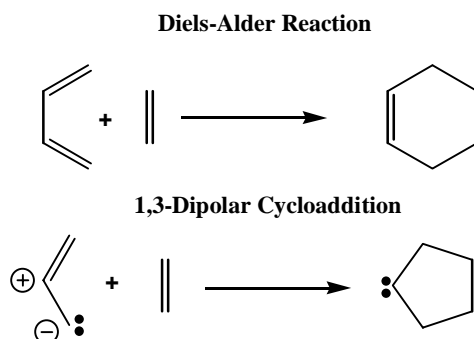


## The Formation of Eight-Membered Rings by Transition Metal-Mediated Cycloaddition Reactions

The formation of eight-membered rings has become increasingly important in organic chemistry, particularly in the synthesis of natural products. Well over one hundred natural products containing eight-membered carbocycles have now been isolated and have become the targets of synthetic projects.<sup>1</sup> These cyclooctanoid species include many terpenoids, as well as several lignans and pigments.<sup>2,3</sup>

There are many strategies for the formation of eight-membered carbocycles, which are among the most difficult of rings to form.<sup>4</sup> These strategies can be broken down into three broad categories: fragmentation reactions, ring expansions, and carbon-carbon bond forming reactions.<sup>2,5</sup> While fragmentations and ring expansions rely on the reaction of a pre-existing ring, carbon-carbon bond forming reactions form a new ring. Among these numerous reactions, cycloadditions are becoming significantly more versatile and are finding increasing use in organic synthesis.<sup>1,6,7,8,9,10,11</sup>

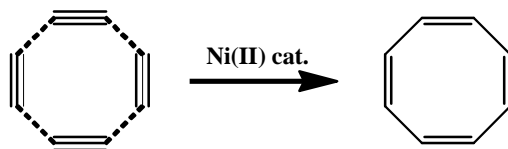
There are two methods of describing a cycloaddition, either a topological or an electronic description.<sup>12,13</sup> The topological description identifies the number of atoms in each fragment joined during the cycloaddition. This is in contrast to the electronic description, which identifies the number of electrons involved in the cycloaddition. Therefore, a typical Diels-Alder reaction is identified as a [4+2] cycloaddition using the topological notation and a  $[\pi 4 + \pi 2]$  cycloaddition using the electronic notation. The differences become apparent with the identification for a 1,3-dipolar addition. For this reaction, the topological notation describes this as a [3+2] cycloaddition, while the electronic notation is a  $[\pi 4 + \pi 2]$  cycloaddition (Figure 1). The topological description is used throughout this abstract.



**Figure 1. Examples of Cycloaddition Reactions.**

There are several advantages to the use of transition metal-mediated cycloadditions.<sup>2,14</sup> With the use of a transition metal, in contrast to thermally or photolytically activated reactions, adjoining fragments are often coordinated to the metal prior to reaction, thus presenting a framework that favors a higher order process over competing pathways as well as a facial-selective method of addition. Coordination can also facilitate activation of relatively inactive species and allow reactions to be run at lower temperatures, often further increasing selectivity. Use of a transition metal can also allow control of stereochemistry, through chirality introduced by a ligand.

The first cycloaddition reaction to form an eight-membered ring was discovered in the early 1940's when Reppe first catalyzed the cyclotetramerization of acetylene with a nickel(0) catalyst (Figure 2).<sup>15</sup> This [2+2+2+2] cycloaddition was a significant improvement over pre-existing methods of forming cyclooctatetraene and provided a glimpse of the potential of transition metal-mediated processes in organic chemistry. Reppe's process can be extended to mono-substituted alkynes, but results in a mixture



**Figure 2. [2+2+2+2] Cycloaddition of Acetylene**

of cyclooctatetraene isomers, and the reaction fails using di-substituted alkynes.<sup>16,17,18</sup> Although of limited use in organic synthesis, cyclooctatetraene and substituted analogues have seen use as a precursor to polyacetylene in ring-opening metathesis polymerization,<sup>19</sup> and its dianion serves as a ligand in lanthanide and actinide complexes.<sup>20</sup>

The [4+4] cycloaddition process was developed nearly 40 years ago, also utilizing a nickel(0) catalyst. In the presence of a phosphine ligand, two equivalents of 1,3-butadiene are cyclodimerized to form cyclooctadiene, as well as vinylcyclohexene and divinylcyclobutane. The necessary use of the phosphine ligand is the means of controlling selectivity in this reaction; a phosphine of low electron donating ability and possessing a large cone angle led to the production of cyclooctadiene in over 90% yield. Altering the phosphine thus leads to different product ratios of cyclooctadiene, vinylcyclohexene and divinylcyclobutane.

Despite the extensive study surrounding the [4+4] cycloaddition of dienes, little progress was made in applying these processes toward organic synthesis.<sup>21,22,23</sup> The use of substituted dienes led to a series of problems, including low reaction rates, difficulty in

cross cycloadditions, and complicated product mixtures. A solution to these problems has been developed by Wender, in which two dienes are tethered via a carbon bridge.<sup>24</sup> Upon cycloaddition, these tethered *bis*-diene species resulted in two fused rings (Figure 3). Further experimentation revealed that use of a three-carbon tether results in high

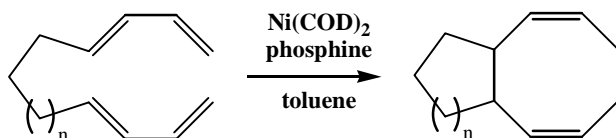


Figure 3. [4+4] Cycloaddition of *bis*-diene.

yields of cis-fused five- and eight-membered rings, in contrast to a four-carbon tether, which results in high yields of trans-fused six- and eight-membered rings. In addition, allylic substitution on the carbon tether results in stereinduction;<sup>25,26</sup> steric factors control the resulting stereochemistry, favoring the diastereomer with equatorial substitution, resulting in diastereomeric ratios of 20:1 or greater. This effect is lost, however, upon movement of the substitution to the homoallylic position, where diastereomeric ratios generally hover around 2:1.

The [4+4] cycloaddition of tethered dienes was subsequently utilized in the formation of the eight-membered ring of (+)-Asteriscanolide, providing the ring formation in the first asymmetric synthesis of a cyclooctane containing terpenoid (Figure 4)<sup>27</sup>. This synthesis provided an example of the utility of the [4+4] cycloaddition, in addition to testing advances in substitution and functional group tolerance.

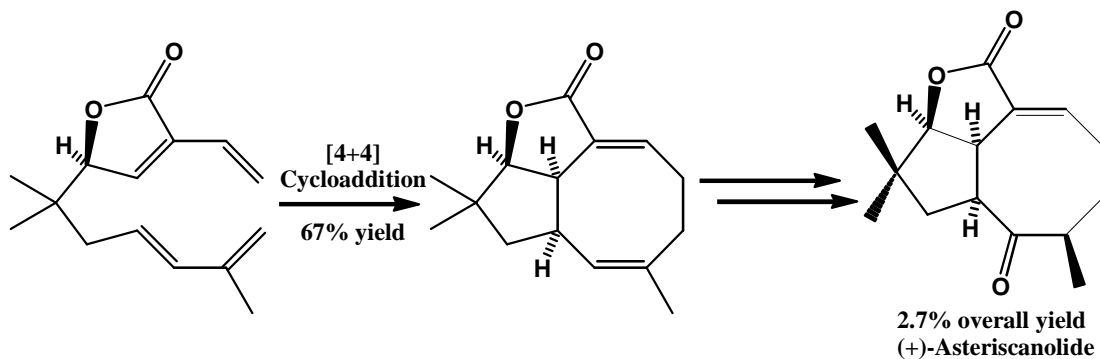


Figure 4. Synthesis of (+)-Asteriscanolide using [4+4] Cycloaddition

Interest in the formation of the taxane skeleton led to further advances of the [4+4] cycloaddition, leading to a type II cycloaddition.<sup>28,29</sup> In this process, the *bis*-diene species is tethered to the terminal position of one diene and to an internal position on the other, rather than to a terminal position of each diene as seen in a type I process. Following the cycloaddition using a three carbon tether, the resulting product is a

bicyclo[5.3.1]undecane species. The use of both a type I and type II cycloadditions are illustrated in formation of the BC and AB rings respectively (Figure 5).

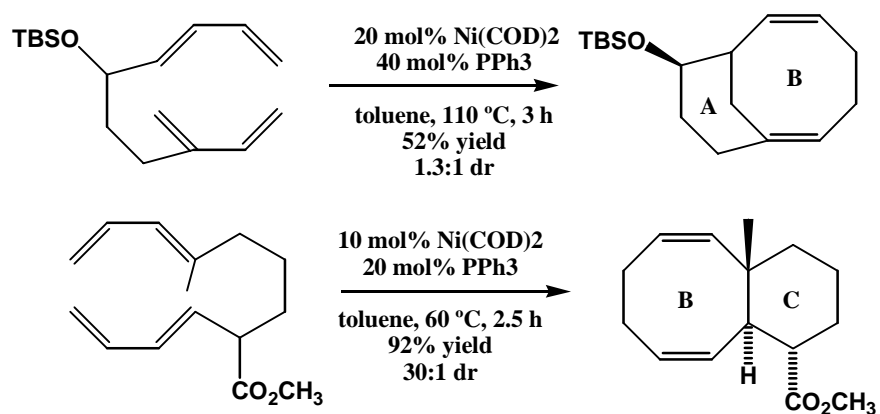


Figure 5. Type II and Type I Cycloadditions in Synthesis of Taxane Skeleton

The [6+2] cycloaddition has also begun to see use in the synthesis of natural products. The most common form of this cycloaddition consists of chromium tricarbonyl coordinated cycloheptatriene undergoing cycloaddition with an electron deficient olefin or alkyne (Figure 6).<sup>30,31</sup>

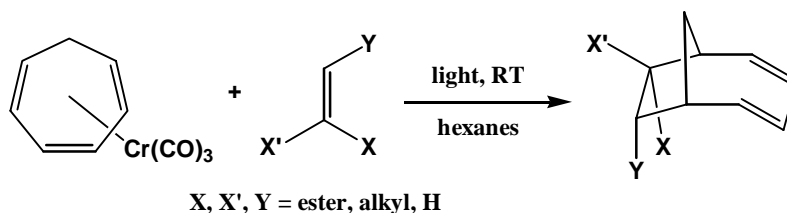
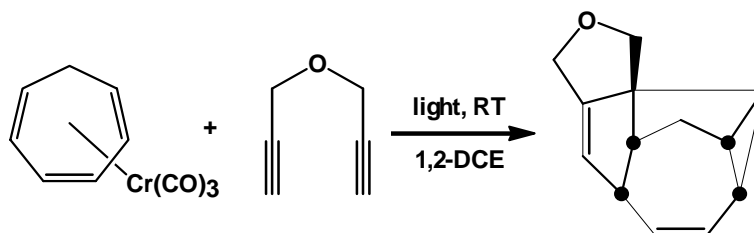


Figure 6. [6+2] Cycloaddition

Significant strides have been made with the [6+2] cycloaddition, allowing a large number of substitutions both on the olefin or alkyne as well as on the cycloheptatriene. Heteroatom substitution on the cycloheptatriene ligand leads to bicyclo[4.2.1]nonane structures in which the smallest bridge contains the heteroatom. Use of nitrogen, usually with an attached ester, provides access into a series of natural products,<sup>32,33</sup> including anatoxin, a strong nerve depolarizing agent used extensively in neurotransmission research.<sup>34,35</sup> Substitution with a sulfone affords a bridged bicyclic species which expels SO<sub>2</sub> upon irradiation, yielding another route to substituted cyclooctatetraene.<sup>36</sup>

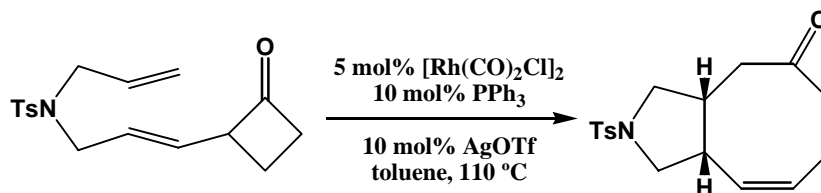
Extremely complex ring systems can be quickly formed using tethered alkynes, as shown in figure 7.<sup>37</sup> This reaction proceeds through a [6+2] cycloaddition and is followed by a [4+2+2] cycloaddition. This single reaction series yields a molecule that



**Figure 7. Complex Ring Structure Formed from Consecutive Cycloaddition Reactions.**

contains 6 new stereocenters, 5 new carbon-carbon bonds, and 4 new rings. Several substitutions and substituents can be added to the reactants, allowing the construction of even more complex and further substituted products.

Wender has recently developed a rhodium catalyzed [6+2] cycloaddition substantially different from previous cycloaddition reactions (Figure 8).<sup>38</sup> This reaction proceeds through cycloaddition of an olefin to a vinylcyclobutanone fragment, leading to a single diastereomer of cis-fused five- and eight-membered rings. This reaction



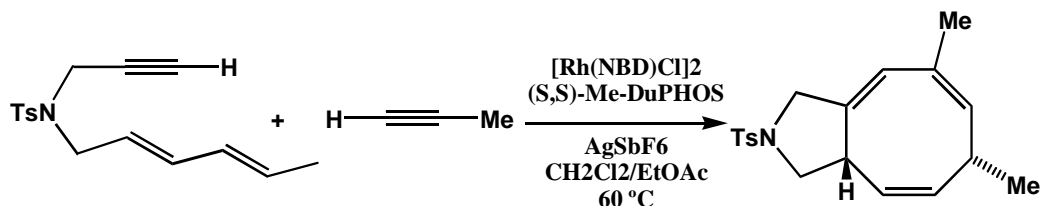
**Figure 8. Rhodium Catalyzed [6+2] Cycloaddition**

proceeds with alkyl substitution of the olefins, allowing the construction of quaternary centers with specific stereochemistry.

The earliest examples of [4+2+2] cycloadditions utilized norbornadiene as the donor of both olefins.<sup>39,40</sup> The constrained arrangement of the olefins led to convenient cycloaddition with 1,3-butadiene. Later advancements and use of chiral phosphine ligands led to a significant enantiomeric excess of the complex carbocyclic products.<sup>41,42</sup> However, due to the complexity and relative inactivity of these rings, these reactions have seen little use in organic synthesis.

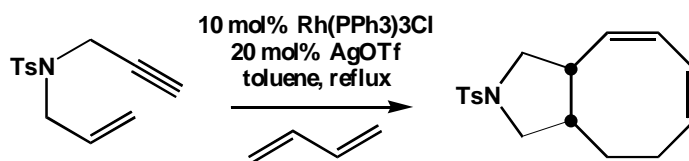
More recent developments include those of Gilbertson and Evans, who both utilize rhodium complexes to catalyze the formation of eight-membered carbocycles through a [4+2+2] cycloaddition. In attempts to catalyze enantioselective Diels-Alder cycloadditions, Gilbertson observed a dimerization of tethered dieneynes in which the alkyne from a second molecule had inserted and resulted in the formation of fused five- and eight-membered rings.<sup>43</sup> Upon optimization of the reaction conditions, the dimerized product could be isolated in up to 80% yield. This led to the use of external alkynes in a

cross [4+2+2] cycloaddition process which yielded fused five- and eight-membered rings with variety of substituents (Figure 9).



**Figure 9. Intermolecular [4+2+2] Reaction to form Single Diastereomer of Fused Five- and Eight-Membered Rings**

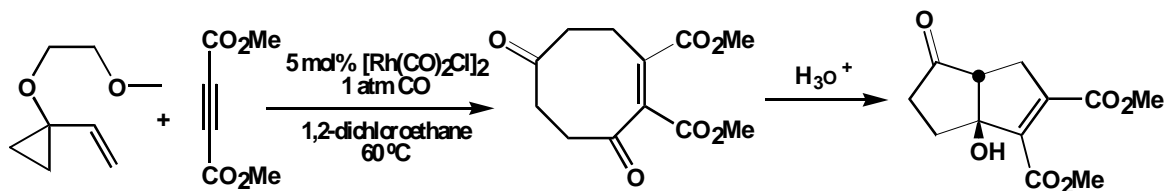
Evans studied a similar reaction, in which a tethered enyne underwent cycloaddition with 1,3-butadiene.<sup>44</sup> Upon addition of different silver(I) salts, the product ratio can be shifted from favoring the dimerization of the ene-yne to the cross cycloaddition of the enyne with 1,3-butadiene (Figure 10). This system has been



**Figure 10. Intermolecular [4+2+2] Reaction using 1,3-butadiene.**

extended to provide diastereoselectivity as well as a three component coupling reaction, both in excellent yields.

Wender has also recently published a [5+2+1] cycloaddition route to the formation of eight-membered rings (Figure 11).<sup>45</sup> These reactions undergo coupling of a



**Figure 11. [5+2+1] Cycloaddition and Subsequent Transannular Closure to Form Bicyclo[3.3.0]octane Species.**

vinylcyclopropane fragment with an alkyne under an atmosphere of carbon monoxide. This results in a three-component coupling and the formation of an eight-membered ring. Due to the acidic workup, however, the primary product of this cycloaddition is a bicyclic structure consisted of two fused five-membered rings, a result of the acid-catalyzed

transannular closure. Optimized conditions afford this bicyclic structure in over 99% yield.

Malacria has recently published a series of papers describing the use of consecutive cycloadditions to quickly form complex eight-membered ring systems, including the ABC system of the taxanes, as shown in figure 12.<sup>46,47</sup> In this example, a significantly functionalized product undergoes a selective [2+2+2] cycloaddition of the

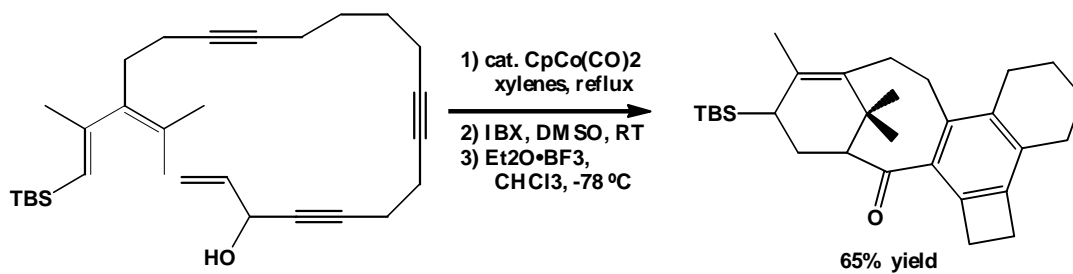


Figure 12. Use of sequential cycloadditions to form taxane ABC ring system.

alkynes to form three fused rings. This is followed by oxidation and a catalyzed Diels-Alder cycloaddition in order to form the completed ABC ring system, with additional substitution, in 65% yield.

Great advances have been made in the development of cycloaddition reactions for use in organic synthesis, and the use of transition metals has significantly improved the capability of these reactions. Studies are currently underway to obtain greater understanding of the processes that form these complex ring systems. Improving the tolerance and selectivity of functional group, gaining greater control of stereochemistry, and the development of more versatile substrates are all advances that may lead to simplified routes to the syntheses of many cyclooctanoid natural products.

## References:

- 1 "Progress in the Construction of Cyclooctanoid Systems: New Approaches and Applications to Natural Product Syntheses" Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881.
- 2 "The Synthesis of Carbocyclic Eight-Membered Rings" Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
- 3 "[4+4] Cycloaddition Reactions in the Total Synthesis of Naturally Occurring Eight-Membered Ring Compounds" Kaupp, G. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 422.
- 4 "Ring Closure of Bifunctional Chain Molecules" Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.
- 5 "Metal-Mediated Synthesis of Medium-Sized Rings" Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

- 
- 6 “Transition Metal-Catalyzed Carbocyclizations in Organic Synthesis” Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.
- 7 “Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis” Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.
- 8 “Toward the Ideal Synthesis. New Transition Metal-Catalyzed Reactions Inspired by Novel Medicinal Leads” Wender, P. A.; Bi, F. C.; Gamber, G. G.; Gosselin, F.; Hubbard, R. D.; Scanio, M. J. C.; Sun, R.; Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25.
- 9 “Transition Metal Promoted Higher-Order Cycloaddition Reactions in Organic Synthesis” Rigby, J. H. *Acc. Chem. Res.* **1993**, *26*, 579.
- 10 “Transition Metal-Mediated Cycloaddition Reactions” Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49.
- 11 “The [4+4] Cycloaddition and its Strategic Applications in Natural Product Synthesis” Sieburth, S. McN.; Cunard, N. T. *Tetrahedron*, **1996**, *52*, 6251.
- 12 “Metal-Assisted Cycloaddition Reactions in Organotransition Metal Chemistry” Fruhauf, H.-W. *Chem. Rev.* **1997**, *97*, 523.
- 13 “Cycloadditions—Definition, Classification, and Characterization” Huisgen, R. *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 321.
- 14 “Metal-Mediated [6+2] Cycloadditions of Alkynes to Cycloheptatriene and N-Carboxyazepine” Chaffee, K.; Hue, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancete, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900.
- 15 Jolly, P. W.; Wilke, G. *The Organic Chemistry of Nickel*, Academic Press: New York, 1975.
- 16 “Two Complementary Syntheses of Symmetrically-Tetrasubstituted Cyclooctatetraenes” Boussie, T. R.; Streitwieser, A. *J. Org. Chem.* **1993**, *58*, 2377.
- 17 “Thermische und Photochemische Umsetzungen von Acetylenen mit Metallcarbonylen-IV” Wagner, F.; Meier, H. *Tetrahedron*, **1974**, *30*, 773.
- 18 “Cyclooligomerization with Transition Metal Catalysts” Heimbach, P. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 975.
- 19 “Substituted Polyacetylenes Through the Ring-Opening Metathesis Polymerization (ROMP) of Substituted Cyclooctatetraenes: A Route into Soluble Polyacetylene” Gorman, C. B.; Ginsburg, E. J.; Sailor, M. J.; Moore, J. S.; Jozefiak, T. H.; Lewis, N. S.; Grubbs, R. H.; Marder, S. R.; Perry, J. W. *Synth. Met.* **1991**, *41*, 1033.
- 20 “Substituted Cyclooctatetraenes as Ligands in *f*-Metal Chemistry” Roesky, P. W. *Eur. J. Inorg. Chem.* **2001**, 1653.
- 21 “Nickel-Catalyzed Oligomerization of Functionalized Conjugated Dienes” Tenaglia, A.; Brun, P.; Waegell, B. *J. Organometallic Chem.* **1985**, *285*, 343.
- 22 “On the Mechanism of the Nickel-Catalysed Regioselective Cyclodimerization of Isoprene” van Leeuwen, P. W. N. M.; Roobeek, C. F. *Tetrahedron*, **1981**, *37*, 1973.
- 23 “Contributions to Organo-Nickel Chemistry” Wilke, G. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 185.

- 
- 24 "Nickel-Catalyzed Intramolecular [4+4] Cycloadditions: A New Method for the Synthesis of Polycycles Containing Eight-Membered Rings" Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678.
- 25 "Nickel-Catalyzed Intramolecular [4+4] Cycloadditions: 2. Allylic Stereinduction and Modelling Studies in the Preparation of Bicyclo[6.4.0]dodecadienes" Wender, P. A.; Ihle, N. C. *Tetrahedron Lett.* **1987**, *28*, 2451.
- 26 "Steroselective Organometallic Reactions: A Force Field Study of  $\pi$ -Allyl Intermediates in Nickel(0)-Catalyzed Cycloadditions" Gugelchuk, M. M.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 330.
- 27 "Nickel-Catalyzed Intramolecular [4+4] Cycloadditions: 4. Enantioselective Total Synthesis of (+)-Asteriscanolid" Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904.
- 28 "Nickel-Catalyzed Intramolecular [4+4] Cycloadditions: 5. The Type II Reaction in the Synthesis of Bicyclo[5.3.1]undecadienes" Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089.
- 29 "Intramolecular Nickel Catalyzed Cycloadditions of bis-Dienes: 3 Approaches to the Taxane Skeleton" Wender, P. A.; Snapper, M. L. *Tetrahedron Lett.* **1987**, *28*, 2221.
- 30 "Transition Metal Template Controlled Cycloaddition Reactions. An Efficient Chromium(0)-Mediated [6 $\pi$ +2 $\pi$ ] Cycloaddition" Rigby, J. H.; Henshilwood, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 5122.
- 31 "Chromium(0)-Promoted Higher-Order Cycloaddition Reactions in Organic Synthesis" Rigby, J. H. *Tetrahedron*, **1999**, *55*, 4521.
- 32 "Chromium(0) Promoted [6 $\pi$ +2 $\pi$ ] Cycloaddition Reactions" Rigby, J. H.; Ateeq, H. S.; Charles, N. R.; Henshilwood, J. A.; Short, K. M.; Sugathapala, P. M. *Tetrahedron*, **1993**, *49*, 5495.
- 33 "Catalytic Chromium(0)-Promoted Higher-Order Cycloaddition Reactions" Rigby, J. H.; Short, K. M.; Ateeq, H. S.; Henshilwood, J. A. *J. Org. Chem.* **1992**, *57*, 5290.
- 34 "Metal Promoted Higher-Order Cycloaddition Reaction. A Facile Entry into Substituted Eight- and Ten-Membered Carbocycles" Rigby, J. H.; Ateeq, H. S.; Kruger, A. C. *Tetrahedron Lett.* **1992**, *33*, 5873.
- 35 "Enantiodivergent Synthesis of (+)- and (-)-Anatoxin from L-Glutamic Acid" Sardina, F. J.; Howard, M. H.; Morningstar, M.; Rapoport, H. *J. Org. Chem.* **1990**, *55*, 5025.
- 36 "A Convenient Synthesis of 1,2-Disubstituted Cyclooctatetraenes" Rigby, J. H.; Warshakoon, N. C. *Tetrahedron Lett.* **1997**, *38*, 2049.
- 37 "Studies of Chromium(0)-Mediated Three Component Cycloaddition Reactions" Rigby, J. H.; Heap, C. R.; Warshakoon, N. C. *Tetrahedron*, **2000**, *56*, 2305.
- 38 "Transition Metal-Catalyzed [6+2] Cycloadditions of 2-Vinylcyclobutanones and Alkenes: A New Reaction for the Synthesis of Eight-Membered Rings" Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.
- 39 "Über die katalytische Anlagerung von Olefinen und Alkinen an Norbornadien mit Ni<sup>0</sup>-Verbindungen und einem neuen Ni<sup>II</sup>-Komplex" Schrauzer, G. N.; Glockner, P. *Chem. Ber.* **1964**, *97*, 2451.
- 40 "Catalytic Behavior of Some Ziegler-Natta Catalysts in the Norbornadiene-Butadiene Codimerization" Carbonaro, A.; Cambisi, F.; Dall'Asta, G. *J. Org. Chem.* **1971**, *36*, 1443.
- 41 "Cobalt-Catalyzed [2 $\pi$  + 2 $\pi$  + 2 $\pi$ ] (Homo Diels-Alder) and [2 $\pi$  + 2 $\pi$  + 4 $\pi$ ] Cycloadditions of Bicyclo[2.2.1]hepta-2,5-dienes" Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863.

- 
- 42 "Enantioselective Cobalt-Catalyzed  $[4\pi + 2\pi + 2\pi]$  Cycloadditions" Lautens, M.; Tam, W.; Sood, C. *J. Org. Chem.* **1993**, 58, 4513.
- 43 "Rhodium Catalyzed  $[4+2+2]$  Cycloaddition and Alkyne Insertion: A New Route to Eight-Membered Rings" Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, 124, 8784.
- 44 "Intermolecular Transition Metal-Catalyzed  $[4+2+2]$  Cycloaddition Reactions: A New Approach to the Construction of Eight-Membered Rings." Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, 124, 8782.
- 45 "Three-Component Cycloadditions: The First Transition Metal-Catalyzed  $[5+2+1]$  Cycloaddition Reactions" Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, 124, 2876.
- 46 "The  $[4+2]$ ,  $[2+2]$  Strategy for the Construction of the AB Taxane Ring System" Phansavath, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1998**, 39, 1561.
- 47 "New Efficient Construction of the ABC Core of the Taxoids via a Sequence of Consecutive Cobalt(I)-Mediated  $[2+2+2]$  and  $[4+2]$  Cyclizations" Petit, M.; Chouraqui, G.; Phansavath, P.; Aubert, C.; Malacria, M. *Org. Lett.* **2002**, 4, 1027.