibberellic acid in which the cycloaddition (47) → (48) is the key step^[21]. Stereoselective methylation of the cyclohexadiene component in the adduct (48), followed

