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Mechanistic Dichotomy in $CpRu(CH_3CN)_3PF_6$ Catalyzed Enyne Cycloisomerizations

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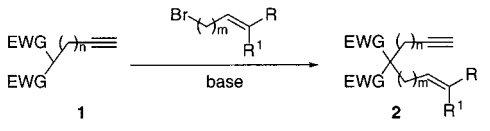
Abstract: Enynes are easily accessible building blocks as a result of the rich chemistry of alkynes and thus represent attractive substrates for ring formation. A ruthenium catalyst for cycloisomerization effects such reaction of 1,6- and 1,7-enynes typically at room temperature in acetone or DMF under neutral conditions. The reaction is effective for forming five- and six-membered rings of widely divergent structure. The alkyne may bear both election-donating and election-withdrawing substituents. The alkene may be di- or trisubstituted. Introduction of a quaternary center at the propargylic position of an ynoate, however, completely changes the nature of the reaction. In the case of a 1,6-enynoate, a seven-membered ring forms in excellent yield under equally mild conditions. Evidence is presented to indicate a complete change in mechanism. In the former case, the reaction involves the intermediacy of a ruthenacyclopentene. In the latter case, a C−H insertion to form a π-allylruthenium intermediate is proposed and supported by deuterium-labeling studies. A rationale is presented for the structural dependence of the mechanism.

Introduction

Transition-metal-catalyzed cyclization reactions offer the unique means by which to achieve efficiency not normally accessible by traditional methods.[1] For example, a number of cycloisomerization reactions of enynes have been reported with a variety of transition metal catalysts.[2] In general, these reactions do not require additional reactants and produce few byproducts, making the cycloisomerization ideal in terms of synthetic efficiency and atom economy.[3] Furthermore, depending on the nature of the catalyst, a number of reaction manifolds can be accessed, leading to a variety of cyclic products. The mechanisms that have been postulated for the cycloisomerization of enynes include (1) initial hydrometalation of the alkyne, followed by carbometalation of the olefin;[4] (2) initial formation of a metalacyclopentene followed by β-hydrogen elimination;[5] (3) formation of a metalacyclopentene, followed by reductive elimination to form a cyclobutene that undergoes a conrotatory cycloreversion;[6] and (4) a metal alkylidene.[7] We have also reported on the ruthenium-catalyzed intermolecular version of this reaction, an alkene−alkyne coupling.[8] Two mechanisms were originally postulated for this reaction. The first, the one we have generally favored, involves a ruthenacyclopentene as an intermediate. The second involves allylic C−H activation to form a ruthenium allyl, followed by carbametalation of the alkyne.[9] In fact, the latter mechanism was the one we favored early in our studies of the intermolecular reaction until we showed it was not operative in that case. Herein, we report that, in the cycloisomerization of enynes, both of these mechanisms are operative, utilizing the same ruthenium catalyst by simply changing the structure of the enyne substrate.[10]

Preparation of Enyne Substrates. One of the advantages of the cycloisomerizations of enynes is their ease of synthesis. One strategy involves the allylation of propargyl (**1a**) or homopropargyl (**1b**) malonate or the bis-sulfone analogue (**1c**) with allyl bromides in the presence of base (eq 1). For the



(1)

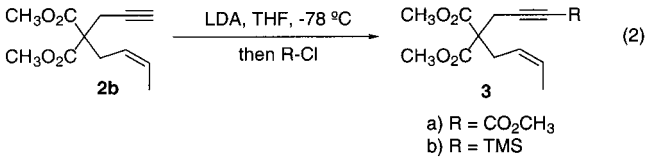
a) EWG = CO_2CH_3, n=1
b) EWG = CO_2CH_3, n=2
c) EWG = SO_2Ph, n=1

a) EWG = CO_2CH_3, m=n=1, R = CH_3, R^1= H (93%)
b) EWG = CO_2CH_3, m=n=1, R = H, R^1= CH_3 (91%)
c) EWG = CO_2CH_3, m=1, n=2, R = CH_3, R^1= H (91%)
d) EWG = SO_2Ph, m=n=1, R = CH_3, R^1= H (74%)
e) EWG = SO_2Ph, m=2, n=1, R = R^1= CH_3 (86%)

malonates, cesium carbonate in acetone was employed, whereas for the bis-sulfones, sodium hydride in DMF was preferred. The *E*-crotyl bromide varied from 3.5 to 4.6:1 *E*:*Z* and this transferred to the corresponding products (*E*:*Z*:**2a** and **2c** 3.5:1, **2d** 4.6:1).[11] Similarly, the *Z*-crotyl bromide had a *Z*:*E* ratio of 12:1, which transferred to its product **2b**. The resulting products

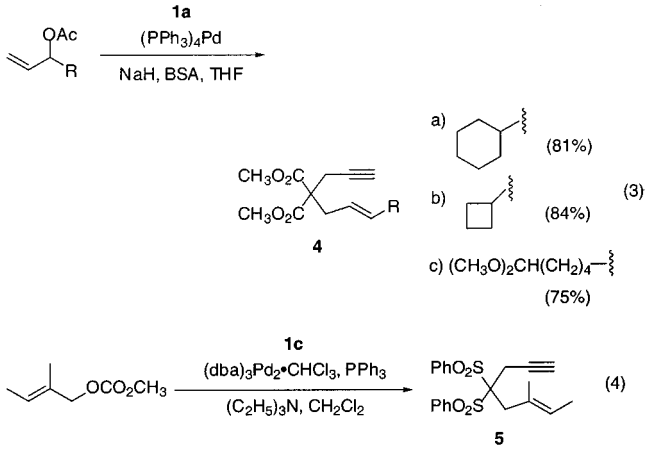
(1) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.
(2) For reviews see: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.
(3) Trost, B. M. *Science* **1991**, *254*, 1471; Trost, B. M. *Angew. Chem.* **1995**, *34*, 259.
(4) Pd: Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268 and references therein. Ru: Mori, M.; Kozawa, Y.; Nishida, M.; Kanamura, M.; Onozuka, K.; Takimoto, M. *Org. Lett.* **2000**, *2*, 3245, and Le PAih, J.; Rodríguez, D. Dérien, S. D.; Dixneuf, P. H. *Synlett* **2000**, 95.
(5) Pd: Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255 and references therein. Ni−Cr: Trost, B. M.; Tour, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 6268. Ni: Radetich, B.; Rajan Babu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007. Co: Kraft, M. E.; Wilson, A. M.; Dasse, O. A.; Bonaga, L. V. K.; Cheung, Y. Y.; Fu, Z.; Shao, B.; Scott, J. L. *Tetrahedron Lett.* **1998**, *38*, 5911. Ti: Sturla, S. J.; Kabalaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976. Rh: Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490. Ir: Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* **2001**, *66*, 4433. See also: Trost, B. M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1085 and Chatani, N.; Kataoka, K.; Murai, S.; Furukawa, N.; Seki, Y. *J. Am. Chem. Soc.* **1998**, *120*, 9104.

could be further derivatized, as shown in eq 2. Thus, the lithium



(2)

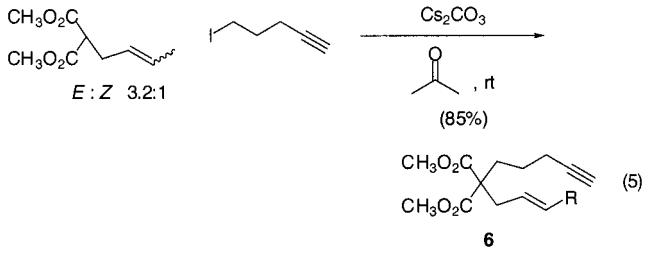
acetylide could be generated and functionalized even in the presence of the two esters. Allylic alkylations were also performed using palladium catalysis as shown in eqs 3 and 4. Good



(3)

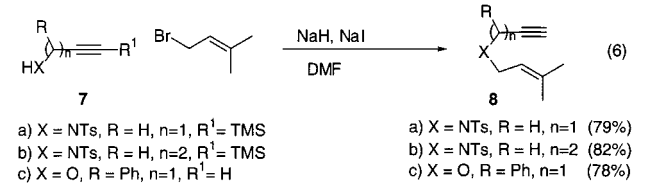
(4)

regioselectivity for attack at the less substituted allyl terminus was observed, regardless of the position of the leaving group in the starting material. While the olefin geometry is not predefined by the starting material in the case of eq 3, the products (**4**) were produced with good *E* selectivity. For the case of eq 1, allylic halides are not required. Thus, reaction of 1-bromo-4-methyl-3-pentene with bis-sulfone **1c** gave the alkylated product **2e** in excellent yield. A similar reaction performed using 1-iodo-4-pentyne (eq 5) gave 1,8-enyne **6**.



(5)

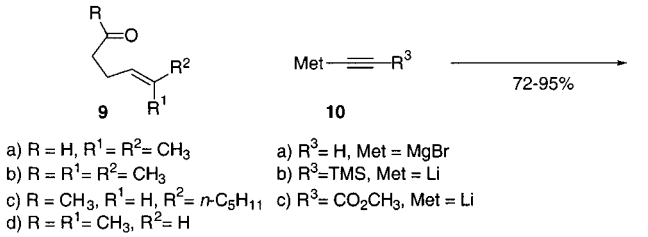
Similar types of reactions were employed to make substrates bearing a heteroatom in the tether, where alkylation occurred at the heteroatom. Equation 6 demonstrates the viability for both

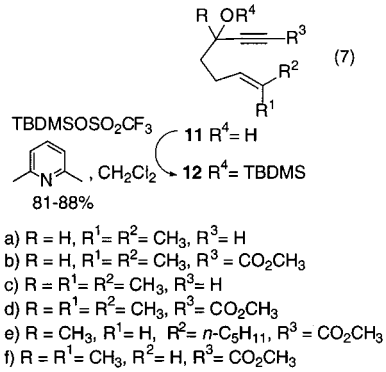


(6)

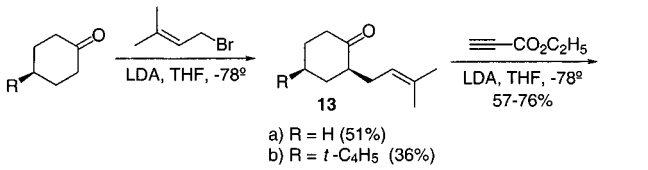
an N and an O in the tether. Desilylation accompanied the alkylation in the case of the sulfonamides **7a** and **7b**.

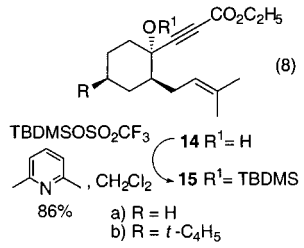
Use of acetylide nucleophiles also constitutes a major entry into the requisite substrates. Simple additions to unsaturated aldehydes and ketones are summarized in eq 7. Suitable unsaturated ketones may be accessed via enolate alkylation (eq 8) or



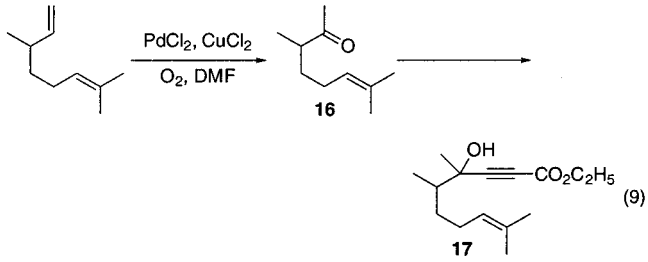


(7)





(8)



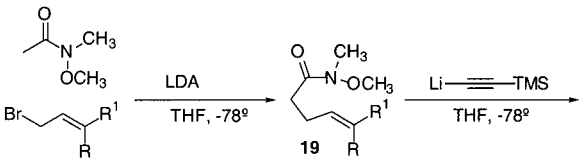
(9)

a chemoselective Wacker[12] oxidation (eq 9), which involves reaction preferentially at the monosubstituted alkene. In the case of **14a** and **15a**, a 2:1 mixture in favor of the equatorial OH was obtained. In the 4-*tert*-butyl series, the thermodynamically more stable *cis*-**13b** was produced as the major product and isolated pure. In this case, the axial selectivity in the addition

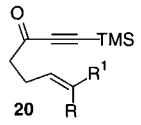
(6) Pd: Trost, B. M.; Trost, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1850. Pt: Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901. Ru: Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049.
(7) Ru: Mori, M.; Sakaibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.
(8) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739.
(9) Trost, B. M.; Indolese, A.; Muller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.*, **1995,** *117*, 615; Trost, B., M.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 615.
(10) For preliminary communication of this work, see; Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 9728. Trost, B. M.; Toste, F. D.; *J. Am. Chem. Soc.* **2000**, *122*, 714.
(11) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1987**, *109*, 4753.

of the acetylide increased to 7:1 to produce **14b**. The relative stereochemistry of the enynoates was expected on the basis of precedent and supported by the ^{13}C NMR data. In general, the signal for the quaternary carbon of equatorial alcohols appears about 2−3 ppm downfield from the signal for the corresponding axial alcohol. Furthermore, the ^{13}C NMR signal for the adjacent alkyne carbon of the equatorial alcohols is generally 3−4 ppm upfield from the analogous signal in the axial alcohols.[13]

Alkynones may be accessed by alkylation of the Weinreb amide of acetic acid, followed by addition of an acetylide anion (eq 10).[14] Thus, reaction with geranyl or neryl bromide gave



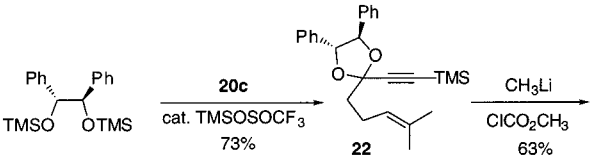
a) R = CH_3, R^1= $(CH_2)_2CH{=}C(CH_3)_2$ (61%)
b) R = $(CH_2)_2CH{=}C(CH_3)_2$, R^1= CH_3 (54%)

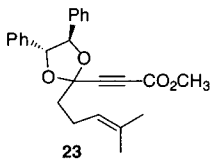


(10)

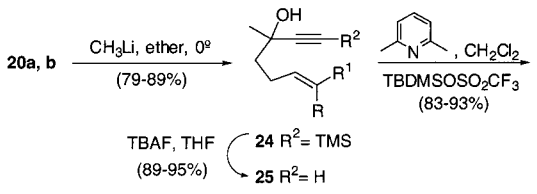
a) R = CH_3, R^1= $(CH_2)_2CH{=}C(CH_3)_2$ (70%)
b) R = $(CH_2)_2CH{=}C(CH_3)_2$, R^1= CH_3 (68%)
c) R = R^1= CH_3 (90%)

19a and **19b**, which were subsequently converted into ynones **20a** and **20b**, respectively. Ketone **20c** was accessed by oxidation of alcohol **11c** (PCC, CH_2Cl_2). Typical carbonyl chemistry provides access to a variety of derivatives, as illustrated by ketal formation (eq 11) and organolithium additions (eq 12). Ketal formation required the method of Noyori.[15] In

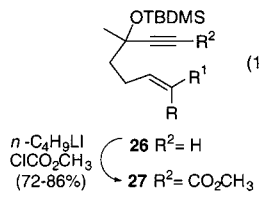




(11)

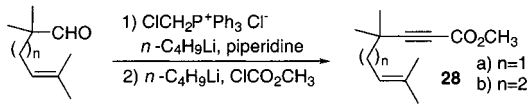


a) R = CH_3, R^1= $(CH_2)_2CH{=}C(CH_3)_2$
b) R = $(CH_2)_2CH{=}C(CH_3)_2$, R^1= CH_3



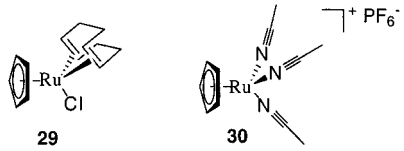
(12)

each case, the silylalkynes were readily converted into the propiolates **23**, **27a**, and **27b** via the corresponding lithium acetylides. A final method takes advantage of creation of the alkyne from an aldehyde, as shown in eq 13.[16] The starting aldehydes can also be easily accessed by enolate alkylations.



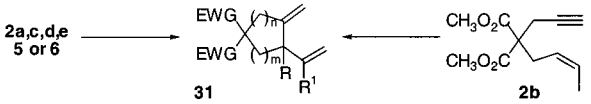
(13)

Cycloisomerizations. Ruthenium-catalyzed additions of alkenes and alkynes show a high sensitivity to substitution on the alkene but virtually none on the alkyne. Indeed, the first generation catalyst **29** required monosubstituted alkenes that, therefore, did not permit intramolecular versions to form normal ring sizes such as five to seven members. The utilization of the



more reactive cationic complex **30** allowed extension of the reaction to substituted alkenes[8] and thus opened the prospect to make the normal ring sizes. As a result, the sensitivity to subtituents of the alkene was examined.

Initially, using the type of conditions that were optimized with **29** for the intermolecular alkyne−alkene coupling were employed. Thus, enyne **2d** was subjected to 10 mol % complex **30** and camphorsulfonic acid (CSA) in DMF at 80° to give a 68% yield of 1,4-diene **31b** (eq 14). Lowering the temperature



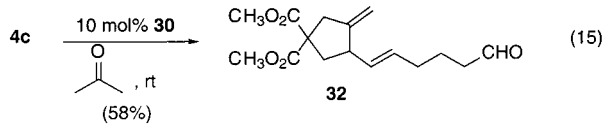
(14)

a) EWG = CO_2CH_3, m=n=1, R = R^1= H (84%)
b) EWG = $PhSO_2$, m=n=1, R = R^1= H (80%)
c) EWG = CO_2CH_3, m=1, n=2, R = R^1= H (67%)
d) EWG = CO_2CH_3, m=1, n=3, R = R^1= H (26%)
e) EWG = $PhSO_2$, m=2, n=1, R = R^1= CH_3 (72%)
f) EWG = $PhSO_2$, m=n=1, R = CH_3, R^1= H (69%)

to room temperature had no significant effect on yield. Furthermore, by removing CSA and using either DMF or acetone as solvent, the cycloisomerized product was isolated in 80% yield. Changing the tether from the bis-sulfone to the bis-ester **2a** gave **31a** in 84% yield under identical conditions in acetone. Changing from the *E*- to the *Z*-alkene (**2b**) slowed the reaction. At room temperature, its cycloisomerization in acetone gave only 41% of **31a**; raising the temperature to 60 °C improved the yield to 69%. Increasing the ring size to six, i.e. **2c**, led to only 32% yield of **31c** at room temperature. Raising the temperature to 60 °C enhanced the yield to 57% in DMF and 67% in 2-butanone. Increasing the ring size to seven, i.e. **6**, led to low yields of **31d** in DMF both at room temperature (12%) and 60 °C (26%). A longer alkyl group as in **4c** also slowed the reaction

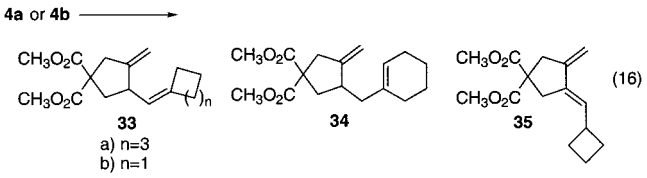
(12) Mcquilli, F. J.; Parker, D. G. *J. Chem. Soc., Perkin Trans. 1* **1974**, 809
(13) Trost, B. M.; Florez, J.; Jebaratanam, D. J. *J. Am. Chem. Soc.* **1987**, *109*, 613. See also: Trost, B. M.; Tour, J. *J. Am. Chem. Soc.* **1988**, *110*, 5231.
(14) Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735.
(15) Tsnunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357.
(16) Spreitzer, H.; Pichler. A.; Holzer, W.; Toth, I.; Zuchart, B. *Helv. Chim. Acta* **1997**, *80*, 139.

somewhat. In the case of the acetal **4c**, cycloisomerization was accompanied by acetal hydrolysis to provide the aldehyde **32** directly (eq 15). Thus, it appears that this catalyst system is acidic and affects very acid labile groups such as a dimethyl acetal.[17]



(15)

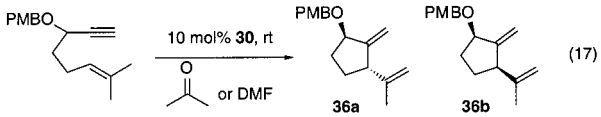
Placing a branch at the allylic position such that insertion into a tertiary C−H bond became required impacted the regioselectivity. Thus, our standard conditions in acetone converted **4a** into a 1:1 mixture of **33a** and **34** in 74% yield (eq 16). The formation of **34** is expected to derive from an acid-



(16)

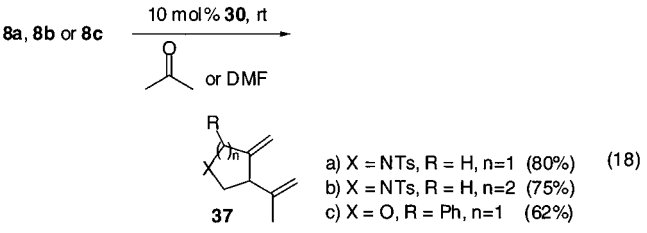
catalyzed isomerization of the kinetic product **33a**. By using a more basic medium, DMF, this problem was avoided and **33a** was isolated in 69% yield. On the other hand, the cyclobutyl analogue, **4b**, gave a 2:1 mixture of the expected 1,4-diene **33b** and 1,3-diene **35** in 70% yield in DMF at room temperature. This product ratio presumably reflects the steric strain of forming an alkylidenecyclobutane such that the normally less favorable endocyclic β-hydrogen elimination in the intermediate ruthenacyclopentene now competes.

Further increasing alkyl substitution on the alkene to trisubstituted olefins is also tolerated. Thus, cycloisomerization of the PMB ethers of **11a** gave an excellent yield of the methylenecyclopentanes **36a** and **36b** in a 1.4:1 ratio both in acetone (83%) and DMF (86%) at room temperature (eq 17). Cyclo-



(17)

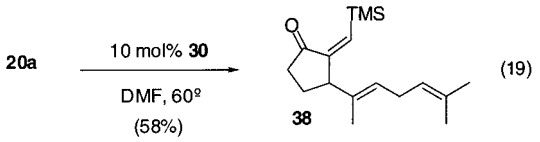
isomerization of bis-sulfone **2e** produced the six-membered ring **31e** with greater facility than the less substituted alkene (eq 14, 72% yield in acetone at room temperature for **31e** compared to 67% in 2-butanone at reflux for **31c**). The alternative trisubstitute alkene, a tiglyl system (**5**), also smoothly isomerized at room temperature in DMF to diene **31f** in 69% yield, although, for inexplicable reasons, it failed to react in acetone. Incorporating a heteroatom such as N in the tether, i.e., **8a** and **8b**, does not affect the reaction (eq 18). The five- and six-membered



(18)

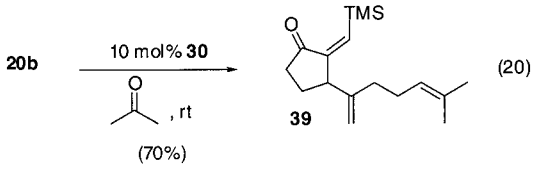
cycloisomerized products **37a** and **37b** formed with equal facility.[18] On the other hand, using O as a substituent does lead to a slower reaction.[19] Thus, **37c** was produced as an 8:1 diastereomeric ratio (dr) in 62% in acetone at room temperature. Assignment of the major diastereomer as *E* is based upon an NOE study. To see if there is any effect of solvent on dr, DMF was also employed, but with rather similar results, a 54% yield of a 7.6:1 dr.

Disubstituted alkynes may be employed, although only a few have been examined. A terminal TMS group on a simple alkyne does inhibit the reaction. Thus, the TMS alkyne **3b** gave no conversion at ambident temperature and less than 25% conversion at 60 °C in DMF.[20] On the other hand, using an activated silyl alkyne does lead to a satisfying reaction. Thus, the geranyl-derived enyne **20a** reacted slowly in acetone at room temperature (eq 19) to give a 7:1 ratio of **38** and **39** but in only 20% yield,



(19)

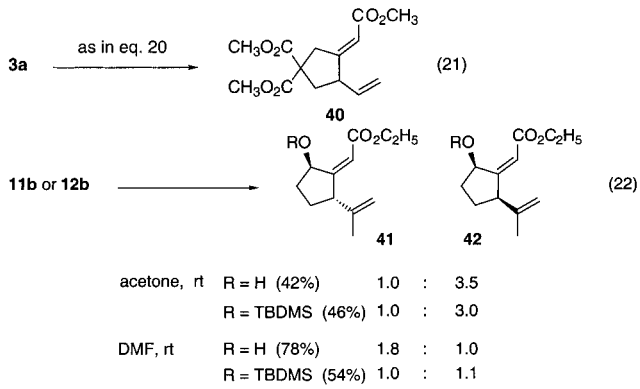
which increased to 52% at 50 °C with no change in regioselectivity (eq 19). A similar result was observed in DMF, wherein a 56% yield of an 8:1 ratio of **38**:**39** was obtained at 60°. Interestingly, the neryl-derived substrate **20b** reacted more readily to provide cyclopentanone **39** in 70% as a 10:1 ratio of **39**:**38**, even at room temperature (eq 20). The regioselectivity



(20)

increased in DMF to 17:1 but at the expense of yield, still 58% at room temperature. Thus, alkene geometry defined the regioselectivity of the β-hydrogen elimination. Furthermore, when the hydrogen is part of a CH_2, as in **20a**, this elimination is significantly slower than that which is part of a CH_3 group, as in **20b**. It is significant to note that the new C−C bond formation occurs α to the carbonyl group.

Placing an alkoxycarbonyl group at the terminal carbon of a monosubstituted alkyne also leads to good substrates. Thus, enyne **3a** gave a 71% yield of the expected 1,4-diene (**40**) under standard conditions (eq 21). The trisubstituted alkene substrates



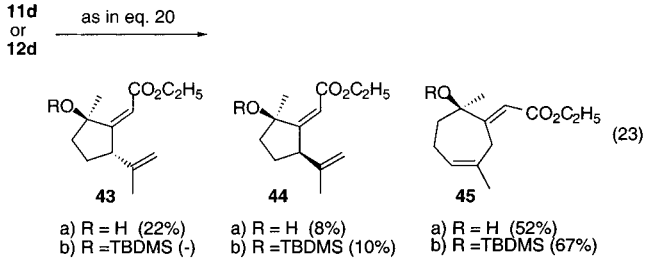
(21)
(22)

11b and **12b** also participated to produce diastereomers **41** and

(17) Ma, S.; Venanzi, L. M. *Synlett* **1993**, 751.
(18) Trost, B. M.; Chen. S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053. Trost, B. M.; Pedregal C. *J. Am. Chem. Soc.* **1992**, *114*, 7292.

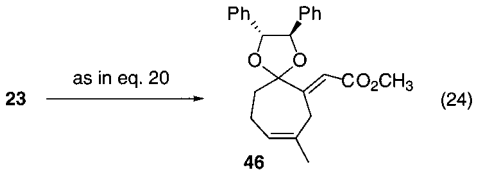
42 (eq 22). While the diastereoselectivity of the reaction is low, it appears that solvent does influence it. A bias for the *Z* isomer exists in acetone, but the trend begins to reverse in DMF.

Changing the tether so that the propargylic carbon is quaternary had a dramatic effect on the course of the reaction. As shown in eq 23, a seven-membered ring product (**45a**) in

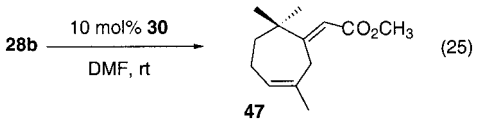


(23)

addition to five-membered ring products **43a** and **44a** was formed (7:5 ring ratio 1.7:1). This ratio increases to 6.7:1 by using the silyl ether **12d** as substrate. Increasing the steric hindrance at the propargylic position increased the selectivity further such that enyne **23** only formed seven-membered ring **46** (eq 24). Placing two methyl groups at the propargylic position



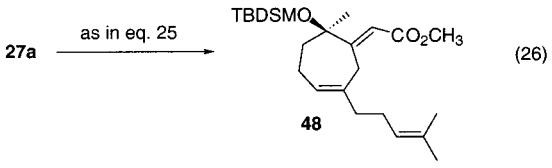
(24)



(25)

as in enyne **28b** gave a similar result—only seven-membered ring formation (**47**) occurred (eq 25). The reaction was slower than previously and was solvent dependent. The yield increased from 40% in acetone at room temperature to 62% in DMF at room temperature. The substrate (**28a**) with one less carbon in the chain gave no cyclization product.

The effect of substituents on the olefin was profound. The reactions of the geranyl−neryl pair **27a**−**27b** were very revealing. As shown in eq 26, the geranyl substrate did react

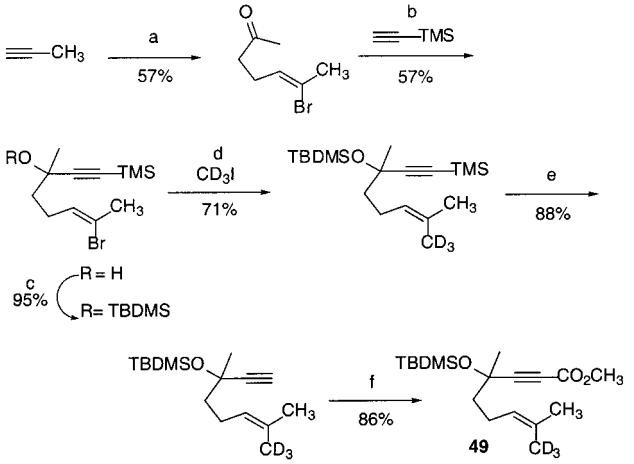


(26)

somewhat more slowly in DMF at room temperature to give a 40% yield of seven-membered ring **48** exclusively, which increased to 53% yield at 60 °C. On the other hand, the neryl substrate **27b** did not give the seven-membered ring product—only a complex mixture was observed at 60 °C in DMF. This

(19) Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489.
(20) For examples of ruthenium-catalyzed intermolecular coupling of alkenes and silyl alkynes, see: Trost, B. M.; Machacek, M.; Schnaderback, M. J. *Org. Lett.* **2000**, *2*, 1761.

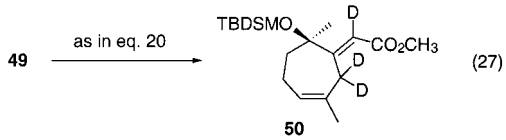
Scheme 1. Preparation of Selectively Labeled Substrate[a]



[a] (a) (i) 9-BBN-Br, CH_2Cl_2, methyl vinyl ketone, (ii) NaOH, H_2O/$PhCH_3$; (b) *n*-C_4H_9Li, THF, −78 °C; (c) $TBDMSOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2; (d) *t*-C_4H_9Li, CuI, Et_2O; (e) K_2CO_3, CH_3OH; (f) *n*-C_4H_9Li, $ClCO_2CH_3$, THF, −78 °C.

result suggests that a methyl group cis on the double bond is needed for good reaction.

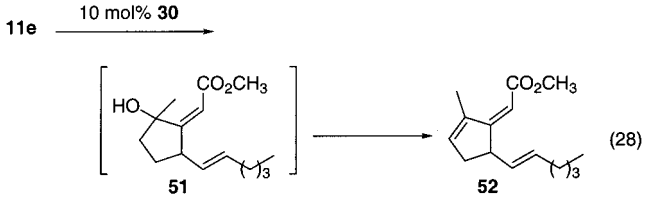
To probe this question further, one of the two methyl groups of **12d** was labeled with deuterium (i.e., **49**). The synthesis of the geometrically defined substrate was performed as shown in Scheme 1.[21] Subjecting enyne **49** to the standard conditions led to a uniquely labeled product, as shown in eq 27. ^1H and ^2H



(27)

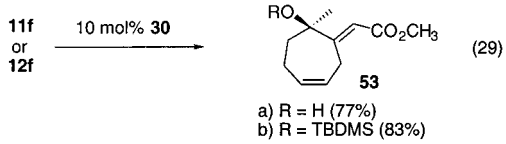
NMR spectra of cycloheptene **50** showed that deuterium was only (>95%) incorporated into the doubly allylic and enoate positions, with no deuterium detected in the vinyl methyl group. Thus, C−H insertion occurs exclusively with the *cis*-methyl group of the trisubstituted alkene.

The requirement for a *cis*-alkene substituent was verified by cycloisomerizing enyne **11e** (eq 28). In acetone at room



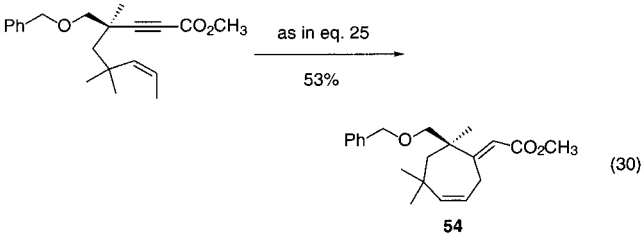
(28)

temperature a 29% isolated yield of triene **52** was obtained that increased to 47% when DMF was employed as solvent. None of the presumed precursor diene **51** was observed. Employing the silyl ether **12e** led to a very slow reaction from which the same triene **52** was isolated in only 10% yield. On the other hand, *cis*-alkene substrates**11f** and **12f** (eq 29) both smoothly



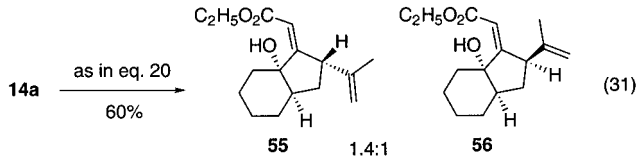
(29)

cycloisomerize to form exclusively cycloheptenes **53a** (DMF, rt, 77%) and **53b** (acetone, rt, 83%). Furthermore, an extremely sterically hindered substrate[22] with quaternary carbons at the allylic position as well as the propargylic position also cycloisomerized smoothly to form seven-membered ring **54** exclusively at room temperature (eq 30).



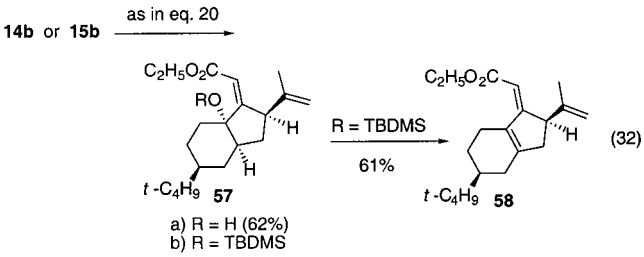
(30)

Interestingly, the fusion of a ring on the tether also affected the regioselectivity. While the minor isomer of the acetylide addition, i.e., the epimer of **14a** having the alkyl substituents *trans*, only produces a complex mixture, the major epimer **14a** nicely cycloisomerizes to form the cyclopentenes **55** and **56** (eq 31) with only a trace of seven-membered ring product. The



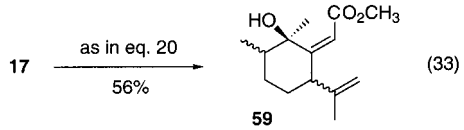
(31)

relative stereochemistry of perhydroindanols **55** and **56** was assigned on the basis of a combination of NOE experiments and ^{1}H NMR coupling constants (Figure 1). The 4-*tert*-butyl-substituted substrate also gave a 62% yield of the cyclopentanol **57a** as a single diastereomer accompanied by <10% of a product tentatively assigned as the cycloheptene (eq 32). The relative



(32)

stereochemistry was assigned by spectral comparison to indanols **55** and **56**. The silyl ether **15b** also reacted, but delivered only **58**, the product of further elimination of the presumed initial cycloisomer **57b** (eq 33).



(33)

A brief examination was made to check the extension of this new cycloisomerization to form eight-membered rings. Thus, exposing **17** (dr 1.6:1) to the ruthenium complex **30** effected cycloisomerization but only to form six-membered ring **59** (eq

(21) Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 5225.
(22) Trost, B. M.; Chang, V. K. *Synthesis* **1993**, 824.

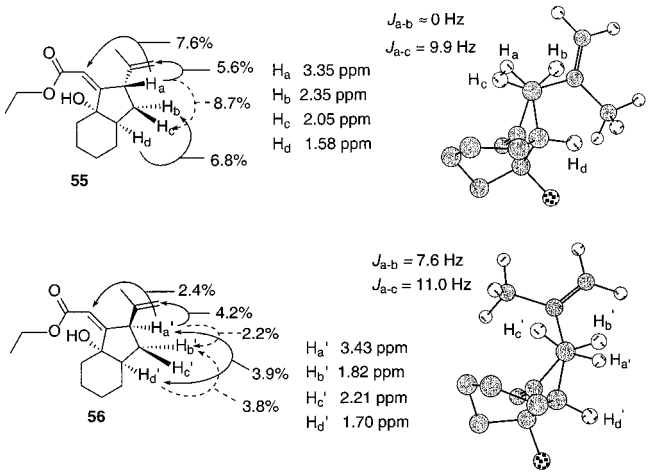
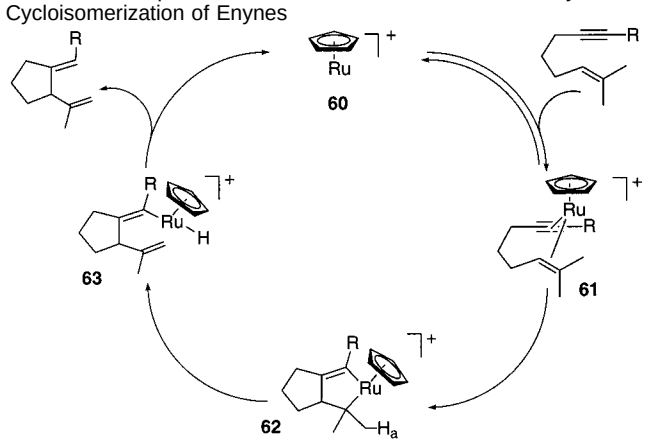


Figure 1. Assignment of relative stereochemistry of perhydroindanols **55** and **56**.

Scheme 2. Proposed Mechanism for the Ruthenium-Catalyzed Cycloisomerization of Enynes



33) in the same diastereomeric ratio as that of starting material—implying that each diastereomer reacted with excellent diastereoselectivity. The relative stereochemistry was not unambiguously established.

Discussion

Upon initiation of our work on the ruthenium-catalyzed intermolecular addition of alkenes and alkynes, two mechanisms were considered viable in our working hypothesis: a π-allylruthenium and a ruthenacyclopentene mechanism. Subsequent studies strongly supported a ruthenacyclopentene (**62**) intermediate (Scheme 2). Coordination of coordinatively unsaturated cyclopentadienylruthenium(+2) (**60**) to the enyne generates complex **61**. Tautomerization of the enyne provides ruthenium(+4) metallacycle **62**, the product of an internal redox process. A β-hydrogen elimination of H_a forms vinylruthenium(+4) hydride **61**, which subsequently undergoes a reductive elimination to regenerate the ruthenium(+2) catalyst and provide the 1,4-diene product.

The ruthenacycle mechanism accounts for the reactivity and selectivity observed in several of the ruthenium-catalyzed cycloisomerizations. For example, *trans*-olefins participate more readily in the cycloisomerization than the corresponding *cis*-olefins (eq 14). Furthermore, geranyl- and neryl-based enynes show a propensity for formation of the new olefin toward the *trans*-substituent (eqs 19 and 20). This observation can be

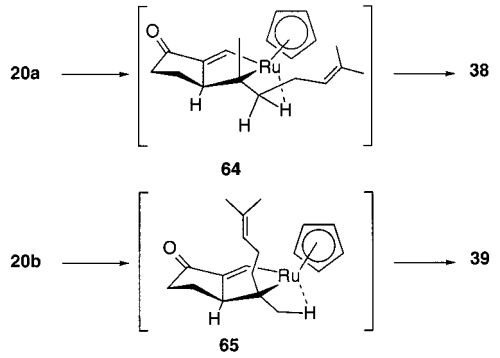


Figure 2. Proposed intermediate ruthenacycles derived from **20a** and **20b**.

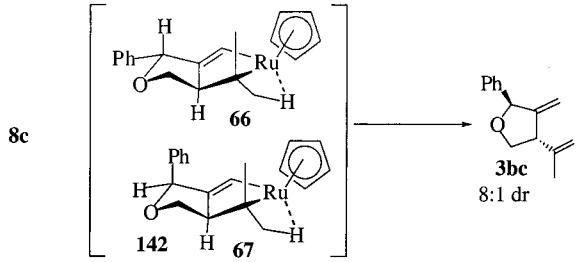


Figure 3. Proposed intermediate ruthenacycles in the diastereoselective formation of furan **36d**.

accounted for by considering the intermediate ruthenacycles (Figure 2). In ruthenacycle **64**, the isohexenyl substituent is situated in a pseudoequatorial position. This conformation places a hydrogen of the isohexenyl group proximal to the metal center—in a position that allows for the necessary overlap for β-hydrogen elimination. On the other hand, the ruthenacycle (**65**) derived from the neryl-based enyne (**20b**) has the methyl group in the pseudoequatorial position. Therefore, β-hydrogen elimination occurs to produce **39** as the major regioisomer. Clearly, β-hydrogen elimination toward the cis-substituent (the pseudoaxial group in the ruthenacycle) is possible; however, this process is of significantly higher energy. This is demonstrated by the difference in temperature required for cycloisomerization of the *trans*- (**2a**) and *cis*-enynes (**2b**) (eq 14).

The diastereoselectivity of the cycloisomerization of enynes containing a propargylic chiral center can also be accounted for by comparing the intermediate ruthenacycles (Figure 3). For example, cycloisomerization of ether **8c** produces furan **37c** as an 8:1 mixture of diastereomers. The major diastereomer derives from ruthenacycle **66**, which places the phenyl group in a pseudoequatorial position. The diastereomeric ruthenacycle (**67**) has the phenyl group in the pseudoaxial position, which has a severe 1,4-diaxial-like interaction. In a carbocylic case (eq 17), wherein the phenyl substituent is replaced by a less bulky alkoxy group, the diastereoselectivity drops to 1.4:1.0.

The ruthenium-catalyzed cycloisomerization of 1,6-enynoates substituted with a propargylic chiral center produces 1,3-*cis* rather than the 1,3-*trans* disubstituted cyclopentanes as the major diastereomer. This reversal in the relative stereochemistry of the major product can be explained by considering intermediate ruthenacycles **68** and **69** (Figure 4). Although in ruthenacycle **68** the *tert*-butyldimethylsilyloxy group is in the pseudoequatorial position, it experiences severe allylic strain ($A_{1,3}$) with the ester group. Placing the silyl ether in the pseudoaxial position, as in **69**, relieves the $A_{1,3}$-strain and therefore favors formation of cyclopentane **42**. There is a delicate balance

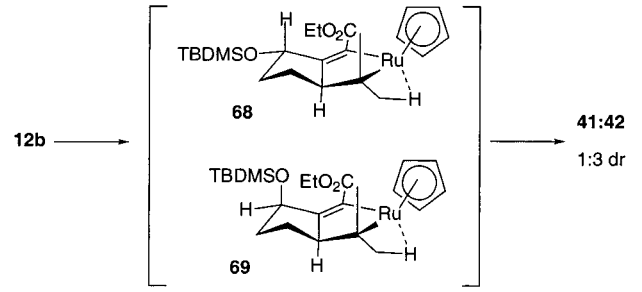
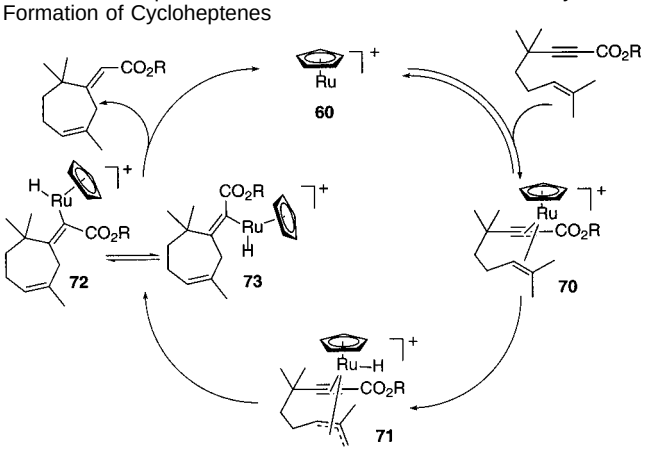


Figure 4. Proposed intermediate ruthenacycles in the diastereoselective formation of cyclopentene **42**.

Scheme 3. Proposed Mechanism for the Ruthenium-Catalyzed Formation of Cycloheptenes



between which interaction (1,4-diaxial or 1,3-allylic) is energetically more costly. For example, in the cycloisomerization of enyne **11b**, simply changing the solvent from acetone to DMF reverses the diastereoselectivity of the reaction (eq 22).

When the enyne is substituted with a quaternary propargylic center, ruthenacycle formation would lead to an intermediate that has both a 1,4-diaxial and 1,3-allylic strain. The high energy of this intermediate inhibits the ruthenacycle pathway and a mechanism involving activation of an allylic C−H becomes operative (Scheme 3). Coordination of coordinatively unsaturated cyclopentadienylruthenium(+2) (**60**) to the enyne produces complex **70**, which undergoes activation of the allylic C−H to give π-allylruthenium(+4) hydride **71**. The coordination step is clearly important, as 1,5-enyne **28a** fails to participate in the reaction, presumably because the tether length does not allow for the bidentate coordination. A 7-exo-dig carbaruthenation[23] produces vinylruthenium(+4) hydride **73**, which is in equilibrium, via the ruthenium(+4) allenolate, with **72**. Substitution of an ester group on the alkyne is presumably required in order to activate the alkyne toward addition of the π-allylruthenium species. Reductive elimination occurs selectively from complex **72** to produce the cycloheptene and regenerate the ruthenium-(+2) catalyst (**60**). Notably, geometry of the enoate is opposite that obtained in the previous cases. Presumably, formation of olefin geometry depicted in Scheme 3 occurs in order to avoid the severe 1,3-allylic strain associated with the vinyl ester group and the allylic quaternary center. Equations 22−26 illustrate the sensitivity of the competition to the steric bulk at the propargylic and alkene positions.

(23) For recent examples of carboruthenation of alkynes by π-allylruthenium complexes, see: (a) Older, C. M.; Stryker, J. M. *Organometallics* **2000**, *19*, 3266. (b) Older, C. M.; Stryker, J. M. *Organometallics* **2000**, *19*, 2661.

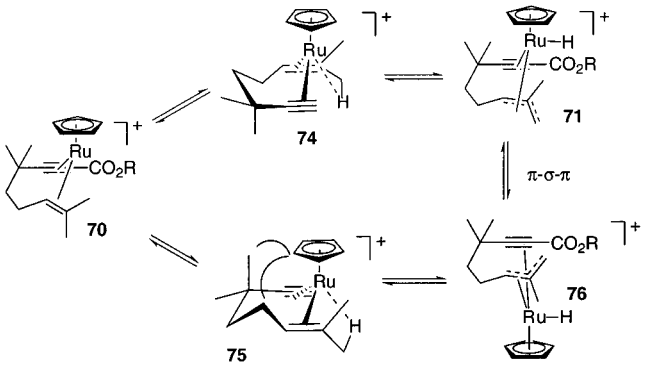


Figure 5. Proposed agostic complexes for the ruthenium-catalyzed C−H activation.

To generate a cycloheptene containing a *cis*-olefin, the carbaruthenation must occur from *anti*-π-allylruthenium complex **71** (see Figure 5). This complex may be directly generated from insertion into the C−H bond of the *cis*-methyl group. Alternatively, complex **71** may arise from insertion into the C−H bond of the *trans*-methyl group to generate *syn*-π-allylruthenium complex **76**, which must then be converted into **71** by a π-σ-π isomerization. The deuterium labeling study shows incorporation of the deuterium from the *cis*-methyl group into the bis-allylic and olefinic positions of the cycloheptene adduct (see eq 27). This result eliminates the possibility that C−H activation is occurring selectively into the *trans*-methyl group to produce **75**, which subsequently isomerizes to **71**. The exclusive reaction via the insertion into the C−H bond of the *cis*-methyl group overrides the kinetic isotope effect, even though that is operating against this pathway with the deuterium-labeled substrate **49**.

Two scenarios for the C−H activation exist that are consistent with the deuterium-labeling study. First, C−H activation is occurring selectively into the *cis*-methyl group's C−H bond. Consideration of the steric interactions present in the agostic complexes **74** and **75** provides one possible explanation for the selective C−H activation of the C−H bond of the *cis*-methyl group. Steric interactions between the propargylic quaternary center and/or the tether with the cyclopentadienyl ligand may inhibit the formation of the agostic complex (**75**) required for insertion into the *trans*-methyl group. These interactions are absent in the agostic complex (**74**), which precludes insertion into the C−H bond of the *trans*-methyl group. The second possibility requires that C−H insertion to generate complexes **71** and **76** be reversible and that these complexes do not interconvert via a π-σ-π isomerization. To the extent that insertion into the C−H bond of the *trans*-methyl group occurs, it simply reverts to starting material, since steric interactions preclude five-membered ring formation (vide infra) and geometric constraints preclude forming a *trans*-cycloheptene. Thus, while C−H insertion may occur indiscriminately, only formation of complex **71** can become productive.

Addition of the alkynoate can occur to either of the two terminal carbons of the π-allylruthenium complex **71** (Figure 6). Addition of the alkynoate to the primary carbon produces a cycloheptene, while addition to the internal secondary carbon produces a cyclopentane product. Although these processes may occur with competitive rates (eq 23), in general, formation of the seven-membered ring dominates. Two factors may account for this reactivity difference. First, for steric reasons, η^1-allylruthenium complex **77** may be more stable than complex **79**, which places the ruthenium on a secondary carbon. Second, transition state **80**, required for addition to the internal carbon, is significantly more congested than the transition state (**78**) for the alkyne insertion which produces the cycloheptene. These factors may be enough to overcome the kinetic bias of a 5-exo-dig cyclization to occur in preference to the 7-exo-dig. Nevertheless, in some cases, the kinetic preference for formation of the five-membered ring may dominate. Thus, for the reasons stated above, substrates **14a**, **14b**, and **15b** should not react via a ruthenacycle mechanism. It is likely that the five-membered ring cycloisomerization products then arise via the π-allyl mechanism. A similar argument applies to the cycloisomerization of an enyne, wherein a six-membered ring forms. In this case, the π-allyl mechanism can form either a six- or eight-membered ring. It is to be expected that formation of the thermodynamically more stable six-membered ring could dominate.

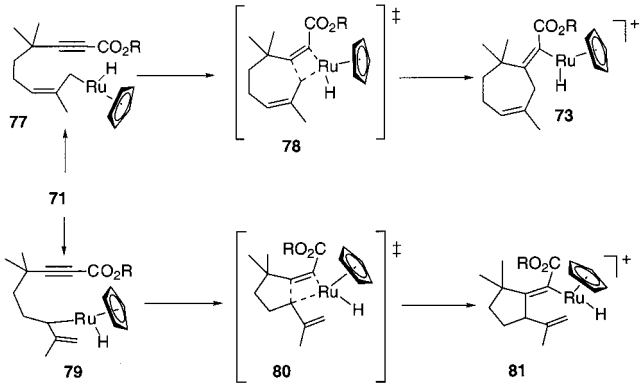


Figure 6. Proposed mechanism for carbaruthenation.

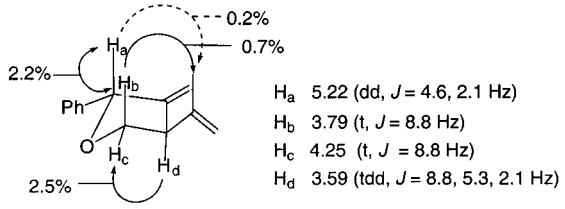


Figure 7. Determination of relative stereochemistry of furan **37c** by NOE.

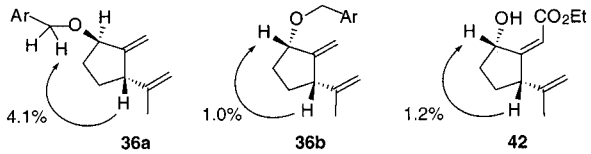


Figure 8. NOE experiments used to determine the relative stereochemistry of 1,3-dienes.

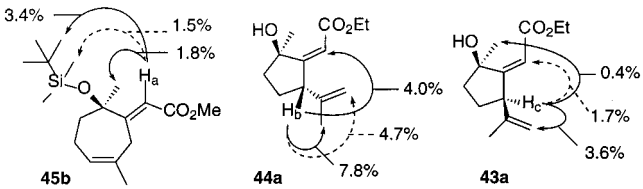


Figure 9. NOE experiments of cycloheptene and cyclopentane adducts.

Conclusion

We have developed several new ruthenium-catalyzed cycloisomerization reactions. The $CpRu(CH_3CN)_3PF_6$-catalyzed cy-

cloisomerization of 1,6- and 1,7-enynes produces cyclopentanes and cyclohexanes with complete selectivity for the 1,4-diene. In many cases, the ruthenium-catalyzed reaction complements the palladium-catalyzed cycloisomerization, which produces both 1,3- and 1,4-dienes. Complementary regiochemical behavior was also observed with the geranyl- and neryl-based enynes. Furthermore, the ruthenium-catalyzed reaction is the first in which the geometry of the starting olefin is reflected in the 1,4-diene regiochemistry of the cyclopentane product. A mechanism involving the formation of an intermediate ruthenacyclopentene accounts for this selectivity as well as the diastereoselectivity of many of the reactions.

We have also shown that a second mechanism is operative in the $CpRu(CH_3CN)_3PF_6$-catalyzed cycloisomerization of 1,6-enynes substituted with a quaternary propargylic center. When these enynes are utilized as substrates, cycloheptenes, not cyclopentanes, are obtained in good yields. On the basis of deuterium-labeling experiments, a mechanism involving ruthenium-catalyzed activation of the allylic C−H to generate a π-allylruthenium species is proposed. This mechanism is unprecedented in other transition-metal-catalyzed cycloisomerizations of enynes. In conclusion, herein we report several ruthenium-catalyzed methods for the generation of a variety of ring systems. These reactions are highly atom economical, since they produce no byproducts and require only $CpRu(CH_3CN)_3PF_6$ as catalyst with no exogenous ligands or cocatalyst.

Experimental Section

General Procedure. In DMF. To a test tube containing $CpRu(CH_3CN)_3PF_6$ (11 mg, 0.025 mmol) was added a solution of enyne **8c** (50 mg, 0.250 mmol) in DMF (1.3 mL). After 4 h at room temperature, the solution was diluted with diethyl ether (10 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography eluting with 5% diethyl ether:petroleum ether afforded **37c** (26 mg, 54%) as a 7.6:1 mixture of diastereomers.

In Acetone. To a test tube containing $CpRu(CH_3CN)_3PF_6$ (11 mg, 0.025 mmol) was added a solution of enyne **8c** (50 mg, 0.250 mmol) in acetone (1.2 mL). After 2 h at room temperature, the solution was concentrated in vacuo and chromatographed eluting with 5% diethyl ether:petroleum ether to afford furan **37c** (31 mg, 62%) as a colorless liquid as a 8:1 mixture of diastereomers.

1,1-Bis(methoxycarbonyl)-3-methylene-4-vinylcyclopentane (31a)[5b] was isolated as a colorless liquid by flash chromatography eluting with 6:1 petroleum ether:diethyl ether.

IR (film): 3080, 2956, 2850, 1732, 1659, 1641, 1435, 1270, 1202, 1169, 1073, 918 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.62 (ddd, J = 17.6, 9.5, and 8.3 Hz, 1H), 5.05 (dd, J = 17.6 Hz, 1H), 5.04 (d, J = 9.5 Hz, 1H), 4.96 (d, J = 2.2 Hz, 1H), 4.80 (q, J = 2.2 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.13 (m, 1H), 3.05 (d, J = 17.0 Hz, 1H), 2.92 (ddd, J = 17.0, 4.6, and 2.5 Hz, 1H), 2.57 (ddd, J = 13.0, 7.8, and 1.2 Hz, 1H), 1.99 (dd, J = 13.0 and 11.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 172.0, 150.3, 139.0, 116.1, 108.1, 58.5, 52.9, 52.8, 47.7, 40.3, 40.2.

1,1-Bis(benzenesulfonyl)-3-methylene-4-vinylcyclopentane (31b)[24] was isolated as a white solid, mp 112−114 °C (lit.[41] mp 113−114 °C) by flash chromatography eluting with 5:1 petroleum ether:diethyl ether.

IR (film): 3058, 2983, 1447, 1329, 1311 1145, 1078, 926, 734, 688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 7.0.5 Hz, 2H), 8.04 (d, J = 7.5 Hz, 2H), 7.77 (t, J = 7.5 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 5.56 (ddd, J = 17.2, 10.0, and 8.5 Hz, 1H), 5.14 (dd, J = 10.0 and 1.1 Hz, 1H), 5.10 (d, J = 17.2 Hz, 1H), 4.90 (d, J = 2.1 Hz, 1H), 4.78 (d, J = 2.1 Hz, 1H), 3.36 (m, 1H), 3.31 (m, 2H), 2.77 (dd, J = 15.0 and 8.5 Hz, 1H), 2.50 (dd, J = 15.0 and 10.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 137.5, 136.4, 136.0, 134.8, 134.6, 131.3, 131.2, 128.8, 128.7, 117.7, 108.7, 91.2, 48.0, 38.0, 37.5.

1,1-Bis(ethoxycarbonyl)-4-methylene-3-vinylcyclohexane (31c) was isolated by flash chromatography eluting with 8:1 petroleum ether: diethyl ether.

IR (film): 2955, 1733, 1437, 1241, 1201, 1087, 1006, 900 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.60 (ddd, J = 17.2, 10.2, and 7.8 Hz, 1H), 5.13 (m, 2H), 4.77 (d, J = 1.6 Hz, 1H), 4.66 (d, J = 1.6 Hz, 1H), 4.27 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 2.87 (m, 1H), 2.44 (m, 3H), 2.21 (m, 1H), 1.80 (td, J = 13.0 and 4.4 Hz, 1H), 1.69 (t, J = 13.0 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.8, 170.9, 148.9, 139.3, 115.6, 115.6, 61.5, 61.3, 54.9, 43.4, 37.6, 32.3, 32.0, 14.1, 14.0. HRMS calcd for $C_{15}H_{22}O_4$: 256.1518. Found: 256.1512.

1,1-Bis(benzenesulfonyl)-4-isopropenyl-3-methylenecyclohexane (31e) was isolated as a white solid, mp 112−114 °C, by flash chromatography eluting with 3:1 petroleum ether:diethyl ether.

IR (film): 3065, 2924, 1650, 1582, 1447, 1328, 1308, 1145, 1077, 904, 734, 688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.09 (m, 4H), 7.75 (m, 2H), 7.62 (m, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 4.89 (s, 1H), 3.07 (s, 2H), 2.79 (dd, J = 10.3 and 4.4 Hz, 1H), 2.52 (ddd, J = 15.0, 5.2 and 4.7 Hz, 1H), 2.43 (ddd, J = 15.0, 10.6 and 4.7 Hz, 1H), 2.19 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 141.4, 136.5, 136.2, 134.5, 131.5, 131.4, 128.6, 128.5, 113.1, 112.9, 88.4, 47.9, 34.0, 25.8, 25.5, 20.7. Anal. calcd for $C_{22}H_{24}O_4S_2$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.54; H, 5.76; S, 15.19.

1,1-Bis(benzenesulfonyl)-3-methylene-4-methyl-4-vinyl-cyclopentane (31f) was isolated by flash chromatography eluting with 3:1 petroleum ether:diethyl ether.

IR (film): 3085, 2958, 2922, 2851 1447, 1329, 1310, 1144, 1077, 926, 734, 688 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.08 (dd, J = 8.6 and 1.3 Hz, 2H), 8.05 (dd, J = 8.6 and 1.3 Hz, 2H), 7.75 (m, 2H), 7.62 (m, 4H), 5.78 (dd, J = 17.2 and 10.5 Hz, 1H), 5.06 (d, J = 17.2 Hz, 1H), 5.00 (dd, J = 10.5 and 1.0 Hz, 1H), 4.80 (t, J = 1.8 Hz, 1H), 4.68 (t, J = 2.0 Hz, 1H), 3.41 (dt, J = 17.4 and 1.8 Hz, 1H), 3.29 (d, J = 17.4 Hz, 1H), 2.84 (d, J = 16.3 Hz, 1H), 2.67 (d, J = 16.3 Hz, 1H), 1.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.1, 144.7, 137.2, 137.0, 135.4, 132.2, 132.1, 129.5, 112.9, 108.7, 92.1, 44.2, 39.5, 30.4 26.0. HRMS calcd for $C_{21}H_{22}O_4S_2$: 402.0959. Found: 402.0957.

6-(4,4-Bis(methoxycarbonyl)-2-methylene-cyclopentyl)-hex-5-enal (32) was isolated by flash chromatography eluting with 3:1 petroleum ether:diethyl ether.

IR (film): 2953, 2848, 1735, 1436, 1270, 1200, 1170, 1073, 970, 890 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 5.45 (dt, J = 15.2 and 6.8 Hz, 1H), 5.27 (dd, J = 15.2 and 8.2 Hz, 1H), 4.96 (d, J = 1.6 Hz, 1H), 4.78 (d, J = 2.2 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.12 (m, 1H), 3.10 (d, J = 17.2 Hz, 1H), 2.93 (dq, J = 17.2 and 2.2 Hz, 1H), 2.55 (dd, J = 13.0 and 7.6 Hz, 1H), 2.45 (dt, J = 7.6 and 1.1 Hz, 2H), 2.08 (q, J = 7.2 Hz, 2H), 1.97 (dd, J = 12.8 and 11.2 Hz, 1H), 1.72 (p, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.6, 172.2, 172.0, 150.9, 132.0, 131.1, 107.8, 58.4, 52.9, 52.8, 46.6, 43.1, 40.6, 40.2, 31.7, 21.7. HRMS calcd for $C_{16}H_{22}O_5$: 294.1467. Found: 294.1459.

(4,4-Bis(methoxycarbonyl-2-methylenecyclopentyl)methylenecyclohexane (33a)[25] was isolated as a colorless liquid by flash chromatography eluting with 10:1 petroleum ether:diethyl ether. IR (film): 2928, 2853, 1738, 1656, 1435, 1269, 1198, 1173, 1158, 1071, 888 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.91 (m, 2H), 4.77 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.40 (m, 1H), 3.10 (d, J = 17.0 Hz, 1H), 3.35 (dq, J = 17.0 and 2.2 Hz, 1H), 2.55.(dd, J = 13.0 and 7.7 Hz, 1H), 2.18−2.08 (m, 4H), 1.90 (dd, J = 12.8 and 11.6 Hz, 1H),

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1.59−1.48 (m, 6H). ^{13}C NMR (55 125 MHz, $CDCl_3$): 172.4, 172.1, 151.5, 141.8, 122.2, 107.0, 58.3, 52.8, 52.7, 41.4, 41.2, 40.1, 37.1, 29.2, 28.7, 28.2, 26.8.

(4,4-Bis(methoxycarbonyl-2-methylenecyclopentyl)methylenecyclobutane (33b) was isolated as a colorless liquid by flash chromatography eluting with 8:1 petroleum ether:diethyl ether. IR (film): 2956, 1733, 1436, 1265, 1204, 1171, 1076, 917, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 (m, 2H), 4.82 (m, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.13 (m, 1H), 3.09 (d, J = 17.2 Hz, 1H), 2.96 (dq, J = 17.2 and 2.2 Hz, 1H), 2.72−2.64 (m, 4H), 2.55.(dd, J = 12.8 and 7.6 Hz, 1H), 2.18−2.08 (m, 4H), 1.97 (m, 2H), 1.92 (t, J = 12.8 Hz, 1H). HRMS calcd for $C_{15}H_{20}0_4$: 264.1362. Found: 264.1356. Additional ^{1}H NMR (500 MHz, $CDCl_3$) signals for 1,3-diene: δ 4.87 (m, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.27 (m, 1H), 3.20 (s, 2H), 2.77.(dd, J = 13.0 and 7.7 Hz, 1H), 2.09 (dd, J = 13.0 and 7.8 Hz, 1H).

1,3-*trans*-1-(4-Methoxybenzyloxy)-3-isopropenyl-2-methylenecyclopentane (36a).[25] Flash chromatography eluting with 10:1 petroleum ether:diethyl ether afforded first **36b** followed by **36a**. IR (film): 3072, 2957, 1714, 1612, 1513, 1458, 1301, 1248, 1172, 1035, 895, 822 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.27 (t, J = 1.3 Hz, 1H), 5.01 (s, 1H), 4.82 (s, 2H), 4.53 (s, 2H), 4.22 (td, J = 6.4 and 1.6 Hz, 1H), 3.83 (s, 3H), 3.32 (m, 1H), 2.03 (m, 2H), 1.70 (m, 1H), 1.59 (s, 3H), 1.53 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 152.8, 146.5, 130.8, 129.2, 113.7, 112.1, 110.0, 81.4, 70.0, 55.2, 50.0, 31.3, 27.6, 18.4. Anal. calcd for $C_{17}H_{22}0_2$: C, 79.03; H, 8.56. Found: C, 78.90; H, 8.66.

1,3-*cis*-1-(4-Methoxybenzyloxy)-3-isopropenyl-2-methylenecyclopentane (36b).[25] IR (film): 3071, 2957, 2871, 1643, 1613, 1513, 1455, 1301, 1248, 1172, 1063, 1038, 891, 822 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 5.26 (s, 1H), 5.10 (t, J = 1.1 Hz, 1H), 4.85 (s, 1H), 4.82 (s, 1H), 4.56 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.16 (m, 1H), 3.83 (s, 3H), 3.18 (m, 1H), 1.91 (m, 2H), 1.85 (m, 1H), 1.72 (m, 1H), 1.70 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.9, 152.2, 147.2, 130.8, 129.2, 113.7, 111.9, 111.4, 80.9, 69.1, 55.2, 51.0, 32.3, 28.7, 18.4.

***N*-(4-Methylbenzenesulfonyl)-3-isopropenyl-4-methylenepyrrolidine (37a)** was isolated as a colorless liquid by flash chromatographed eluting with 3:1 petroleum ether:diethyl ether. IR (film): 3075, 2923, 2858, 1645, 1597, 1347, 1163, 1094, 1043, 896, 815 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 4.99 (dd, J = 4.6 and 2.1 Hz, 1H), 4.85 (dd, J = 4.6 and 2.0 Hz, 1H), 4.81 (p, J = 1.5 Hz, 1H), 4.78 (s, 1H), 3.87 (d, J = 14.0 Hz, 1H), 3.77 (ddd, J = 14.0, 4.2, and 2.1. Hz, 1H), 3.44 (dd, J = 9.5 and 8.1 Hz, 1H), 3.29 (br t, J = 6.6 Hz, 1H), 2.77 (dd, J = 9.5 and 7.2 Hz, 1H), 2.42 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.8, 143.7, 142.7, 132.7, 129.7, 127.8, 114.3, 108.3, 52.2, 51.9, 50.8, 21.6, 18.6. Anal. calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 66.14; H, 7.10; N, 4.75.

***N*-(4-Methylbenzenesulfonyl)-3-isopropenyl-4-methylenepiperidine (37b)** was isolated as a colorless liquid by flash chromatography eluting with 3:1 petroleum ether:diethyl ether. IR (film): 3081, 2919, 2849, 1645, 1597, 1340, 1165, 1102, 941, 900, 816, 749 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 4.97 (s, 1H), 4.87 (s, 1H), 4.77 (s, 1H), 4.68 (s, 1H), 3.14 (dd, J = 11.2 and 4.4 Hz, 1H), 3.08 (m, 2H), 2.94 (ddd, J = 10.8, 8.0, and 4.2 Hz, 1H), 2.83 (t, J = 5.7 Hz, 1H), 2.40 (s, 3H), 2.38 (ddd, J = 13.6, 7.0, and 4.2 Hz, 1H), 2.25 (ddd, J = 13.6, 8.0 and 4.2 Hz, 1H), 1.71 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.9, 143.5, 142.9, 133.1, 129.6, 127.6, 113.2, 110.7, 50.3, 48.6, 48.0, 32.9, 22.2, 21.5. HRMS calcd for $C_{16}H_{21}NO_2S$: 291.1293. Found: 291.1295.

2,4-*trans*-4-Isopropenyl-3-methylene-2-phenyltetrahydrofuran (37c) was isolated as a colorless liquid by flash chromatography eluting with 5% diethyl ether:petroleum ether. The ratio of diastereomers was determined using ^{1}H NMR by integration of one of the vinyl protons: a triplet at 4.80 ppm for major diastereomer and a triplet at 4.73 ppm for the minor diastereomer. IR (film): 3065, 2924, 2855, 1719, 1646, 1449 1377, 1007, 1069, 1027, 898, 713 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (m, 3H), 7.28 (m, 2H), 5.22 (dd, J = 4.6 and 2.1 Hz, 1H), 4.95 (t, J = 2.5 Hz, 1H), 4.92 (s, 1H), 4.91 (t, J = 1.7 Hz, 1H), 4.80 (t, J = 2.5 Hz, 1H), 4.25 (t, J = 8.8 Hz, 1H), 3.79 (t, J = 8.8 Hz, 1H), 3.59 (ddd, J = 8.8, 5.3, and 2.1 Hz, 1H), 1.73 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 142.9, 141.4, 128.4, 127.9, 127.1, 114.2, 107.9, 84.0, 71.2, 52.9, 18.6. Anal. calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.12; H, 7.99.

3-(1,5-Dimethylhexa-1,4-dienyl)-2-(trimethylsilylmethylene)cyclopentanone (38)[14] was isolated as a colorless liquid by flash chromatography eluting with 15:1 petroleum ether:diethyl ether. The ratio of **38:39** was determined by GC (2 min at 20 °C and then increase 20 °C/min to 250 °C); retention times: **39**, 10.58 min; **38**, 10.73 min.

IR (film): 2964, 1720, 1604, 1448, 1376, 1245, 1120, 1047, 863, 842 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.96 (d, J = 2.8 Hz, 1H), 5.30 (t, J = 6.9 Hz, 1H), 5.15 (t, J = 7.2 Hz, 1H), 3.36 (td, J = 7.7 and 2.5 Hz, 1H), 2.78 (m, 2H), 2.41 (ddd, J = 18.1, 8.5, and 2.8 Hz, 1H), 2.29 (dt, J = 18.1, 10.2, and 9.0 Hz, 1H), 2.07 (m, 2H), 1.73 (s, 3H), 1.67 (s, 1H), 1.52 (s, 3H), 0.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.6, 153.5, 140.8, 134.4, 131.9, 127.9, 122.8, 54.1, 37.6, 37.1, 25.9, 25.0, 17.7, 12.4, −0.8.

3-(5-Methyl-1-methylenehex-4-enyl)-2-(trimethylsilylmethylene)-cyclopentanone (39)[14] was isolated as a colorless liquid by flash chromatography eluting with 15:1 petroleum ether:diethyl ether. The ratio of **39:38** was determined by GC (2 min at 20 °C and then increase 20 °C/min to 250 °C); retention times: **39**, 10.58 min; **38**, 10.73 min.

IR (film): 2951, 1720, 1604, 1448, 1376, 1244, 1118, 1047, 863, 842 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.00 (d, J = 2.4 Hz, 1H), 5.09 (td, J = 5.7 and 1.3 Hz, 1H), 4.93 (s, 1H), 4.82 (d, J = 0.5 Hz, 1H), 3.39 (tdd, J = 8.2, 2.2 and 0.5 Hz, 1H), 2.38 (ddd, J = 18.1, 8.4 and 4.6 Hz, 1H), 2.26 (dt, J = 18.1 and 9.0 Hz, 1H), 2.11 (m, 3H), 1.96 (t, J = 7.7 Hz, 2H), 1.84 (m, 1H), 1.67 (s, 3H), 1.59 (s, 3H), 0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.3, 153.6, 149.7, 141.3, 131.9, 123.9, 112.1, 51.9, 37.4, 32.7, 26.7, 25.7, 25.6, 17.7, −0.8. HRMS calcd for $C_{17}H_{28}OSi$: 276.1417. Found: 267.1414.

1,1-Bis(methoxycarbonyl)-3-methoxycarbonylmethylene-4-vinylcyclopentane (40). Flash chromatography eluting with 3:1 petroleum ether:diethyl ether afforded **40**, followed by a simple hydration product, methyl 5,5-bis(methoxycarbonyl)-3-oxo-7-nonen-2-oate.

IR (film): 2954, 1736, 1715, 1660, 1436, 1355, 1270, 1211, 1171, 1067 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.71 (q, J = 2.6 Hz, 1H), 5.60 (ddd, J = 17.0, 10.0, and 8.2 Hz, 1H), 5.20 (dd, J = 10.0 and 1.3 Hz, 1H), 5.16 (d, J = 17.0 Hz, 1H), 3.78 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H), 3.71 (br d, J = 20.0 Hz, 1H), 3.35 (dt, J = 20.0 and 2.6 Hz, 1H), 3.31 (m, 1H), 2.63 (ddd, J = 12.5, 7.5, and 2.0 Hz, 1H), 2.04 (t, J = 12.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 171.5, 166.8, 164.6, 137.0, 118.3, 114.0, 58.6, 53.0, 52.9, 51.2, 49.8, 40.1, 39.3. Anal. calcd for $C_{14}H_{18}0_6$: C, 59.57; H, 6.43. Found: C, 59.47; H, 6.32.

1,3-*cis*-3-Isopropenyl-2-ethoxycarbonylmethylene-cyclopentan-1-ol (42) (R = H) was isolated as a colorless liquid by flash chromatography eluting with 3:1 petroleum ether:diethyl ether. The ratio of **42:41 (**R═H) was determined using ^{1}H NMR by integration of the bis-allylic methine: a ddd at 3.29 ppm for **42** (R═H) and a ddt at 3.37 ppm for **41** (R═H). IR (film): 3438, 2968, 1692, 1645, 1373, 1347, 1306, 1233, 1201, 1149, 1036 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.75 (dd, J = 2.5 and 1.6 Hz, 1H), 4.92 (m, 1H), 4.89 (s, 1H), 4.81 (s, 1H), 4.29 (s, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.19 (ddd, J = 9.5, 7.3 and 2.4 Hz, 1H), 2.12 (ddd, J = 13.0, 12.3, and 5.9 Hz, 1H), 1.98−188 (m, 2H), 1.82−1.74 (m, 2H), 1.65 (s, 3H), 1.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 168.1, 144.6, 115.5, 114.4, 71.7, 60.5, 54.7, 32.7, 28.2, 18.2, 14.1. Anal. calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.62. Found: C, 68.70; H, 8.49.

Additional signals for minor diastereomer **41** (R═H): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.72 (t, J = 2.4 Hz, 1H), 5.27 (d, J = 2.0 Hz, 1H), 4.94 (s, 1H), 4.86 (m, 1H), 3.37 (ddt, J = 11.3, 1.9 and 2.6 Hz, 1H),

2.28 (m, 1H), 1.58 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 168.3, 143.7, 115.9, 114.5, 72.9, 60.6, 54.4, 32.2, 26.6, 18.2, 14.0.

1,3-*cis*-1-(*tert*-Butyldimethylsilyloxy)-3-isopropenyl-2-ethoxycarbonylmethylenecyclopentane was isolated as a colorless liquid by flash chromatography eluting with 3% diethyl ether:petroleum ether. The ratio of **42:41** (R = TBDMS) was determined using ^{1}H NMR by integration of the bis-allylic methine: a ddd at 3.17 ppm for **42** (R = TBDMS) and a multiplet at 3.50 ppm for **41** (R = TBDMS). IR (film): 2957, 2930, 2857, 1721, 1665, 1250, 1207, 1184, 836, 778 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (dd, J = 3.8 and 1.5 Hz, 1H), 5.46 (d, J = 1.5 Hz, 1H), 4.85 (s, 1H), 4.84 (s, 1H), 4.17 (m, 2H), 3.17 (ddd, J = 10.8, 7.8, and 2.2 Hz, 1H), 2.12 (ddd, J = 13.0, 12.3, and 5.9 Hz, 1H), 1.84 (dd, J = 13.4 and 5.9 Hz, 1H), 1.78 (ddd, J = 13.4, 12.3, and 6.6 Hz, 1H), 1.68 (s, 3H), 1.51 (ddd, J = 13.0, 6.6, and 3.8 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 0.86 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 165.8, 146.5, 115.2, 113.3, 70.5, 59.7, 53.5, 35.5, 27.4, 25.7, 18.2, 17.9, 14.4, −4.9. HRMS calcd for $C_{18}H_{32}O_3Si$ ($M^+ - t$-Bu): 267.1417. Found: 267.1414.

Additional signals for minor diastereomer **41** (R = TBDMS): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.62 (dd, J = 2.5 and 1.5 Hz, 1H), 4.89 (q, J = 1.3 Hz, 1H), 4.83 (s, 1H), 3.50 (m, 1H), 2.13 (m, 1H), 1.60 (s, 3H), 0.78 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 71.0, 35.0, 25.8, 18.0.

1,4-Dimethyl-2-(ethoxycarbonylmethylene)cyclohept-4-en-1-ol (45a). Flash chromatography eluting with 5:1 petroleum ether:diethyl ether (5% triethylamine) afforded **43a**, followed by **44a** and finally **45a**. IR (film): 3482, 2975, 2933, 2852, 1715, 1697, 1645, 1441, 1370, 1279, 1239, 1176, 1102. 1042, 884 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.09 (s, 1H), 5.28 (m, 1H), 4.10 (qd, J = 7.1 and 1.5 Hz, 2H), 3.75 (d, J = 14.4 Hz, 1H), 2.84 (d, J = 14.4 Hz, 1H), 2.13−2.00 (m, 2H), 1.82 (s, 3H), 1.94 (dt, J = 12.4 and 7.2 Hz, 1H), 1.68 (dd, J = 12.4 and 1.6 Hz, 1H), (m, 2H), 1.50 (br s, 1H), 1.35 (s, 3H), 1.23 (t, J = 7.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 164.6, 136.0, 123.9, 113.4, 102.7, 76.5, 59.7, 39.3, 32.5, 28.9, 25.9, 25.9, 23.2, 14.3. HRMS calcd for $C_{13}H_{20}O_3$ ($M - H^+$): 224.1412. Found: 224.1415.

1,3-*cis*-(1-Methyl-3-isopropenyl)-2-ethoxycarbonylmethylenecyclopentan-1-ol (44a).[5] IR (film): 3433, 2965, 2924, 2853, 1692, 1643, 1372, 1346, 1302, 1232, 1201, 1149, 1037, 880 cm−1. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.98 (s, 1H), 5.61 (d, J = 2.8 Hz, 1H), 4.86 (s, 1H), 4.79 (s, 1H), 4.13 (m, 2H), 3.46 (ddd, J = 11.2, 8.6 and 2.8 Hz, 1H), 1.91−1.78 (m, 3H), 1.62−1.58 (m, 1H), 1.56 (s, 3H), 1.40 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.5, 168.4, 144.1, 115.0, 113.2, 78.8, 60.7, 55.2, 40.1, 27.0, 25.9, 17.9, 14.1.

1,3-*trans*-(1-Methyl-3-isopropenyl)-2-ethoxycarbonylmethylenecyclopentan-1-ol (43a).[5] IR (film): 3439, 3076, 2968, 2876, 1693, 1645, 1373, 1347, 1306, 1233, 1201, 1149, 1036, 898, 880 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (s, 1H), 5.59 (d, J = 2.4 Hz, 1H), 4.84 (s, 1H), 4.74 (d, J = 1.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.46 (td, J = 7.7 and 2.3 Hz, 1H), 2.03 (dt, J = 12.6 and 6.8 Hz, 1H), 1.78 (q, J = 7.3 Hz, 2H), 1.71 (m, 1H), 1.62 (s, 3H), 1.42 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.1, 168.4, 145.2, 114.4, 113.6, 78.3, 60.8, 54.9, 40.5, 27.0, 27.1, 18.8, 14.1.

1-(*tert*-Butyldimethylsilyloxy)-1,4-dimethyl-2-methoxycarbonylmethylenecyclohept-4-ene (45b). Flash chromatography eluting with 8:1 petroleum ether:diethyl ether afforded cycloheptene **45b**, followed by cyclopentanol **44b**.[5]

IR (film): 2955, 2931, 2857, 1720, 1649, 1434, 1255, 1167, 835 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.36 (br d, J = 3.9 Hz, 1H), 3.71 (s, 3H), 2.91 (d, J = 14.4 Hz, 1H), 2.22 (m, 1H), 1.98 (m, 2H), 1.90 (s, 3H), 1.85 (m, 2H), 1.42 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 165.4, 136.0, 124.4, 113.1, 79.0, 50.9, 39.3, 32.3, 25.9, 25.8, 23.2, 18.4, 14.0, −2.1, −2.2. HRMS calcd for $C_{14}H_{23}O_3Si$ ($M^+ - t$-Bu): 267.1416. Found: 267.1409.

1,3-*trans*-(1-Methyl-3-isopropenyl)-2-methoxycarbonylmethylenecyclopentan-1-ol (44b).[5] IR (film): 3440, 2968, 2860, 1692, 1644, 1373, 1346, 1304, 1232, 1201, 1149, 1037 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.00 (s, 1H), 5.71 (d, J = 2.5 Hz, 1H), 4.94 (s, 1H), 4.87 (s, 1H), 3.76 (s, 3H), 3.46 (ddd, J = 11.7, 7.9 and 2.5 Hz, 1H), 2.00−1.88 (m, 3H), 1.66 (dd, J = 12.1 and 7.2 Hz, 1H), 1.63 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 165.8, 146.5, 115.2, 113.3, 70.5, 59.7, 53.5, 35.5, 27.4, 25.7, 18.2, 17.9, 14.4, −4.9.

2,3-*trans*-Diphenyl-6-methoxycarbonylmethylene-8-methyl-1,4-dioxaspiro[4.6]undec-8-ene (46) was isolated as a colorless liquid by flash chromatography eluting with 10:1 petroleum ether:diethyl ether. IR (film): 3033, 2946, 1722, 1650, 1453, 1433, 1236, 1163, 763, 699 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.32 (m, 6H), 7.26 (m, 2H), 7.20 (m, 2H), 6.36 (s, 1H), 5.57 (br t, 1H), 4.82 (d, J = 8.6 Hz, 1H), 4.73 (d, J = 8.6 Hz, 1H), 3.78 (s, 3H), 3.73 (d, J = 14.8 Hz, 1H), 3.55 (d, J = 14.8 Hz, 1H), 2.35 (m, 1H), 2.23−2.12 (m, 3H), 1.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 157.1, 138.0, 136.0, 135.8, 128.5, 128.4, 127.7, 127.0, 126.8, 124.7, 112.7, 110.9, 85.8, 85.0, 51.2, 39.2, 31.4, 25.5, 22.4. Anal. calcd for $C_{25}H_{26}O_4$: C, 76.90; H, 6.71. Found: C, 76.74; H, 6.59.

2-Methoxycarbonylmethylene-1,1,4-trimethylcyclohept-4-ene (47) was isolated as a colorless liquid by flash chromatography eluting with 5% diethyl ether:petroleum ether.

IR (film): 2965, 1718, 1636, 1432, 1236, 1167 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.73 (s, 1H), 5.31 (br t, 1H), 3.71 (s, 3H), 3.42 (s, 2H), 2.00 (m, 2H), 1.91 (d, J = 0.9 Hz, 3H), 1.76 (m, 2H), 1.17 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.9, 167.6, 135.8, 124.0, 112.6, 50.9, 41.3, 38.6, 32.1, 27.8, 26.1, 24.5. HRMS calcd for $C_{13}H_{20}O_2$: 208.1463. Found: 208.1457.

1-(*tert*-Butyldimethylsilyloxy)-2-methoxycarbonylmethylene-1-methyl-4-(4-methylpent-3-enyl)cyclohept-3-ene (48) was isolated as a colorless liquid by flash chromatography eluting with 5:1 petroleum ether:methylene chloride. IR (film): 2957, 2930, 2859 1722, 1650, 1434, 1256, 1167, 836 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.16 (s, 1H), 5.36 (br d, J = 6.6 Hz, 1H), 5.14 (t, J = 6.4 Hz, 1H), 3.77 (d, J = 14.4 Hz, 1H), 3.71 (s, 3H), 2.90 (d, J = 14.4 Hz, 1H), 2.28−2.12 (m, 5H), 2.02 (dd, J = 13.7 and 11.9 Hz, 1H), 1.93 (m, 1H), 1.85 (dd, J = 13.7 and 7.1 Hz, 1H), 1.71 (s, 3H), 1.64 (s, 3H), 1.43 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 165.6, 139.8, 131.2, 124.3, 124.0, 113.2, 79.1, 78.7, 50.9, 39.8, 39.3, 31.3, 28.7, 26.6, 25.9, 25.7, 23.3, 18.4, 17.7, −2.1, −2.2. HRMS calcd for $C_{19}H_{31}O_3Si$ ($M^+ - t$-Bu): 335.2038. Found: 335.2042.

1-(tert-Butyldimethylsilyloxy)-3,3-dideutero-1,4-dimethyl-2-(methoxycarbonyldeuteriomethylene)cyclohept-4-ene (50) was isolated as a colorless liquid by flash chromatography eluting with 5% diethyl ether:petroleum ether.^{1}H NMR (500 MHz, $CDCl_3$): δ 5.36 (br d, J = 3.9 Hz, 1H), 3.71 (s, 3H), 2.22 (br t, 1H), 1.98 (dd, J = 13.6 and 11.9 Hz, 1H), 1.90 (s, 3H), 1.85 (m, 2H), 1.42 (s, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.9, 136.0, 124.4, 79.0 (J_{C-D} = 30. 2 Hz), 50.9, 39.3, 32.3, 25.9, 25.8, 23.2, 18.4, 14.0, −2.1, −2.2. HRMS calcd for $C_{14}H_{20}D_3O_2Si$ ($M^+ - t$-Bu): 270.1602. Found: 270.1595.

3-(Ethoxycarbonylmethylene)-4-(hex-1-enyl)-2-methylcyclopent-1-ene (52) was isolated as a colorless liquid by flash chromatography eluting with 15:1 petroleum ether:diethyl ether. IR (film): 2959, 2922, 2850, 1719, 1620, 1443, 1266, 1039, 968 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.20 (m, 1H), 5.58 (s, 1H), 5.51 (dt, J = 15.2 and 6.7 Hz, 1H), 5.32 (ddt, J = 15.2, 9.0, and 1.3 Hz, 1H), 4.17 (qd, J = 7.1 and 1.3 Hz, 2H), 3.39 (m, 1H), 2.63 (ddt, J = 18.0, 7.1 and 2.2 Hz, 1H), 2.21 (dm, J = 18.0 Hz, 1H), 2.07 (dd, J = 3.6 and 2.0 Hz, 3H), 2.06 (m, 2H), 1.42−1.26 (m, 6H), 1.31 (t, J = 7.1 Hz, 3H), 0.89 (dt, J = 8.6 and 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.5, 165.0, 144.9, 140.6, 133.5, 132.4, 110.7, 60.6, 51.1, 38.2, 32.8, 32.3, 23.0, 17.3, 15.1, 14.7. HRMS. calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1779.

2-Ethoxycarbonylmethylene-1-methylcyclohept-4-en-1-ol (53a) was isolated as a colorless liquid by flash chromatography eluting with 5:1 petroleum ether:methylene chloride. IR (film): 3478, 2979, 2932,

1714, 1698, 1644, 1238, 1177 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.15 (s, 1H), 5.86 (br t, J = 8.5 Hz, 1H), 5.63 (ddd, J = 13.9, 6.7, and 2.7 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.96 (dd, J = 14.7 and 8.0 Hz, 1H), 2.85 (d, J = 14.7 Hz, 1H), 2.24 (m, 2H), 2.12 (m, 1H), 1.84 (dd, J = 13.4 and 6.8 Hz, 1H), 1.44 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 165.3, 130.3, 127.1, 113.0, 76.5, 59.8, 39.0, 28.8, 27.7, 24.0, 14.3. Anal. calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.69; H, 8.55.

1-(*tert-Butyldimethylsiloxy)-2-ethoxycarbonylmethylene-1-methylcyclohept-4-ene* (53b) was isolated as a colorless film by flash chromatography eluting with 2% diethyl ether:petroleum ether.

IR (film): 2956, 2932, 2857, 1716, 1644, 1258, 1163, 836 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.10 (s, 1H), 5.86 (ddd, J = 13.9, 7.5 and 2.7 Hz, 1H), 5.63 (ddd, J = 13.9, 6.7 and 2.3 Hz, 1H), 4.16 (m, 2H), 3.84 (dd, J = 14.5 and 6.7 Hz, 1H), 2.89 (dd, J = 14.5 and 2.3 Hz, 1H), 2.32 (t, J = 14.4 Hz, 1H), 1.96−2.07 (m, 2H), 1.84 (dd, J = 13.7 and 6.4 Hz, 1H), 1.44 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.1, 166.2, 131.6, 128.2, 113.9, 79.7, 60.4, 40.1, 29.5, 28.2, 26.7, 24.7, 19.2, 15.0, −1.3, −1.4. Anal. calcd for $C_{18}H_{32}O_3Si$: C, 66.61; H, 9.94. Found: C, 66.83; H, 9.75.

1-(Benzyloxycarbonylmethyl)-2-methoxycarbonylmethylene-1,6,6-trimethylcyclohept-4-ene (54) was isolated as a colorless liquid by flash chromatography eluting with 5:1 petroleum ether:methylene chloride.

IR (film): 2959, 2917, 2850, 1721, 1640, 1269, 1169, 710 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 7.9 Hz, 2H), 7.69 (t, J = 7.3 Hz, 1H), 7.48 (dd, J = 7.9 and 7.3 Hz, 2H), 5.78 (s, 1H), 5.75 (ddd, J = 10.8, 7.9, and 3.5 Hz, 1H), 5.28 (d, J = 10.8 Hz, 1H), 4.31 (d, J = 10.9 Hz, 1H), 3.78 (dd, J = 14.2 and 7.9 Hz, 1H), 3.71 (s, 3H), 3.21 (ddd, J = 14.2, 3.5, and 2.9 Hz, 1H), 2.10 (d, J = 14.7 Hz, 1H), 1.60 (d, J = 14.7 Hz, 1H), 1.45 (s, 3H), 1.07 (s, 3H), 1.05 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 166.3, 163.8, 140.3, 133.1, 129.6, 128.4, 122.9, 114.0, 71.4, 51.1, 45.4, 45.0, 37.7, 33.1, 29.6, 26.9, 24.6. HRMS calcd for $C_{20}H_{22}O_3$ ($M^+ - CH_3OH$): 310.1568. Found: 310.1573.

1-Ethoxycarbonylmethylene-2-isopropenyloctahydroindan-7a-ol (55). Flash chromatography eluting with petroleum ether:diethyl ether afforded indanol **55**, followed by **56**.

IR (film): 3406, 2932, 2853, 1688, 1640, 1373, 1221, 1184, 1165, 1051 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.89 (s, 1H), 5.69 (d, J = 2.0 Hz, 1H), 4.83 (s, 1H), 4.77 (d, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.35 (d, J = 9.9 Hz, 1H), 2.35 (m, 1H), 2.05 (td, J = 13.4 and 9.9 Hz, 1H), 1.81 (d, J = 13.9 Hz, 1H), 1.83−1.65 (m, 2H), 1.72 (s, 3H), 1.59 (s, 3H), 1.58−1.37 (m, 6H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 168.3, 147.2, 113.4 (2), 79.6, 60.7, 50.7, 42.9, 31.9, 30.1, 23.2, 20.7, 20.0, 19.6, 14.1. Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.80; H, 9.41.

1-Ethoxycarbonylmethylene-2-isopropenyloctahydroindan-7a-ol (56). IR (film): 3417, 2934, 2859, 1689, 1642, 1372, 1346, 1221, 1184, 1168, 1130, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (s, 1H), 5.64 (d, J = 2.8 Hz, 1H), 4.94 (s, 1H), 4.86 (s, 1H), 4.19 (m, 2H), 3.43 (ddd, J = 11.0, 7.6, and 2.5 Hz, 1H), 2.21 (dt, J = 12.6 and 7.0 Hz, 1H), 1.95 (d, J = 14.0 Hz, 1H), 1.87−1.70 (m, 4H), 1.67 (s, 3H), 1.62 (d, J = 14.6 Hz, 1H), 1.58−1.38 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1, 169.2, 145.2, 115.6, 113.6, 79.1, 61.4, 54.0, 43.7, 31.3, 31.2, 24.0, 21.6, 21.4, 19.0, 14.9. HRMS calcd for $C_{16}H_{24}O_3$: 264.1725. Found: 264.1729.

5-*tert-Butyl-1-ethoxycarbonylmethylene-2-isopropenyloctahydroindan-7a-ol* (57a) was isolated as a colorless liquid by flash chromatography eluting with 6:1 petroleum ether:diethyl ether. IR (film): 3406, 2948, 2868, 1693, 1644, 1367, 1208 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.66 (d, J = 2.8 Hz, 1H), 4.95 (d, J = 1.5 Hz, 1H), 4.88 (d, J = 1.5 Hz, 1H), 4.76 (br s, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.50 (ddd, J = 11.3, 7.8, and 2.5 Hz, 1H), 2.24 (td, J = 11.9 and 7.3 Hz, 1H), 2.05 (m, 2H), 1.81 (ddd, J = 13.7, 8.8, and 4.3 Hz, 1H), 1.71 (m, 2H), 1.67 (s, 3H), 1.51 (ddd, J = 12.3, 7.8, and 1.8 Hz, 1H), 1.68 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H), 0.86 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.3, 168.6, 145.0, 114.8, 114.0, 79.8, 60.8, 53.8, 45.4, 44.0, 34.7, 33.2, 32.7, 29.0, 27.2, 22.4, 18.1, 14.1. HRMS calcd for $C_{20}H_{32}O_3$: 320.2351. Found: 320.2351.

5-*tert-Butyl-1-(2-ethylperoxyethylidene)-2-isopropenyl-2,3,4,5,6,7-hexahydro-1H-indene (58)* was isolated as a colorless liquid by flash chromatography eluting with 2% diethyl ether:petroleum ether. IR (film): 2960, 1715, 1610, 1443, 1365, 1161, 1058 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 5.43 (s 1H), 4.86 (s, 2H), 4.25 (m, 2H), 3.49 (m, 1H), 2.62−2.44 (m, 3H), 2.32−2.19 (m, 2H), 2.05−1.92 (m, 2H), 1.59 (s, 3H), 1.57 (s, 3H), 1.41 (tdd, J = 12.3, 5.1, and 1.1 Hz, 1H), 1.30 (t, J = 7.2 Hz, 3H), 1.09 (qd, J = 12.2 and 4.8 Hz, 1H), 0.92 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.8, 164.6, 157.4, 146.1, 136.4, 114.0, 106.5, 59.6, 53.1, 44.0, 39.1, 33.1, 29.6, 27.2, 26.7, 24.5, 17.4, 14.4. HRMS calcd for $C_{20}H_{30}O_2$: 302.2246. Found: 302.2168.

1,6-Dimethyl-3-isopropenyl-2-ethoxycarbonylmethylenecyclohexan-1-ol (59) was isolated as a colorless film by flash chromatography eluting with 3:1 petroleum ether:diethyl ether. The diastereomeric ratio was determined by ^1H NMR by integration of the signal for the olefinic proton of the α,β-unsaturated ester: a singlet at 6.45 ppm for the major diastereomer and a singlet at 6.37 ppm for the minor diastereomer.

IR (film): 3457, 2922, 2859, 1714, 1628, 1447, 1370, 1174, 1120, 1030, 885 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.45 (s, IH), 4.92 (s, 2H), 4.84 (br s, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.24−2.20 (m, 1H), 2.05−1.99 (m, 1H), 1.73 (s, 3H), 1.65−1.54 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.22 (s, 3H), 1.01 (d, J = 5.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.4, 164.7, 146.0, 114.5, 109.3, 76.7, 59.8, 45.6, 40.8, 28.1, 27.9, 22.3, 20.9, 15.5, 14.3. HRMS calcd for $C_{15}H_{22}O_2$ ($M^+ - H_2O$): 234.1619. Found: 234.1635.

Additional ^1H NMR (500 MHz, $CDCl_3$) signals for the minor diastereomer: 6.37 (s, IH), 4.89 (s, 1H), 4.78 (m, 1H), 1.48 (s, 3H), 0.96 (d, J = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.1, 146.3, 116.3, 109.1, 76.4, 59.7, 42.6, 40.6, 28.7, 26.3, 22.2, 22.0, 13.6.

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Supporting Information Available: Spectral data and procedures for the preparation of **2a−e, 3a−b, 4a−c, 5, 6, 8a−c, 9, 11b−f, 12b−f, 13a−b, 14a−b, 15b, 20a−c, 22, 23, 24a−b, 25a−b, 26a−b, 27a−b, 28a−b,** all intermediates of Scheme 1, and **49**. This material is available free of charge via the Internet at http/::pubs.acs.org.

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