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The First Metal-Catalyzed Intramolecular [5+2] Cycloadditions of Vinylcyclopropanes and Alkenes: Scope, Stereochemistry, and Asymmetric Catalysis§

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Abstract

The first studies of the metal-catalyzed [5+2] cycloadditions of vinylcyclopropanes and alkenes are described. These reactions proceed with exceptional diastereoselectivity and in good to excellent yields. The effect of tether and substituent variations are examined. In addition, preliminary studies show that enantioselective cycloadditions can be achieved through the use of catalysts modified with chiral phosphine ligands. This novel, general, and efficient procedure provides a fundamentally new approach to the synthesis of a variety of products of structural and medicinal significance.

Introduction

The continuing evolution of organic synthesis is heavily dependent on the discovery of reactions and strategies that allow for the production of complex products from fundamental building blocks in a safe, practical, and environmentally acceptable fashion [1a,b]. Cycloaddition reactions represent powerful procedures for achieving these objectives as they generally allow for the formation of multiple bonds and multiple stereogenic centers in a single synthetic operation based on simple, often commercially available, starting materials [1]. One only needs to consider the utility of the Diels-Alder reaction (Scheme 1a) in the synthesis of six-membered ring compounds to appreciate the value of such processes in fundamental and applied science [2].

§*Dedicated to a true pioneer and friend Professor Madeleine M. Joullie in celebration of forty years of distinguished teaching and research at the University of Pennsylvania*

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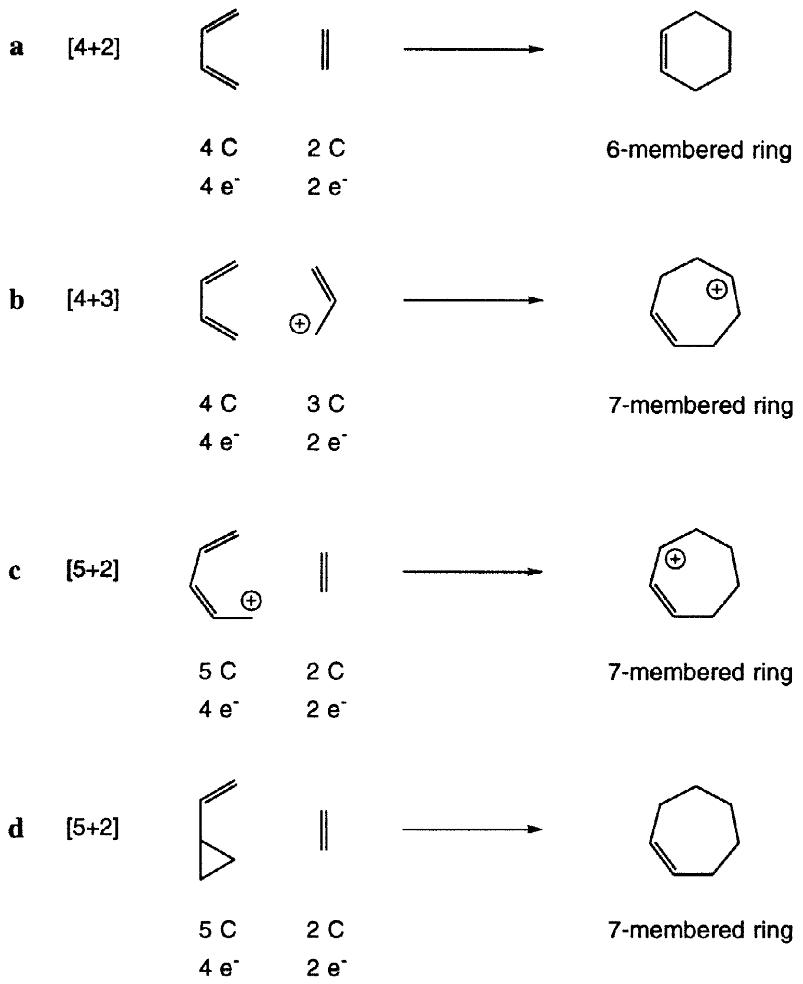
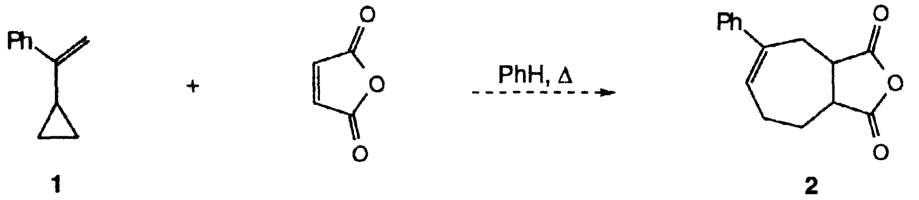
Scheme 1. The Diels-Alder Cycloaddition and Isoelectronic Variants for the Synthesis of Seven-Membered Rings



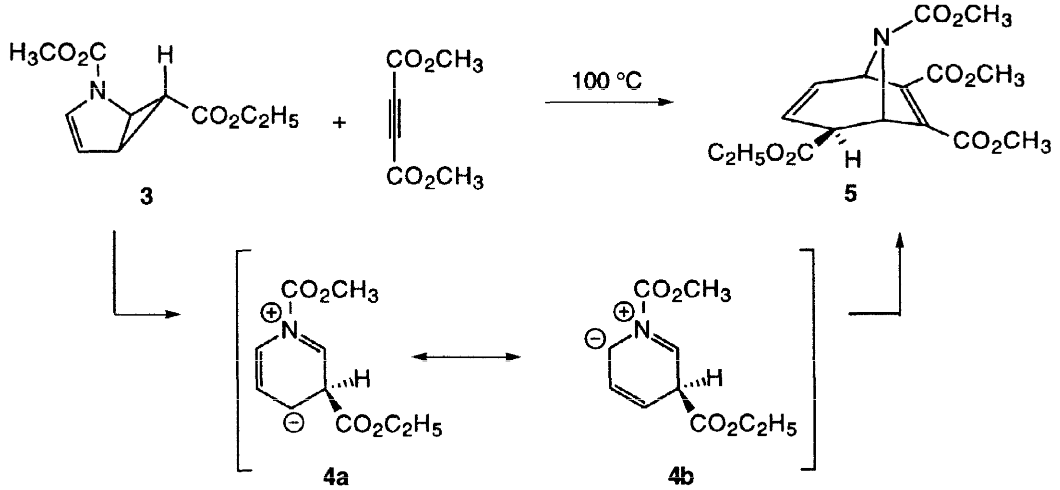
In contrast to the situation with six-membered rings, cycloaddition methods for seven-membered ring synthesis have been few in number and limited in scope [3,4], even though targets containing a seven-membered ring are numerous and are frequently biochemically and medicinally significant [5]. Methods for seven-membered ring synthesis have been largely limited to two isoelectronic variants of the Diels-Alder cycloaddition [6,7], although other approaches to seven-membered rings have been reported [8]. In one variant (Scheme 1b), the dienophile (two pi-electrons, two carbons) of the Diels-Alder reaction is replaced by an allyl cation (two pi-electrons, three carbons). Reaction of the allyl cation with a suitable diene allows for the formation of a seven-membered ring through a [4+3] cycloaddition [3,6,9]. The second variant (Scheme 1c) involves substitution of the diene (four pi-electrons, four carbons) with a pentadienyl cation (four pi-electrons, five carbons), providing a process for the synthesis of seven-membered rings through a [5+2] cycloaddition [4,7]. Both cases involve the often difficult generation of ionic or zwitterionic intermediates.

Recognizing the often similar reactivities of cyclopropanes and alkenes [10], Sarel and Breuer examined another cycloaddition approach to form seven-membered rings in which vinylcyclopropanes were used in place of conventional Diels-Alder dienes (Scheme 1d). In 1959, they reported that the reaction of the phenyl substituted vinylcyclopropane **1** and maleic anhydride produced a homolog of the Diels-Alder cycloadduct, specifically the seven-membered ring product **2** (eqn. 1) [11]. However, subsequent attempts to reproduce this result in other laboratories were unsuccessful [12]. Moreover, reports on the extension of this process even to other simple vinylcyclopropanes have not appeared. Subsequently, it was shown that vinylcyclopropanes do indeed react with some specially activated alkenes (e.g., tetracyanoethylene), although the initial product is a [2+2] cycloadduct [13].



(1)

In contrast to simple vinylcyclopropanes, certain bicyclic variants have been shown to react with activated alkenes and alkynes to produce a seven-membered ring product. An early example of this process is seen in the 1971 report from Fowler on the conversion of homopyrrole **3** to cycloadduct **5** (eqn. 2) [14]. While both concerted and stepwise mechanisms are possible for this reaction, preliminary studies were found to support initial opening of the homopyrrole to zwitterion **4** and capture of the latter in a dipolar cycloaddition.



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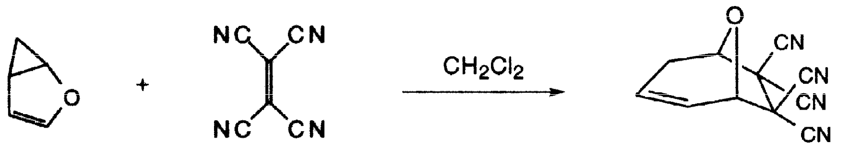
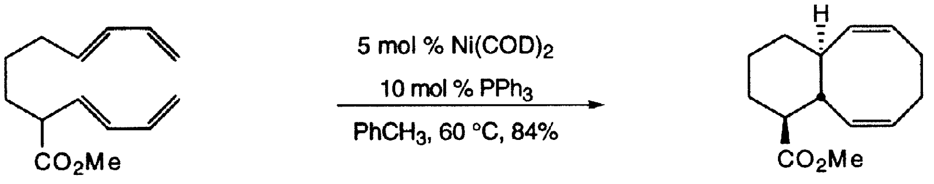
A similar process has been reported by Herges and Ugi for the reactions of homofurans with activated pi-systems (eqn. 3), although these authors favored a concerted



(3)

mechanism [15]. In general, however, these reactions have been limited to systems in which the vinylcyclopropane is constrained in a bicyclic array and is activated by heteroatom substitution or strain [10,16]. These limitations and the status of vinylcyclopropanes as components in [5+2] cycloadditions were effectively summarized by Herges in a 1988 review in which he noted that "vinylcyclopropanes do not react even with the strongest dienophiles" [17].

Beginning in the early 1980's, in research that eventually led to a solution to the problems encountered with vinylcyclopropanes in [5+2] cycloadditions, our group became interested in *the use of transition metals to catalyze reactions that are otherwise impossible or difficult to achieve using conventional methods* [18]. The [4+4] cycloaddition of a *bis*-diene is representative, as it is forbidden under thermal conditions and is often inefficient under photochemical conditions relative to the entropically favored [2+2] cycloaddition process. The groups of Reed and particularly Wilke, as well as others, have shown that these limitations on the reactivity of some dienes can be overcome through the use of transition metal catalysts [19]. However, severe limitations were encountered in attempts to extend this process to all but the simplest of dienes, thereby precluding its use in complex molecule synthesis. In 1986, Wender and Ihle reported the first examples of the metal-catalyzed intramolecular [4+4] cycloadditions of *bis*-dienes (eqn. 4) [20]. Treatment of *bis*-diene **8** with

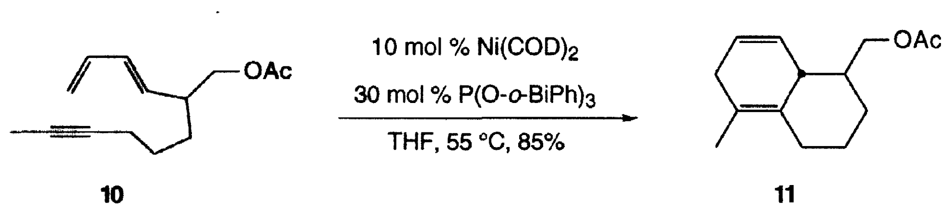


8 **9**

(4)

a catalyst system derived from 5 mol % $Ni(COD)_2$ and 10 mol % PPh_3 in toluene at 60 °C gave bicycle **9** in 84% with >99:1 stereoselectivity (as determined by GC analysis). The [4+4] cycloaddition reaction tolerates a range of substituents and accordingly provides access to a variety of synthetic targets [21], including asteriscanolide, salsolene oxide, and the ring system of the ophiobolanes.

We have subsequently demonstrated that metal catalysis can also be used to effect otherwise difficult or impossible Diels-Alder reactions [22]. For example (eqn. 5), the unactivated alkyne **10** undergoes decomposition more readily than Diels-Alder cycloaddition

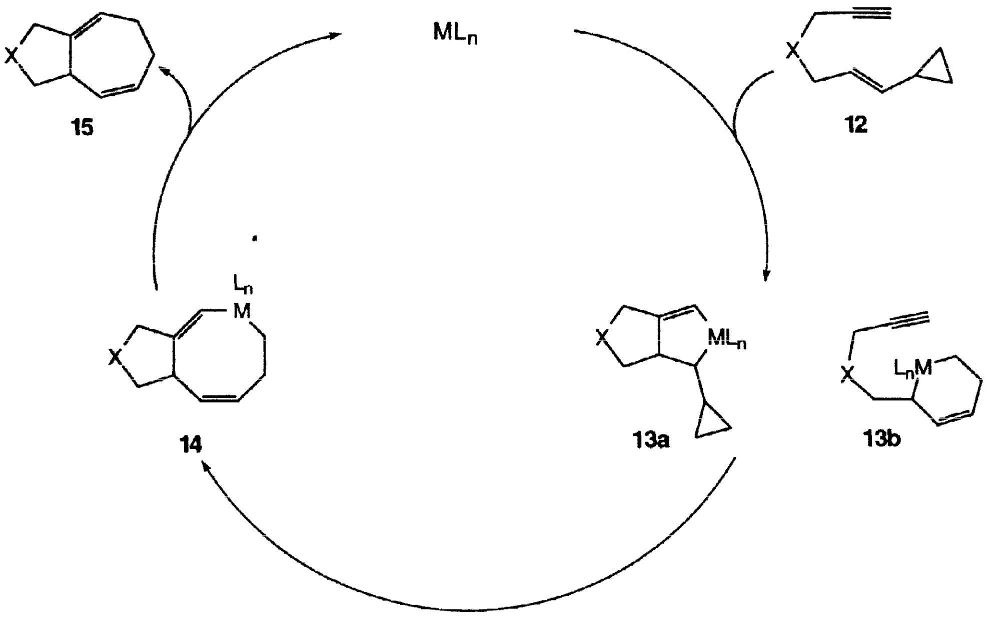


(5)

under thermal conditions. In contrast, in the presence of certain nickel (0) catalysts, this same substrate undergoes a multistep, metal-mediated [4+2] cycloaddition to provide the otherwise inaccessible "Diels-Alder" cycloadduct **11** [23]. Catalyst control over stereoselectivity and regioselectivity, as well as applications to the synthesis of steroids, terpenes, and alkaloids, have subsequently been reported [24].

Given the success of transition metal-catalyzed [4+4] and [4+2] cycloadditions, the difficulties encountered in attempts to effect a [5+2] cycloaddition with vinylcyclopropanes under conventional conditions, coupled with the observation that various transition metals are capable of cleaving cyclopropanes [25], our group began to investigate whether transition metal catalysts could be used to effect the aforementioned [5+2] cycloaddition between vinylcyclopropanes and alkynes. Our reasoning followed the analysis summarized in Scheme 2. According to this analysis, coordination of the metal species to yne-vinylcyclopropane **12**

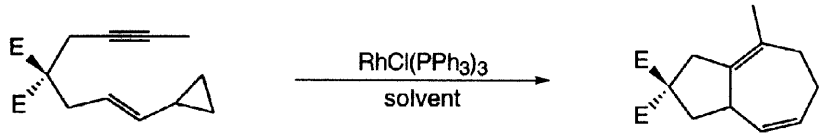
Scheme 2. The Design Concept for Metal-Mediated [5+2] Cycloadditions



would lead to the formation of metallacyclopentene **13a** through a well-precedented cyclometallation pathway. With a carbon-metal bond positioned proximate to a cyclopropane, **13a** would be expected to undergo strain driven ring expansion to provide metallacyclooctadiene **14**. Alternatively, initial reaction of **12** might involve metal coordination to the vinylcyclopropane followed by rearrangement to produce **13b**. Alkyne association with the metal center in **13b** followed by serial C-C bond formation would provide an alternative path to **14**. Subsequent reductive elimination of **14** would lead to the 5,7-fused bicyclic product **15**, *representing overall a potential catalytic mechanism for achieving the long sought [5+2] cycloaddition of a vinylcyclopropane and an alkyne.*

In 1995, we reported that this approach can indeed be reduced to practice and serves as an exceptionally efficient and fundamentally new process for the formation of seven-membered rings [26,27]. As illustrated in Table 1, yne-vinylcyclopropane **16** (E=CO_2Me),

Table 1. Rhodium-Catalyzed [5+2] Cycloaddition of Yne-Vinylcyclopropane 16



16 **17**

entry	solvent	additive	temp (°C)	time (h)	yield (%)
1	$PhCH_3$	none	110	48	84
2	CF_3CH_2OH	none	55	19	90-95
3	$PhCH_3$	AgOTf	110	0.3	83

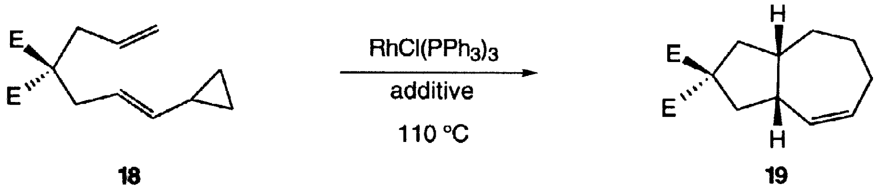
in the presence of 10 mol % $RhCl(PPh_3)_3$ in toluene at 110 °C, undergoes a [5+2] cycloaddition to provide cycloadduct **17** in 84% yield. Remarkably, when the polarity of the solvent is increased, the reaction proceeds more rapidly even at a lower temperature, presumably due to facilitated ligand dissociation. The use of AgOTf, which precipitates AgCl and thereby irreversibly forms a cationic rhodium(I) species, is a particularly effective additive. *Thus, when the cycloaddition of **16** is conducted in the presence of 0.5 mol % $RhCl(PPh_3)_3$ and 0.5 mol % AgOTf in toluene at 110 °C cycloadduct ,17 is obtained in only 20 minutes and in 83% yield.* Subsequent studies have revealed that this reaction is general for a variety of alkynes, including terminal, internal, electron rich, electron poor, conjugated, and sterically encumbered systems.

Having established the viability of a metal-catalyzed [5+2] cycloaddition, we subsequently sought to address questions related to its generality, mechanism, and utility in synthesis. The extension of this process to alkenes was considered to be of great importance for several reasons. The use of alkene components set the stage for the first investigation of the relative stereochemistry associated with this new reaction class. Secondly, the alkene [5+2] cycloaddition would provide direct access to ring systems that are otherwise difficult to obtain using existing methods, opening a new range of strategic opportunities for the synthesis of targets containing seven-membered rings. Thirdly, the issue of whether alkenes could be used in place of alkynes was as yet unaddressed despite being of great importance and non-trivial, particularly since we previously found that a similar change was not tolerated in metal-catalyzed [4+2] cycloadditions without a corresponding change in the metal catalyst [23,24]. We describe herein the first studies on the [5+2] cycloadditions of alkenes and vinylcyclopropanes including a preliminary investigation of asymmetric catalysis of such reactions. As documented below, these reactions have been found to proceed with remarkable efficiency and selectivity [27].

Results and Discussion

Our investigation began with substrate **18** (Table 2). Treatment of this compound with a catalyst prepared from 0.1 mol % $RhCl(PPh_3)_3$ and 0.1 mol % AgOTf, gives cycloadduct **19** in 86-90% isolated yield. Only a *single* diastereomer is formed, as determined by HPLC analysis of the crude reaction mixture. The *cis*-fused stereochemistry of this cycloadduct was assigned on the basis of the planar symmetry of its hydrogenation product as determined by ^1H and ^{13}C NMR spectroscopy. The corresponding *trans*-fused cycloadduct would, upon hydrogenation, provide a product with a C_2 symmetry axis and a correspondingly distinct ^{13}C NMR spectrum.

Table 2. Rhodium-Catalyzed [5+2] Cycloaddition of Ene-Vinylcyclopropane 18



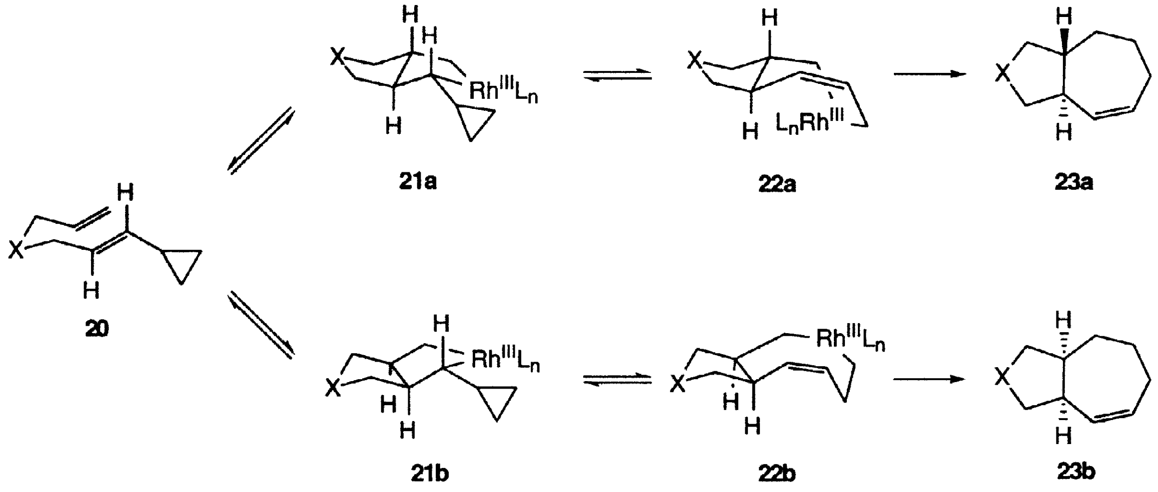
entry	mol % $RhCl(PPh_3)_3$	additive[a]	concentration	time	yield
1	0.1	AgOTf	1.0 M	15 h	90%
2[b]	0.1	AgOTf	1.0 M	17 h	86%
3	0.1	AgOTf	0.4 M	17 h	88%
4	1	AgOTf	0.05 M	5 h	93%
5	5	AgOTf	0.01 M	2 h	91%
6	10	none	0.005 M	2.5 h	91%

[a] mol % AgOTf = mol % $RhCl(PPh_3)_3$. [b] Reaction run on 1 g scale.

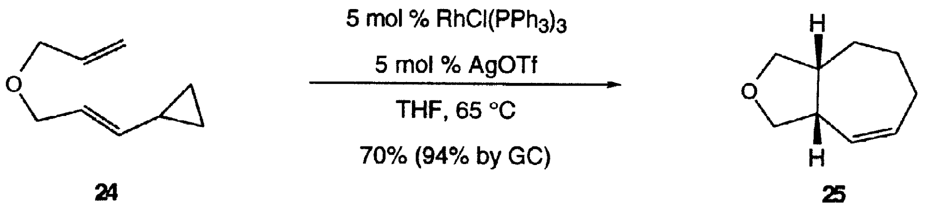
Subsequent studies have shown that this reaction is equally effective over the milligram to gram scale examined thus far. The process is expected to be suitable for even larger scale cycloadditions, a point that is under investigation. In this context, it is noteworthy that the cycloaddition proceeds even at substrate concentrations of up to 5M, in which case the solvent to substrate volume ratio is approximately 1:1. At concentrations above 5M, oligomerization reactions arise. Quite apart from the initial thrust of this study, the resulting oligomers are novel and certainly merit further investigation, although such studies are beyond the immediate scope of this investigation. As is normally found, the reaction time varies with concentration and amount of catalyst. Finally, the reaction can also be effected in the absence of AgOTf, although our general finding is that such conditions require longer reaction times.

A preliminary mechanistic rationale for the diastereoselectivity of the cycloaddition of **18** is presented in Scheme 3. As illustrated for only the cyclometallation mechanism, the [5+2] cycloaddition of an alkene and a vinylcyclopropane could give two diastereoisomeric products, **23a** and **b**. The stereochemistry of these cycloadducts arises during the initial cyclometallation process leading to **21a** and **21b** and is fixed by the turnover of these intermediates to products. The formation of **23b** thus reflects a kinetic preference for reaction via the *cis*-fused intermediates **21b** and **22b**, relative to their *trans*-fused counterparts. It is not clear at present whether the rate determining step in this sequence is associated with the initial cyclometallation process or the further processing of these and related metallacyclic intermediates. Computational and mechanistic studies are currently being conducted to define the relative energetics of these and related competing paths.

Scheme 3. Analysis of Stereoselectivity in the [5+2] Cycloaddition



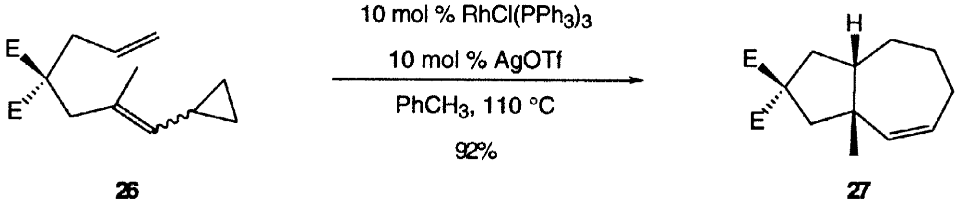
Concurrent with these mechanistic studies, we have initiated several studies directed at elucidating the scope of this new reaction. An issue of importance in this context is whether the geminal diester moiety in the tether of **18** is required for efficient cycloaddition. The cycloaddition of ene-vinylcyclopropane **24** (eqn. 6), which possesses an ether linkage, was examined for this purpose. When **24** is treated 5 mol % RhCl(PPh$_3$)$_3$ in the presence of 5 mol % AgOTf, the *cis*-fused cycloadduct **25** is gratifyingly produced within 10 h in 94% yield (as determined by GC analysis). The isolated yield in this case is lower due to the



(6)

volatility of **25**. In agreement with our previous results [26], this result clearly indicates that geminal substitution is not required for efficient reaction. Moreover, it demonstrates that this cycloaddition proceeds faster than alkene isomerization, a potentially competing process which is also mediated by Rh(I) catalysts [28]. This study further shows that there is generality to the previously observed stereoselectivity. The stereochemistry of this cycloadduct was established by the nOe (3.6%) exhibited between the ring junction protons.

The next substrates for study (**26** and **28**) were selected in order to determine whether this process could be used for the introduction of quaternary centers, a rather difficult synthetic objective even with cycloadditions such as the Diels-Alder process. Of special note is the number of natural products that incorporate an angular methyl group into a bicyclo[5.3.0]decane ring system [5]. Methyl-substituted substrates **26** (*E*:*Z* = 5.5:1) and **28** (eqns. 7 and 8) react rapidly, typically in less than 1 hour, and with high efficiency (>90%) to afford exclusively the *cis*-fused products **27** and **29**, respectively. In these cases, AgOTf is required for clean conversion. In its absence, decomposition occurs more rapidly than cycloaddition. At higher substrate concentrations and lower catalyst loads, the cycloadditions of **26** and **28** are also successful, although the increase in the efficiency of the reaction is also accompanied by a slight reduction in yield. The stereochemistries of cycloadducts **27** and **29** were assigned on the basis of their conversion (hydrogenation) to a common product and the nOe (4.0%) exhibited between the angular methyl and ring junction proton of **29**.



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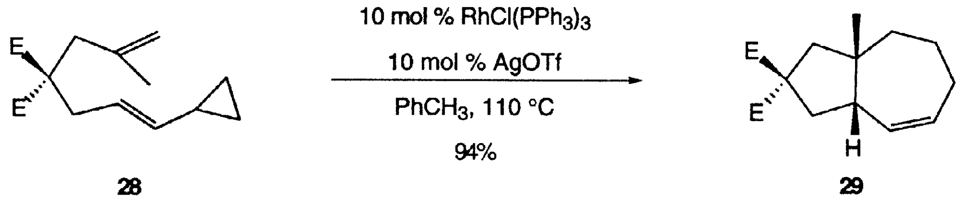
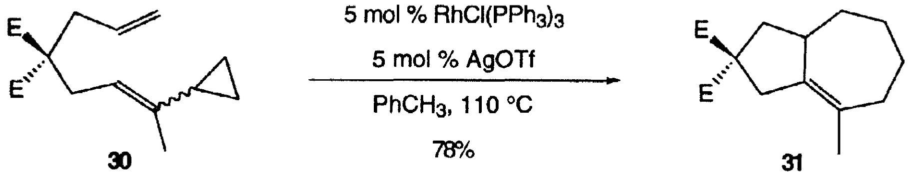


(8)

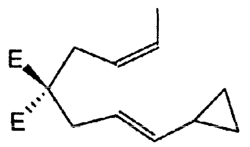
Attempts to effect cycloadditions of substrates which would produce two angular quaternary centers are unproductive.

Continuing our investigation of the effect of methyl substitution of the alkene subunits, we prepared substrates **30**, **32**, and **33**. Methyl substitution of the alkene group of the vinylcyclopropane is tolerated, as evidenced by the cycloaddition of **30** (*E*:*Z* = 6.5:1) which provides **31** in 78% yield (eqn. 9). In this case, the initially produced cycloadduct undergoes a secondary isomerization mediated by the Rh(I) catalyst to produce **31**. At lower temperatures, this isomerization is not complete and thus results in a mixture of products. While this overall cycloaddition-isomerization process represents an interesting *catalytic cascade*, a process of growing importance in synthesis, isomerization of the initial cycloadduct in related reactions can be inhibited, if needed, by a change in catalyst [29].



30 **31** (9)

In contrast to the efficient cycloadditions of methyl substituted substrates **26**, **28**, and **30**, cycloadditions of the corresponding methyl substituted alkenes **32** and **33** are largely unsuccessful. While a detailed analysis of the resultant complex product mixtures has not been conducted, it appears that products arising from β-hydride elimination and ring opening pathways are formed in these cases. It is noteworthy however that even the corresponding phenyl substituted alkenes fail to react efficiently suggesting that steric effects are also of consequence in these cases.



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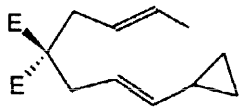

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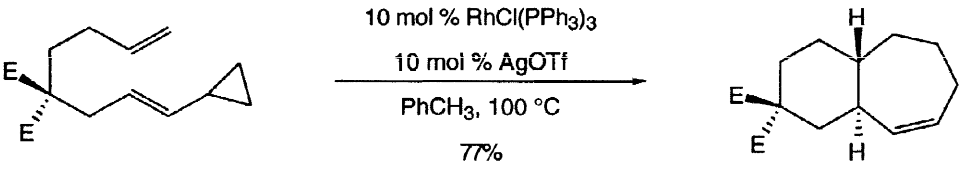
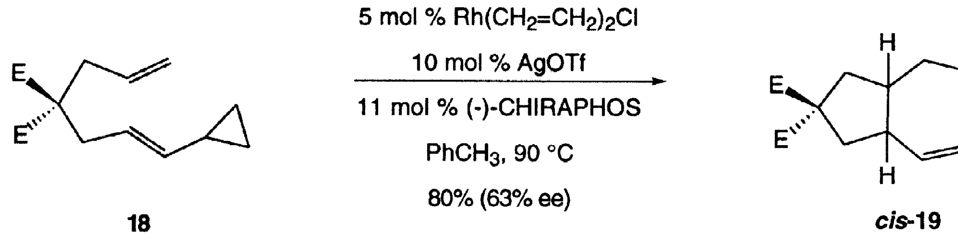
As a final point of synthetic significance, we examined whether the reaction could be conducted with 4-atom tethers (eqn. 10). Although in this case a longer reaction time (5 days) is required to offset the less favorable entropy, the reaction proceeds in the



34 **35** (10)

presence of 10 mol % $RhCl(PPh_3)_3$ and 10 mol % AgOTf in toluene at 100 °C to provide cycloadduct **35** in 77% yield. Remarkably, a single diastereomer is formed. This stereochemistry has been tentatively assigned as *trans* [30].

While much remains to be done in the investigation of this new class of reactions, we were especially interested in examining whether the process could be rendered enantioselective through the use of chiral catalysts. There has been considerable effort focused on developing chiral phosphine ligands for asymmetric synthesis [31] and several of these have been particularly useful in rhodium(I)-catalyzed asymmetric hydrogenation reactions. As a first test, we elected to use (2*S*,3*S*)-(-)-bis(diphenylphosphino)butane (CHIRAPHOS) as our chiral modifier. In the presence of 11 mol % of this ligand, 5 mol % μ-dichlorotetraethylene dirhodium(I), and 10 mol % AgOTf in toluene at 90 °C, **18** undergoes cycloaddition to *cis*-fused cycloadduct **19** in 80% yield, providing an enantiomeric enrichment of 63% (eqn. 11). Treatment of cycloadduct **19** with osmium tetroxide provides the corresponding diol as a single diastereomer. The enantiomeric excess of the reaction is determined by analysis of the diol with the chiral shift reagent $Eu(tfc)_3$. Of the chiral *bis*phosphines initially investigated (BINAP, CHIRAPHOS, PROPHOS, and DIOP), the best enantioselectivity was achieved using CHIRAPHOS. While optimization of this process is being pursued, it is clear from this preliminary work that the reaction can be rendered asymmetric through modification of the ligands of the metal species.



(11)

Conclusion

The intramolecular metal-catalyzed [5+2] cycloaddition of vinylcyclopropanes and alkenes has been established as a new, flexible, efficient, and practical homolog of the Diels-Alder reaction for the synthesis of seven-membered rings. The cycloadditions work with a wide variety of substrates, and generally proceed with exceptional diastereoselectivies and in yields ranging from good to excellent. A range of bicyclic ring structures can be attained via the rhodium(I)-catalyzed [5+2] cycloaddition. Additionally, initial investigation into the use of chiral ligands in the [5+2] cycloaddition indicates that this process can be rendered asymmetric.

Experimental Section

General Methods

The following general procedures were carried out in all reactions unless otherwise noted. Oxygen- or moisture-sensitive reactions for substrate preparations were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen from a manifold. Cycloaddition reactions were carried out in oven-dried Schlenk flasks sealed with gas-inlet adapters under a positive pressure of dry argon. Oxygen- or moisture-sensitive liquids and solutions were transferred by gas-tight syringe or cannula. Elevated temperatures were maintained using Thermowatch-controlled silicone oil baths. In the following reported procedures, concentration of solutions was accomplished using a Buchi rotary evaporator with a water aspirator or recirculating aspirator pump. Residual solvents were removed from non-volatile samples on a vacuum line with a pressure of 0.1-2.0 mmHg. Glassware which was "base-washed" was soaked overnight in a solution of sodium hydroxide in wet ethanol.

Analytical TLC was performed with 0.25 mm silica gel 60F plates with 254 nm fluorescent indicator from Merck. Plates were developed in a covered chamber and visualized by ultraviolet light and treatment with acidic *p*-anisaldehyde, ceric ammonium molybdate, or 2,4-DNP stain followed by gentle heating.

The term flash chromatography refers to preparative silica gel column chromatography as described by Still and co-workers [32]. Silica gel 60, 230-400 mesh (0.040-0.063 mm particle size), was purchased from EM. Solvent was eluted at a flow rate of approximately 25% column volume/min with 6-8 pounds of dry nitrogen pressure.

GC analyses were carried out on a Hewlett-Packard 5880A instrument equipped with a 50 m by 0.20 mm flexible fused silica 5% methyl phenyl silicone capillary column, H_2 as the carrier gas, a flame ionization detector, and a digital integrator. Retention times are reported in minutes. NMR spectra were measured in Fourier transform mode on a Varian INOVA 500 (^1H at 500 MHz, ^{13}C at 125 MHz), Varian XL-400 (^1H at 400 MHz, ^{13}C at 100 MHz), Varian Gemini-300 (^1H at 300 MHz, ^{13}C at 75 MHz) or Varian Gemini-200 (^1H at 200 MHz, ^{13}C at 50 MHz) magnetic resonance spectrometer. Proton NMR spectra are reported as chemical shifts in parts-per-million (ppm) downfield from a tetramethylsilane internal standard (0.00 ppm). The following abbreviations are used to describe spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, m = multiplet. Coupling constants are reported in Hertz (Hz). Carbon-13 NMR spectra are reported as chemical shifts in ppm from the middle peak of the chloroform-δ solvent (77.00 ppm). Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of

California, San Francisco. Reported mass values are within the error limits of ±13 millimass units. Elemental analyses (%C, %H) were determined by Desert Analytics, Tucson, Arizona. Reported atomic percentages are within the error limits of ±0.4%.

Reagents and Solvents

Unless indicated otherwise, reagents and solvents were purchased and used without further purification, with the following exceptions. THF was distilled from sodium-benzophenone ketyl under nitrogen. Toluene was distilled from sodium without added benzophenone. Chromatography grade hexane was distilled through a 50 cm packed column at atmospheric pressure. Commercially available $RhCl(PPh_3)_3$ from Aldrich was obtained as an orange-brown solid and was stored in a dessicator. Commercially available AgOTf from Aldrich was obtained as a white solid and was stored in a dessicator.

General Procedure for the Preparation of Ene-Vinylcyclopropanes 18, 24, 26, 28, 30 and 34: To a stirred solution of 3-cyclopropyl-2-propen-1-ol [33] (5.41 g, 55.1 mmol, 1.0 equiv) in THF (200 mL) at -78 °C was added *n*-BuLi (24.24 mL, 2.5 M in hexanes, 60.6 mmol, 1.1 equiv) via a gas tight syringe. The solution was stirred for 5 min, and mesyl chloride (6.17 g, 60.6 mmol, 1.1 equiv) was added over 5 min via a gas tight syringe, followed by LiBr (12.0 g, 137 mmol, 2.5 equiv) which was added in one batch. After stirring for 2.5 h, the mixture was transferred via cannula to a solution containing the anion of allyl dimethylmalonate, which had been prepared by adding allyl dimethylmalonate [34] dropwise over 30 min (9.84 g, 57.2 mmol, 1.0 equiv) to a solution of NaH (2.43 g, 60% in mineral oil, 60.6 mmol, 1.1 equiv) in THF (250 mL) at 0 °C and stirring for 30 min. After stirring for four hours, the reaction was quenched by addition of saturated aqueous NaCl (400 mL) and was extracted with ether (3 x 400 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 5% EtOAc / hexanes) gave ene-vinylcyclopropane **18** (5.71 g, 41%) as a clear, colorless oil. The reaction was not optimized.

General Cycloaddition Procedure for the Preparation of Cycloadducts 19, 25, 27, 29, 31, and 35: Tris(triphenylphosphine)rhodium(I) chloride (3.65 mg, 0.004 mmol, 0.001 equiv) and silver triflate (1.02 mg, 0.004 mmol, 0.001 equiv) were added sequentially, each in one batch, to a base-washed, oven-dried Schlenk flask containing freshly distilled, oxygen-free toluene (2 mL) under an argon atmosphere. The solution was stirred for 5 min at room temperature, after which ene-vinylcyclopropane **18** (1.00 g, 3.95 mmol, 1.0 equiv) in toluene (2mL) was added over 10 s and the resultant solution was heated at 110 °C for 17 h. After cooling, the reaction mixture was filtered through a plug of alumina and concentrated in vacuo. Purification by flash chromatography (SiO_2, 5% ethyl acetate in hexane) gave cycloadduct **19** (0.857 g, 86%) as a clear, colorless oil.

Ene-Vinylcyclopropane 18: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.57-5.71 (m, 1H), 5.26-5.36 (m, 1H), 4.99-5.12 (m, 3H), 3.71 (s, 6H), 2.63 (d, J = 7.4 Hz, 2H), 2.56 (d, J = 7.4 Hz, 2H), 1.28-1.38 (m, 1H), 0.63-0.69 (m, 2H), 0.27 - 0.32 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.30 (2C), 139.00, 132.42, 120.68, 118.44, 57.97, 52.26 (2C), 36.86, 35.64, 13.58, 6.54 (2C) ppm.; IR (FTIR, film): ν = 3081 (w), 3004 (m), 2953 (m), 2847 (w), 1736 (s), 1664 (w), 1641 (w), 1438 (m), 1327 (w), 1290 (m), 1269 (m), 1247 (m), 1215 (s), 1164 (m), 1047 (w), 1025 (w), 995 (w), 965 (m), 922 (m), 850 (w), 812 (w) cm^{-1}.; Anal. calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.69; H, 8.14.

Cycloadduct 19: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.58 (ddt, *J* = 11.0 Hz, *J* = 6.1 Hz, *J* = 2.3 Hz, 1H), 5.38 (ddd, *J* = 11.0 Hz, *J* = 4.0 Hz, *J* = 1.4 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.89-2.95 (m, 1H), 2.52 (dd, *J* = 13.2 Hz, *J* = 7.5 Hz, 1H), 2.47 (dd, *J* = 13.2 Hz, *J* = 7.4 Hz, 1H), 2.14-2.23 (m, 2H), 2.05 (dd, *J* = 13.2 Hz, *J* = 10.4 Hz, 1H), 1.97-2.03 (m, 1H), 1.86 (dd, *J* = 13.2 Hz, *J* = 8.2 Hz, 1H), 1.41-1.63 (m, 4H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.04, 172.87, 131.35, 128.33, 59.01, 52.63, 52.56, 41.69, 41.00, 40.08, 30.25, 27.60, 23.56 ppm.; IR (FTIR, film): ν = 3016 (w), 2951 (m), 2927 (m), 2856 (w), 1735 (s), 1458 (m), 1435 (m), 1251 (s), 1196 (m), 1173 (m), 1134 (m), 1072 (w), 1036 (w), 967 (w), 889 (w), 690 (w) cm^{-1}. Anal. calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.57; H, 8.04.

Ene-Vinylcyclopropane 24: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.92 (m, 1H), 5.64 (dt, *J* = 15.4 Hz, *J* = 6.3 Hz, 1H), 5.23 (m, 3H), 3.96 (dt, *J* = 5.7 Hz, *J* = 1.4 Hz, 2H), 3.91 (dd, *J* = 6.4 Hz, *J* = 1.1 Hz, 2H), 1.40 (m, 1H), 0.71 (m, 2H), 0.38 (m, 2H) ppm; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 138.64, 135.02, 123.81, 116.94, 70.82, 70.73, 13.30, 6.58 (2C) ppm; IR (FTIR, film): ν = 3082 (m), 3007 (m), 2924 (s), 2854 (s), 1667 (m), 1461 (m), 1377 (m), 1096 (m), 1054 (m), 1019 (m), 963 (m), 924 (m) cm^{-1}; MS (70 ev): m/e (%) = 138 (7), 120 (6), 110 (8), 109 (12), 108 (6), 107 (15), 105 (10), 99 (8), 97 (29), 96 (8), 95 (13), 94 (18), 93 (57), 92 (14), 91 (29), 87 (11), 85 (68), 84 (22), 83 (13), 83 (100), 82 (8), 81 (77), 80 (57), 79 (96), 78 (12), 77 (31), 73 (14), 71 (11), 70 (10), 69 (42), 67 (42), 66 (8), 65 (6).; HRMS calcd for $C_9H_{14}O$: 138.1045. Found: 138.1049.

Cycloadduct 25: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.64 (m, 1H), 5.37 (ddd, *J* = 10.8 Hz, *J* = 3.8 Hz, *J* = 1.6 Hz, 1H), 4.04 (m, 2H), 3.45 (t, *J* = 8.5 Hz, 1H), 3.33 (dd, *J* = 8.5, J = 6.6, 1H), 3.06 (m, 1H), 2.26 (m, 2H), 2.06 (m, 1H), 1.57 (m, 4H) ppm; ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 128.89, 128.11, 75.38, 73.65, 42.17, 40.78, 27.86, 27.64, 23.17 ppm; IR (FTIR, film): ν = 3017 (m), 2926 (s), 2859 (s), 1478 (m), 1450 (m), 1366 (w), 1102 (m), 1072 (m), 1044 (m), 941 (m), 696 (m) cm^{-1}; MS (70 ev): m/e (%) = 138 (11), 120 (12), 110 (11), 107 (19), 105 (12), 94 (30), 93 (100), 92 (16), 91 (34), 81 (12), 80 (42), 79 (83), 78 (15), 77 (28), 69 (12), 67 (33), 66 (12).; HRMS: calcd for $C_9H_{14}O$: 138.1045. Found: 138.1048.

Ene-Vinylcyclopropane 26 (5.5:1 mixture of *E*:*Z* isomers): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.61-5.73 (m, 1H), 5.04-5.09 (m, 2H), 4.61 (d, *J* = 9.9 Hz, 1H), 3.71 (s, 6H, *Z*), 3.70 (s, 6H, *E*), 2.89 (s, 2H, *Z*), 2.68 (d, *J* = 7.3 Hz, 2H, *Z*), 2.62-2.64 (m, 4H, *E*), 1.65 (d, *J* = 1.1 Hz, 3H, *E*), 1.57 (d, *J* = 1.2 Hz, 3H, *Z*), 1.37-1.46 (m, 1H), 0.67-0.73 (m,2H), 0.24-0.29 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.97 (2C, Z), 171.80 (2C, *E*), 135.10 (*Z*), 134.86 (*E*), 133.10 (Z), 132.94 (*E*), 128.22, 118.79 (*E*), 118.72 (*Z*), 57.74, 52.15 (2C, *Z*), 52.03 (2C, *E*), 42.20 (*E*), 37.57 (*Z*), 36.92 (*E*), 35.14 (*Z*), 23.76 (*Z*), 16.89 (*E*), 10.21 (*Z*), 9.88 (*E*), 6.76 (2C, *Z*), 6.53 (2C, *E*) ppm.; IR (FTIR, film): ν = 3081 (w), 3003 2952 (m), 1739 (vs), 1640 (w), 1436 9m), 1329 (w), 1287 (m), 1253 (m), 1211 (s), 1137 (m), 1066 (m), 1021 (w), 966 (w), 924 (m), 810 (w) cm^{-1}.; MS (70 ev): m/e (%) =

266 (1), 234 (3), 206 (13), 198 (10), 193 (13), 175 (14), 172 (21), 165 (19), 161 (23), 147 (20), 140 (19), 139 (11), 139 (17), 131 (10), 108 (30), 105 (30), 95 (100), 79 (35), 67 (39).; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1506.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.47; H, 8.32.

Cycloadduct 27: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.53 (ddd, *J* = 11.9 Hz, *J* = 7.2 Hz, *J* = 4.7 Hz, 1H), 5.29 (dd, *J* = 1.1 Hz, *J* = 12.0 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 2.56 (d, *J* = 13.5 Hz, 1H), *J* = 11.4 Hz, 1H), 2.38 (dd, *J* = 13.3 Hz), 2.26 (dd, *J* = 13.3 Hz, *J* = 6.7 Hz, 1H), 2.03-2.10 (m, 2H), 2.00 (d, *J* = 13.5 Hz, 1H), 1.89-1.94 (m, 1H), 1.76-1.84 (m, 2H), 1.52-1.62 (m, 2H), 1.14 (s, 3H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.95, 173.19, 138.36, 128.89, 56.81, 52.67, 52.58, 50.55, 48.36, 47.16, 38.05, 28.76, 28.72, 25.22, 22.16 ppm.; IR (FTIR, film): ν = 3009 (m), 2952 (s), 2926 (s), 2865 (m), 1735 (vs), 1435 (vs), 1369 (w), 1332 (w), 1253 (vs), 1199 (s), 1160 (s), 1128 (m), 1112 (m), 1065 (m), 1035 (m), 966 (w), 879 (w), 853 (w), 834 (w), 750 (m), 702 (m) cm^{-1}.; MS (70 ev): m/e (%) = 266 (11), 234 (24), 207 (21), 206 (81), 191 (25), 177 (13), 164 (11), 148 (11), 147 (100), 146 (16), 145 (29), 119 (15), 113 (18), 107 (27), 105 (38), 100 (13), 93 (23), 91 (35, 79 (26), 77 (18), 67 (11).; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1518.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.54; H, 8.26.

Ene-Vinylcyclopropane 28: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.29-5.39 (m, 1H), 5.01 (dd, *J* = 15.1 Hz, *J* = 8.6 Hz, 1H), 4.87 (s, 1H), 4.73 (s, 1H), 3.70 (s, 6H), 2.69 (s, 2H), 2.59 (d, *J* = 7.4 Hz, 2H), 1.65 (s, 3H), 1.31-1.35 (m, 1H), 0.63-0.69 (m, 2H), 0.26-0.31 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.69 (2C), 140.56, 138.82, 121.09, 115.60, 57.67, 52.22 (2C), 40.23, 35.75, 23.18, 13.59, 6.51 (2C) ppm.; IR (FTIR, film): ν = 3079 (m), 3002 (m), 2954 (m), 2847 (m), 1735 (s), 1647 (m), 1440 (s), 1378 (w), 1328 (m), 1266 (s), 1206 (s), 1079 (m), 1028 (m), 964 (m), 901 (m), 857 (w), 816 (m), 756 (w), 682 (w) cm^{-1}.; MS (70 ev): m/e (%) = 266 (, 0.5), 207 (58), 206 (53), 203 (12), 179 (22), 164 (16), 151 (54), 147 (93), 122 (44), 119 (21), 107 (40), 105 (71), 93 (21), 91 (53), 81 (100), 79 (60), 77 (26), 67 (25), 65 (19).; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1532.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.57; H, 8.24.

Cycloadduct 29: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.69 (ddd, *J* = 11.6 Hz, *J* = 7.4 Hz, *J* = 4.1 Hz, 1H), 5.46 (ddd, *J* = 11.6 Hz, *J* = 6.7 Hz, *J* = 2.3 Hz, 1H), 3.73 (s, 3H), 3.72 (s, 3H), 2.50 (dd, *J* = 12.4 Hz, *J* = 6.3 Hz, 1H), 2.35-2.43 (m, 1H), 2.02-2.30 (m, 5H), 1.62-1.71 (m, 1H), 1.47-1.55 (m, 3H), 1.07 (s, 3H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 173.73, 173.37, 131.42, 129.58, 57.72, 52.69, 52.65, 50.03, 49.66, 43.18, 39.70, 38.43, 29.14, 25.78 , 21.35 ppm.; IR (FTIR, film): ν = 3012 (w), 2953 (m), 2932 (m), 1735 (s), 1456 (m), 1435 (m), 1254 (s), 1197 (m), 1170 (m), 1152 (m), 1135 (m), 1096 (m), 1071 (m), 1023 (w), 968 (w), 953 (w), 914 (w), 877 (w), 732 (w), 710 (w) cm^{-1}.; MS (70 ev): m/e (%) = 266 (18), 234 (10), 207 (19), 206 (93), 203 (16), 191 (16), 164 (15), 152 (16), 148 (12), 147 (100), 145 (86), 131 (13), 119 (15), 113 (23), 107 (18), 105 (28), 93 (19), 91 (26), 79 (21), 77 (14), 67 (11).; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1522.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.23; H, 8.30.

Ene-Vinylcyclopropane 30 (6.5:1 mixture of *E*:*Z* isomers): ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.63 (m, 1H), 5.04 (m, 3H), 3.70 (s, 6H, *Z*), 3.69 (s, 6H, *E*), 2.72 (m, 4H, *Z*), 2.60 (m, 4H, *E*), 1.48 (s, 3H), 1.34 (m, 1H), 0.53 (m, 2H), 0.40 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.44 (2C), 139.80, 132.60, 118.83 (*E*), 118.34 (*Z*), 115.83, 57.96, 52.2 (2C), 36.96, 30.95 (*E*), 30.45 (*Z*), 18.93 (*E*), 18.86 (*Z*), 14.19 (*E*), 12.37 (*Z*), 4.43 (*E*), 4.08 (*Z*) ppm.; IR (FTIR, film): ν = 3082 (m), 3003 (m), 2953 (m), 2844 (m), 1737 (s), 1642 (m), 1437 (m), 1322 (m), 1288 (s), 1253 (m), 1212 (s), 1143 (m), 1085 (m), 1047 (m), 923 (m) cm^{-1}.; MS (70 ev): m/e (%) = 266 (1), 235 (2), 225 (11), 206 (15), 193 (46), 165 (14), 161 (21), 147 (16), 145 11), 140 (10), 139 (11), 108 (24), 105 (16), 95 (100), 93 (19), 91 (16), 82 (14), 79 (20), 77 (14), 67 (28).; HRMS calcd for $C_{15}H_{22}O_4$: 226.1518. Found: 266.1520.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.63; H, 8.38.

Cycloadduct 31: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 6H), 2.97 (d, *J* = 16.2 Hz, 1H), 2.80 (d, *J* = 16.4 Hz, 1H), 2.58 (m, 2H), 2.16 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.70 (m, 1H), 1.65 (s, 3H), 1.46 (m, 1H), 1.21 (m, 4H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.63, 172.53, 137.14, 130.84, 58.81, 52.75, 52.55, 42.26, 42.06, 39.51, 35.90, 33.84, 30.60, 26.14, 22.53 ppm.; IR (FTIR, film): ν = 2953 (m), 2922 (m), 2859 (m), 1744 (s), 1450 (m), 1435 (m), 1283 (m), 1262 (s), 1199 (m), 1168 (m), 1074 (m), 1011 (w) cm^{-1}.; MS (70 ev): m/e (%) = 266 (23), 235 (6), 207 (23), 206 (100), 191 (11), 177 (8), 148 (8), 147 (70), 131 (6), 107 (7), 105 (18), 91 (16), 79 (8), 77 (7).; HRMS calcd for $C_{15}H_{22}O_4$: 226.1518. Found: 266.1520.

Ene-Vinylcyclopropane 34: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.72-5.82 (m, 1H), 5.26-5.36 (m, 1H), 4.95-5.06 (m, 3H), 3.71 (s, 6H), 2.58 (dd, *J* = 7.5 Hz, *J* = 1.0 Hz, 2H), 1.96 (s, 4H), 1.29-1.36 (m, 1H), 0.63-0.69 (m, 2H), 0.27-0.32 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 171.69 (2C), 138.77, 137.51, 120.83, 114.97, 57.28, 52.24 (2C), 35.91, 31.57, 28.31, 13.55, 6.55 (2C) ppm.; IR (FTIR, film): ν = 3081 (w), 3004 (m), 2953 (m), 2844 (m), 1736 (s), 1665 (w), 1642 (w), 1434 (m), 1265 (m), 1240 (m), 1209 (s), 1163 (m), 1085 (w), 1047 (w), 1022 (w), 996 (w), 965 (m), 915 (m), 853 (w), 813 (w), 745 (w) cm^{-1}.; MS (70 ev): m/e (%) = 266 (1), 234 (10), 212 (13), 206 (22), 179 (11), 167 (10), 165 (10), 152 (10), 147 (14), 145 (68), 133 (32), 105 (52), 93 (12), 91 (28), 81 (100), 79 (37), 77 (17), 68 (12), 67 (17), 65 (11).; HRMS: calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1509.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.41; H, 8.31.

Cycloadduct 35: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.75-5.84 (m, 1H), 5.25 (dt, *J* = 11.5 Hz, *J* = 2.8 Hz, 1H), 3.71 (s, 3H), 3.71 (s, 3H), 2.40 (ddd, *J* = 13.5 Hz, *J* = 3.9 Hz, *J* = 2.8 Hz, 1H), 2.30 (dq, *J* = 13.3 Hz, *J* = 3.0 Hz, 1H), 2.10-2.20 (m, 1H), 1.92-2.08 (m, 2H), 1.82-1.87 (m, 1H), 1.54-1.76 (m, 4H), 1.18-1.37 (m, 2H), 1.05-1.17 (m, 2H) ppm.; ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 172.89, 171.45, 136.25, 131.96, 55.00, 52.61, 52.38, 40.06, 39.88, 39.51, 38.76, 31.67, 30.69, 29.00, 27.07 ppm.; IR (FTIR, film): ν = 3010 (w), 2952 (m), 2920 (m), 2863 (m), 1735 (s), 1451 (m), 1434 (m), 1323 (w), 1301 (w), 1257 (m), 1240 (m), 1222 (m), 1186 (m), 1158 (m), 1109 (m), 1087 (m), 1040 (w), 998 (w), 980 (w), 933 (w), 912 (w), 762 (w), 682 (m) cm^{-1}.; MS (70 ev): m/e (%) = 266 (11), 235 (7), 207 (18), 206 (100), 175 (5), 174 (5), 148 (8), 147 (67), 146 (33), 131 (6), 119 (6), 105 (14), 93 (11), 91 (29), 79 (20), 77 (11), 67 (15).; HRMS calcd for $C_{15}H_{22}O_4$: 266.1518. Found: 266.1522.; Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.65; H, 8.26.

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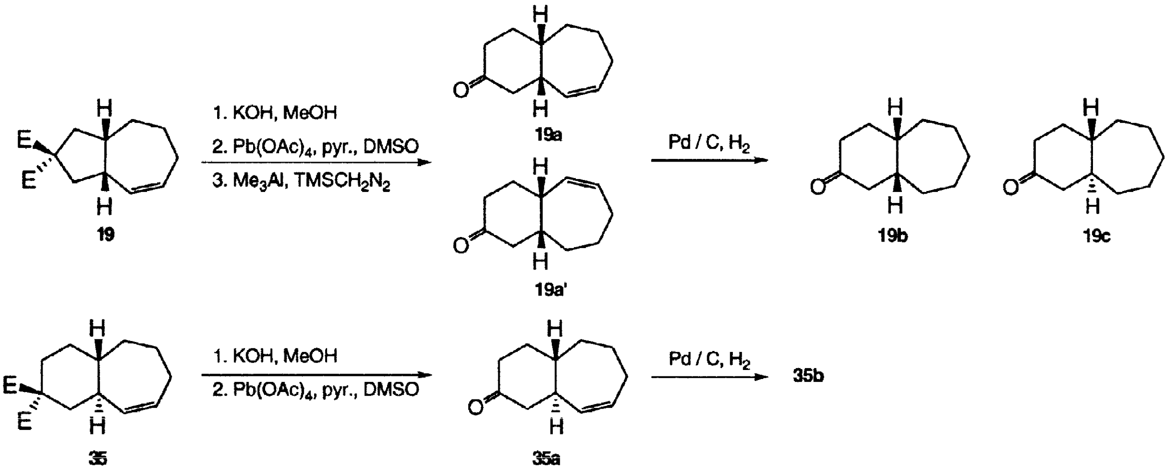

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