Nickel-Catalyzed Organozinc-Promoted Carbocyclizations of Electron-Deficient Alkenes with Tethered Unsaturation

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Abstract: A nickel-catalyzed method for cyclizations of electron-deficient alkenes with tethered unsaturation in the presence of organozincs was developed. Considerable flexibility in the structure of each reactive component was observed. Enones, alkylidene malonates, unsaturated β-ketoesters, and nitroalkenes participated as the electron-deficient alkene; alkynes, enones, 1,3-dienes, and aldehydes participated as the tethered unsaturation; and a variety of sp^2 and sp^3-hybridized organozincs, including those that possess β-hydrogens, participated as the nucleophilic component. Substrate structure, organozinc structure, and ligand structure all played a significant role in determining product selectivities. Of particular synthetic significance was the opportunity to prepare either *E* or *Z* tri- or tetrasubstituted alkenes from a common alkyne. A discussion of probable mechanisms is provided.

Introduction

Transition-metal catalysis provides the basis for many important methods for complex ring system construction.[1] Features of metal-mediated cyclizations that contribute to their general utility include the impressive levels of complexity that may be rapidly introduced from simple precursors, the facility with which sterically-congested quaternary centers may be introduced, and the mildness of reaction conditions accompanied by high chemoselectivities and functional group tolerance. Numerous strategies for initiating transition metal-catalyzed cyclizations exist, with oxidative addition,[2] metallacycle formation,[3] and olefin metathesis[4] representing some of the more commonly encountered methods. The observation by Mackenzie that nickel(0) undergoes oxidative addition to enals in the presence of trialkylsilyl chlorides led us to consider this fundamental process as a method for initiating metal-catalyzed cyclizations (eq 1).[5] Whereas the mechanistic issues associated with the transformations described herein are complex and somewhat speculative at this stage (*vide infra*), we have considered the oxidative addition of nickel(0) to enones in the presence of Lewis acids to produce reactive π-allyl complexes as a working mechanistic model for the development of a new method for initiating metal-catalyzed cyclizations.[6]

$$(1)$$
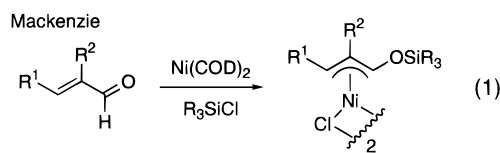
Three principal reaction manifolds have been discovered during the course of our investigations: direct conjugate addition, alkylative cyclization, and reductive cyclization.[7] An electron deficient alkene, a tethered unsaturation, and a Lewis acidic main group organometallic are essential components of the cyclizations. Whereas the results of Mackenzie dealt exclusively with silyl chlorides as the Lewis acidic component in the oxidative addition described above, we initially considered the use of organozincs as an integral component in the coupling reactions. The choice of this particular main group organometallic derives from the studies of Negishi,[8] Knochel,[9] Grigg,[10] and others who demonstrated many applications of organozincs in metal-mediated cross-coupling procedures, and from the studies of Luche who demonstrated that organozincs smoothly underwent conjugate addition to enones in the presence of Ni-(acac)$_2$.[11] Apparently organozincs offer appropriate Lewis acidity to facilitate the interaction of low valent nickel catalysts with enones while maintaining sufficient nucleophilicity to allow unstabilized carbon substituents to readily transmetalate with reactive intermediate nickel complexes. Our studies reported herein provide a description of the range of electron-deficient alkenes, tethered unsaturations, and organozincs that efficiently undergo nickel-catalyzed cyclizations as well as preliminary insight into the reaction mechanism.

Results

Cyclizations of electron deficient alkenes tethered to terminal alkynes upon exposure to Ni(COD)$_2$ and an organozinc in THF

[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1997.

(1) For representative examples: (a) Trost, B. M; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. (b) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304. (c) Copéret, C.; Ma, S.; Negishi, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2125. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

(2) (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science: Mill Valley, CA, 1994; pp 103−113. (b) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(3) (a) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science: Mill Valley, CA, 1994; pp 115−123. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. (c) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 6787. (d) Knight, K. S.; Wang, D.; Waymouth, R. M. Ziller, J. *J. Am. Chem. Soc.* **1994**, *116*, 1845.

(4) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem Res.* **1995**, *28*, 446.

(5) (a) Johnson, J. R.; Tully, P. S.; Mackenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172. (b) Grisso, B. A.; Johnson, J. R.; Mackenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160.

(6) For other examples of π-allyl complex-initiated cyclizations: (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 38. (b) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941.

(7) Portions of this work have previously been communicated. (a) Montgomery, J.; Savchenko, A. V. *J. Am. Chem. Soc.* **1996**, *118*, 2099. (b) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562.

(8) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323.

(9) Knochel, P. *Synlett* **1995**, 393.

(10) Grigg, R.; Dorrity, M. J.; Malone, J. F.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1990**, *31*, 1343.

(11) Petrier, C.; de Souza Barbosa, J. C.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761.

at 0 °C were generally efficient in the production of alkylidene cycloalkanes, with a significant ligand effect being observed. Reactions carried out in the absence of additional ligands led to completely stereoselective alkylative cyclizations in which the organozinc ligand was incorporated into the cycloadduct, whereas pretreatment of the catalyst with 4 equiv of triphenylphosphine and the use of organozincs bearing sp^3-hybridized substituents with β-hydrogens led to efficient reductive cyclizations with hydrogen atom incorporation rather than introduction of the organozinc substituent (eq 2). Variation of the electron-deficient component demonstrated that a highly electrophilic alkene is a requirement for the organozinc/nickel (0)-promoted cyclizations. Enones, nitroalkenes, and doubly-activated olefins such as alkylidene malonates and unsaturated β-ketoesters were the most efficient electron-deficient components that we have studied (Table 1).

(2)
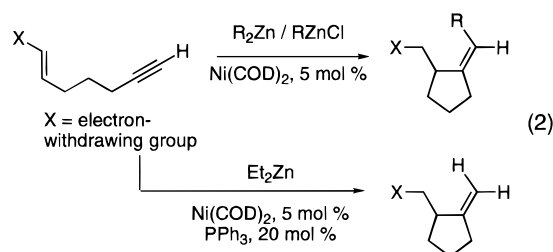
The exceedingly mild reaction conditions (often minutes at 0 °C in THF) afford obvious advantages in terms of chemoselectivities. For instance, the nickel-catalyzed direct conjugate addition of organozincs to each of the above-mentioned functional groups readily proceeds at room temperature; however, this undesired reaction pathway rarely competes with alkyne insertion under the catalytic conditions. Reaction efficiencies rapidly diminish as the electrophilicity of the enone component decreases. Reactions with enoates tethered to alkynes led to poor yields of the expected cyclized products. In most instances, alkylidene malonate cyclization followed by decarboxylation should be the most efficient strategy for obtaining products in the carboxylic acid oxidation state. With sterically-demanding substrates, such as those leading to spirocyclizations (entry 2, Table 1), alkylative cyclizations were generally more efficient than reductive cyclizations. Alkylative cyclizations were also more efficient than reductive cyclizations involving nitroalkenes, even with unhindered substrates.

Considerable flexibility was also observed in the scope of tethered unsaturations tolerated in the nickel-catalyzed cyclizations (Table 2). Both aliphatic and aromatic internal alkynes were cyclized in modest yield by both alkylative (no PPh$_3$) and reductive (with PPh$_3$) cyclization protocols (entries 1−3, Table 2). Whereas reductive cyclizations of terminal alkynes proceeded in very high yield, internal alkynes were less efficient and typically led to alkylative cyclization byproducts. Reactions with alkynyl silanes were efficient, leading to stereodefined exocyclic vinylsilanes (entry 4, Table 2).[12] As noted above, both alkylative and reductive cyclizations occurred by a syn addition mechanism, leading to the introduction of a single isomer of the exocyclic tri- or tetrasubstituted alkenes.

Enones tethered to unactivated alkenes failed to cyclize under all conditions examined (entry 5, Table 2). Both in the presence and absence of triphenylphosphine, only direct conjugate

Table 1. Variation of the Electron-Deficient Component^d

^{a} 9% direct conjugate addition was observed. ^{b} 45% direct conjugate addition was observed. ^{c} Obtained as an inseparable mixture. ^{d} Method A: [MeLi + ZnCl$_2$], 5 mol % Ni(COD)$_2$, THF, 0 °C. Method B: Et$_2$Zn, 5 mol % Ni(COD)$_2$, 20 mol % PPh$_3$, THF, 25 °C.

addition products were observed.[13] Enones tethered to another electron-deficient alkene, however, were efficiently cyclized. In contrast to reactions with alkynyl enones, reductive cyclizations were observed in the *absence* of triphenylphosphine with bis-enones when sp^3-hybridized organozincs were employed (entries 6 and 7, Table 2). High cis selectivities of the cyclopentyl substituents were typically observed, making the nickel-catalyzed process complementary to related free-radical reactions.[14] The ketoenolates that resulted from reductive cyclizations of bis-enones underwent aldol addition to produce [3.3.0]bicyclooctanes in a stereoselective fashion. The stereoselectivity of the aldol addition was variable according to bis-enone structure. Alkylative cyclization of bis-enones was not observed under any conditions examined.

Enones tethered to dienes were cyclized in good yield in the presence of diethylzinc and the catalyst generated from Ni-(COD)$_2$/PPh$_3$ (entry 8, Table 2). Exclusively *trans*-alkenyl side chains were introduced during the cyclizations. However, only the conjugate addition product was obtained with Ni(COD)$_2$/Me$_2$Zn-promoted reactions, both in the presence and absence of PPh$_3$. It is well established that migratory insertions involving conjugated dienes produces π-allyl complexes,[15] and we speculate that the formation of such an η^3-stabilized intermediate explains why enones tethered to dienes are efficient substrates for nickel-catalyzed cyclizations, whereas enones

(12) Intermolecular alkyne silylcupration/conjugate addition sequences afford the opposite alkene stereoisomer. Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. I* **1981**, 2527.

(13) These conjugate additions are considerably slower than additions to enones lacking the pentenyl side chain. Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.

(14) (a) Enholm, E. J.; Kinter, K. S. *J. Org. Chem.* **1995**, *60*, 4850. (b) Enholm, E. J.; Kinter, K, S. *J. Am. Chem. Soc.* **1991**, *113*, 7784. (c) Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 4.

(15) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.

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Table 2. Variation of the Tethered Unsaturation[d]

entry	substrate	product	method (yield)
1	13	14	B (R = H, 83 %)
2	15	16	A (R = Bu, 68 %)[a] B (R = H, 69 %)
3	17	18	A (R = Ph, 38 %) B (R = H, 58 %)[b]
4	19	20	A (R = Me, 70 %) B (R = H, 62 %)[c]
5	21	22	A (R = Bu, 75 %)
6	23	24	A (60–90 %)
7	25	26a + 26b	A (3:1, 71 %)
8	27	28a + 28b	A (28a, 66 %.) B (28b, 70 %)
9	29	30	B (1.5:1, 47 %)
10	31	32	B (2:1, 57 %)
11	33	34 + 35	A (34, R = Me, 73 %) B with TMSCl (34, R = H, 25 %; 35, R = H, 58 %)

[a] 8% of **16** (R = H) was isolated. [b] 16% of **18c** (R = Bu) was isolated. [c] contaminated with 13% of **20** (R = Et). Method A: [MeLi + ZnCl₂], 5 mol % Ni(COD)₂, THF, 0 °C. Method B: Et₂Zn, 5 mol % Ni(COD)₂, 20 mol % PPh₃, THF, 25 °C.
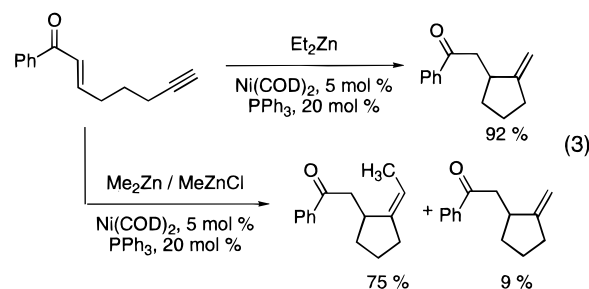
tethered to isolated double bonds afforded only conjugate addition products. Considering the large body of work developed by the Wender and Lautens groups on a variety of Ni-(0)-catalyzed cycloadditions involving unactivated dienes and dienophiles,[16] it is interesting that substrate **27**, which is activated for a normal-demand Diels−Alder reaction, is converted in a completely chemoselective fashion to the reductive cyclization product with no cycloaddition products being observed. The observed reductive cyclizations are reminiscent of the recent report from Takacs involving diene/allylic ether reductive cyclizations[17] and from Mori involving diene/aldehyde reductive cyclizations.[18ab] Further exploration of the chemoselectivity with related substrates and different catalyst/ligand formulations is currently in progress.

Aldoenones were also cyclized in moderate yield in the presence of Ni(COD)₂/PPh₃ (entries 9−10, Table 2). Both five- and six-membered rings were formed as diastereomeric mixtures.[18] This substrate class provides another example of the highly chemoselective nature of the nickel-mediated cyclizations, as only traces of products derived from organozinc addition to the aliphatic aldehydes were observed.

With cyanoenones, direct conjugate addition was observed, even with sp³-hybridized organozincs that typically effected cyclization with other substrate classes (entry 11, Table 2). Treatment of cyanoenone **33** with ZnMe₂/MeZnCl in the presence of Ni(COD)₂ resulted in formation of direct conjugate adduct **34a** (R = Me) in 73% yield. Reactions with diethylzinc

in the presence of triphenylphosphine were sluggish. However, addition of trimethylsilyl chloride to the ZnEt₂/PPh₃ reactions resulted in a 2.3:1 mixture of acyclic products **34b** (R = H) and **35b** (R = H) derived from 1,4-reduction and 1,2-reduction. Within the cyanoenone substrate class, no cyclization was observed, but the PPh₃ effect of favoring products derived from β-hydride elimination is consistent with the results previously obtained with substrate classes that underwent cyclization.

In addition to the electron-deficient component and the tethered unsaturation, the organozinc substituent is a third variable that influences product distributions and selectivities. In reductive cyclizations, the influence of organozinc structure depends heavily on substrate structure. With alkynylenone reductive cyclizations, deuterium labeling studies demonstrated that the major reaction pathway involves β-hydride elimination.[7a] As a result, in the presence of triphenylphosphine, diethylzinc led to reductive cyclization products, whereas dimethylzinc led nearly exclusively to alkylative cyclization products (eq 3). Diethylzinc (commercial) and dibutylzinc (generated *in situ* from butyllithium and anhydrous zinc chloride) both led to reductive cyclization, although commercial diethylzinc led to cleaner reactions with smaller amounts of the product of alkylative cyclization.

$$\text{(3)}$$

With bis-enone reductive cyclizations, all sp³-hybridized organozincs examined, including those that lack β-hydrogens,

(16) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Wender, P. A. Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Gugelchuk, M. M.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 330.

(17) Takacs, J. M.; Mehrman, S. J. *Tetrahedron Lett.* **1996**, *37*, 2749.

(18) For nickel-catalyzed cyclizations involving aldehydes: (a) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc.* **1994**, *116*, 9771. (b) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett.* **1996**, *37*, 887. For representative radical cyclization methods: (c) Enholm, E. J.; Prasad, G. *Tetrahedron Lett.* **1989**, *30*, 4939. (d) See ref 14c.

Table 3. Dependence of Bicyclooctane Stereochemistry on Organozinc Structure and Formulation[a]

organozinc	% 24	% 36	% 37
BuLi / ZnCl₂	60	13	< 5
MeLi / ZnCl₂	39	19	32
Et₂Zn (neat)	42	42	< 5
Et₂Zn / ZnCl₂	70	10	< 5
Et₂Zn / LiCl	18	27	26

[a] Isolated yields are given.

led to reductive cyclization. This stands in sharp contrast to the results obtained with reductive cyclizations of alkynyl substrates (eq 3). However, selectivities between cis-fused bicyclooctane **24**, monocyclic trans-disubstituted isomer **36**, and bis-enone dimer **37** were variable (Table 3). The most efficient organozinc formulations leading selectively to cis-fused bicyclooctanes were 3:2 mixtures of butyllithium:zinc chloride or 3:1 mixtures of diethylzinc and zinc chloride. The poor selectivities obtained with diethylzinc alone or with diethylzinc plus lithium chloride suggest that more Lewis acidic alkylzinc halides may be important for the substrate preorganization that leads to high cis selectivities.

Although direct conjugate addition to substrates with tethered unsaturation was rarely observed in these studies, reactive sp²-hybridized organozincs such as diphenylzinc cleanly underwent conjugate addition with bis-enones and aldoenones. In both instances, the kinetic enolate derived from the conjugate addition efficiently underwent subsequent Michael[19] or aldol[20] reactions with the tethered electrophilic component. Bis-enones possessing a three carbon tether between the enone β-carbons produced trisubstituted cyclohexanes **38** and **39** with predominantly a triequatorial arrangement of substituents (eq 4), whereas the corresponding aldoenone produced trisubstituted cyclohexanol **40** possessing an axial hydroxyl as judged by ¹H NMR coupling constants (eq 5). Direct conjugate addition products also predominated with enones possessing a tethered cyano substituent and with enones possessing a tethered alkene (entries 5 and 11, Table 2). The involvement of direct conjugate addition is also problematic with alkynylenone and bis-enone cyclizations if the tether length is increased.[21]

(4)

38a R = Ph (65 %)
39a R = Me (58 %)
39b R = Me (12 %)

(5)

29
40 (41 %)
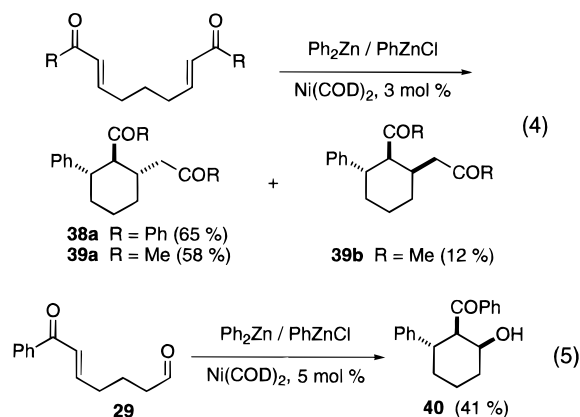
Organozinc structural variation in *alkylative* cyclizations of

Table 4. Scope of Organozincs in Alkynylenone Cyclizations

entry	R¹	R²	Products[a] (yield)
1	H	Me	**2** (82 %)
2	H	Me	**2** (65 %)[b]
3	H	Bu	**41a** (51 %) + **41b** (R²=H, 11 %)
4	H	Ph	**42** (61 %)
5	H	CH=CH₂	**43a** (59 %) + **43b** (R²=H, 8 %)
6	Ph	Bu	**16a** (68 %) + **16b** (R²=H, 8 %)
7	Bu	Ph	**18a** (38 %)

[a] Unless otherwise noted, alkylative cyclization products were obtained. [b] 1.2 equiv each of MeLi and ZnCl₂ was employed.

alkynyl substrates had little effect on reaction outcomes. Alkynyl substrates were the only class of compounds examined that underwent alkylative cyclization. A range of organozincs generated by transmetalation of the requisite organolithium or organomagnesium with zinc chloride, including aryl, alkenyl, and alkyl, either lacking or possessing β-hydrogens, were efficient components in alkynyl enone cyclizations (Table 4). A 2- to 3-fold excess of the organozinc was typically used; however, an experiment with 1.2 equiv each of zinc chloride and methyl lithium proceeded in only slightly suppressed yield (Table 4, entry 2). Initial studies employing organozinc iodides generated by direct insertion of activated zinc into primary alkyl iodides[22] were not successful. In addition to the various cyclization protocols reported herein, we recently reported intermolecular three-component couplings of enones, alkynes, and organozincs.[21] Important studies in related intermolecular three component couplings involving both organozincs and alkynyltins were reported by Ikeda and Sato.[23]

Discussion

Whereas the methodological investigations described in this report involve relatively simple structures, the mild reaction conditions and operational simplicity should make the general synthetic procedure amenable to complex applications. One issue that we imagine will ultimately display particular synthetic significance is the manner in which tri- and tetrasubstituted alkenes may be stereoselectively introduced during the cyclization of alkynyl enones. Beginning with a simple terminal alkyne of general structure **44**, alkylative cyclization in the absence of triphenylphosphine produces exclusively the *Z* isomer of the trisubstituted alkene **45** (Scheme 1). However, alkylation of the same terminal alkyne followed by reductive cyclization of the resulting internal alkyne **46** in the presence of triphenylphosphine leads exclusively to the *E* isomer of the trisubstituted alkene **47**. The same flexibility is available in the production of tetrasubstituted alkenes. Alkylative cyclization of the internal alkyne **46** produces a single isomer of the tetrasubstituted alkene **48**. However, given that the substituents R² and R³ are

(19) For related tandem Michael additions using other classes of nucleophiles: (a) Klimko, P. G.; Singleton, D. A. *Synthesis* **1994**, 979. (b) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049. (c) Saito, S.; Hirohara, Y. Narahara, O. Moriwake T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. (d) Yoshii, E.; Hori, K.; Nomura, K.; Yamaguchi, K. *Synlett* **1995**, 569 and references therein.

(20) For other examples of tandem Michael/aldol reactions: (a) Näf, F.; Decorzant, R.; Thommen, W. *Helv. Chim. Acta* **1975**, *58*, 1808. (b) Ho, T. *Tandem Organic Reactions*; Wiley: New York, 1992; pp 4−18.

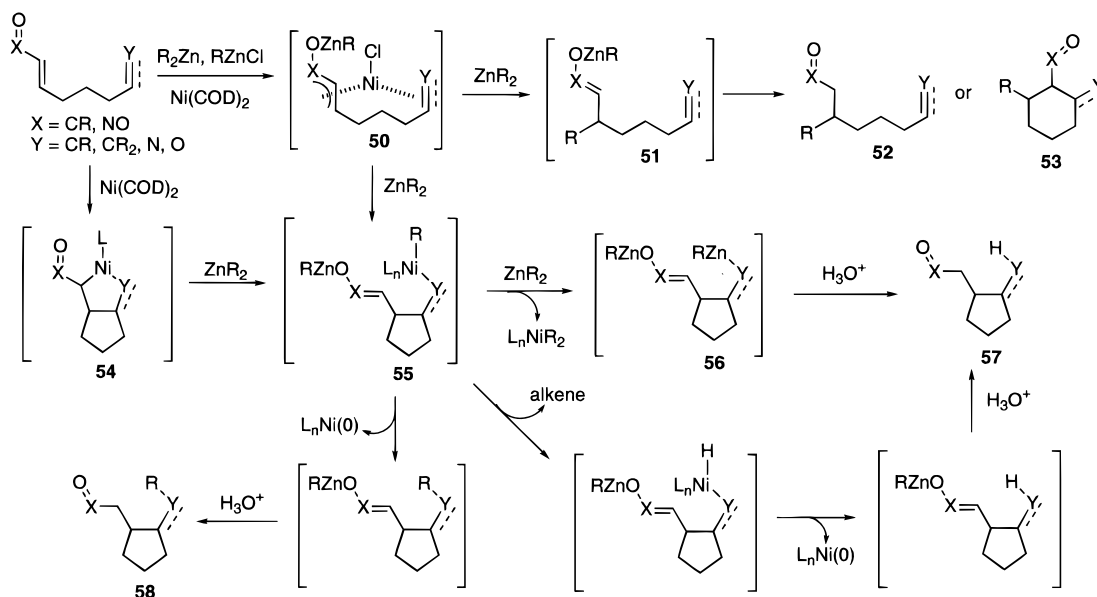(21) Montgomery, J.; Seo, J.; Chui, H. M. P. *Tetrahedron Lett.* **1996**, *37*, 6839.

(22) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117.

(23) (a) Ikeda, S.; Sato, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5975. (b) Ikeda, S.; Yamamoto, H.; Kondo, K.; Sato, Y. *Organometallics* **1995**, *14*, 5015. (c) Ikeda, S.; Kondo, K.; Sato, Y. *J. Org. Chem.* **1996**, *61*, 8248.

Scheme 1. Stereoselectivity of Alkylidenecyclopentane Formation
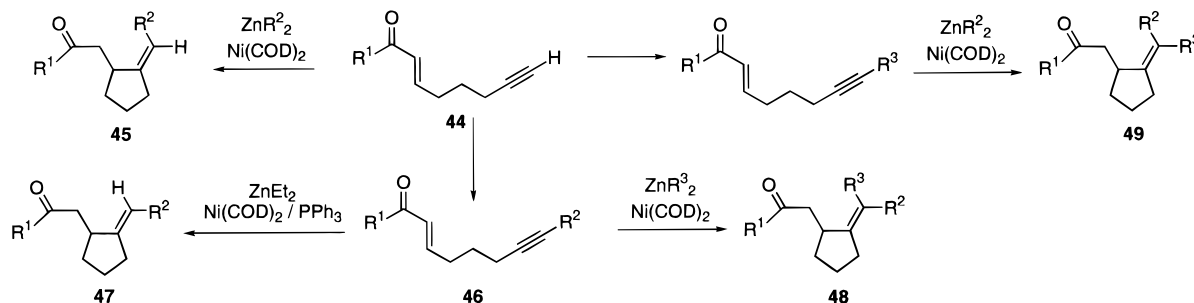
Scheme 2. Proposed Mechanisms

introduced in a stepwise, controlled, stereoselective fashion, the order of substituent introduction may be simply reversed in order to obtain **49**, the opposite isomer with respect to the tetrasubstituted double bond geometry. The broad range of methods available for the alkylation of alkynes (i.e., acetylide alkylation, Sonogashira reaction,[24] etc.) coupled with the generality of the nickel-mediated reductive and alkylative cyclizations provides a powerful strategy for stereoselective alkene introduction.[25]

Whereas the seminal contributions from Mackenzie on the preparation of enal-derived nickel π-allyl complexes led us to initiate these studies,[5] it is important to stress that the mechanistic issues associated with the transformations described herein are highly speculative. Moreover, a common mechanism for all substrate classes may be somewhat unlikely. However, two general mechanistic pathways leading to a key common intermediate **55** appear to be most consistent with the data at hand (Scheme 2). The first of these two pathways involves oxidative addition of a low valent nickel catalyst to an organozinc-activated electron-deficient alkene to afford nickel π-allyl complex **50** in direct analogy to the studies of Mackenzie. If either the organozinc rapidly transmetalates to nickel (i.e., ZnPh₂) or if the tethered unsaturation presents a sufficiently high kinetic barrier toward migratory insertion (i.e., tethered nitriles or unactivated alkenes), then π-allyl complex **50** may undergo a transmetalation/reductive elimination sequence to enolate **51**, ultimately leading to conjugate addition products

52 or 53. Alternatively, insertion of the tethered unsaturation and organozinc transmetalation would afford intermediate **55**. A second mechanistic possibility for the production of **55**, in direct analogy to the mechanism of zirconocene-catalyzed cyclomagnesiations of dienes,[3d,26] involves oxidative cyclization to produce metallacycle **54**. Transmetalation of the organozinc to metallacycle **54** would directly afford the same key intermediate **55** discussed above. Nickel metallacyclopentanes have been rigorously studied by Grubbs,[27] and several have been fully characterized by X-ray crystallography.[28] Less, however, is known about nickel metallacyclopent*ene*s, although their existence is commonly invoked in the mechanism of many nickel-promoted processes.[29]

With the substrates that possess tethered enones and aldehydes, intermediate **55** would be labile toward ligand displacement by further reaction with the organozinc to afford dianionic product **56** (as the bis-zinc reagent) which would be hydrolyzed to reductive cyclization product **57** on workup. The resulting

(24) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(25) For other methods that allow the selective preparation of either *E* or *Z* trisubstituted alkenes from a common intermediate, see: (a) Martinez-Grau, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 8332. (b) Demark, S. E.; Amburgey, J. *J. Am. Chem. Soc.* **1993**, *115*, 10386. (c) Barrett, A. G. M.; Hill, J. M.; Wallace, E. M. *J. Org. Chem.* **1992**, *57*, 386.

(26) (a) Taber, D. F.; Louey, J. P.; Wang, Y.; Nugent, W. A.; Dixon, D. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1994**, *116*, 9457. (b) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C. J.; Negishi, E. *J. Am. Chem. Soc.* **1991**, *113*, 6266. (c) Didiuk, M. T.; Johannes, C. W.; Morken, J. P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 7097.

(27) (a) Grubbs, R. H.; Miyashita, A.; Liu, M. M.; Burk, P. L. *J. Am. Chem. Soc.* **1977**, *99*, 3863. (b) Grubbs, R. H.; Miyashita, A. *J. Am. Chem. Soc.* **1978**, *100*, 1300. (c) Grubbs, R. H.; Miyashita, A.; Burk, P. J. Am. Chem. Soc. **1978**, *100*, 2418. (d) McKinney, R. J.; Thorn, D. L.; Hoffman, R.; Stockis, A. *J. Am. Chem. Soc.* **1981**, *103*, 2595.

(28) (a) Binger, P.; Doyle, M. J.; Krüger, C.; Tsay, Y. *Naturforsch. Teil B.* **1979**, *34*, 1289. (b) See ref 5 of the McKinney & Hoffman theoretical study (ref 27d above).

(29) (a) Metallacycles were proposed as intermediates in closely related intermolecular couplings by Ikeda and Sato, see ref 23c. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett*, **1992**, 539. (c) Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133.
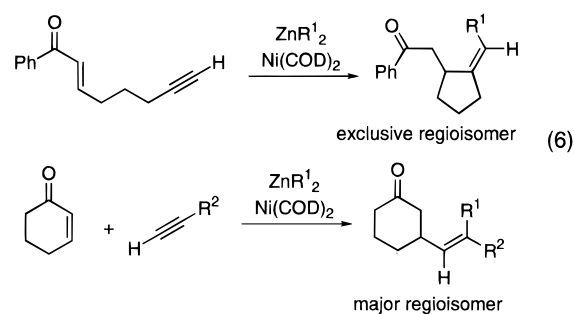
dialkylnickel complex would then regenerate the active catalyst species. However, a different pathway for decomposition of intermediate **55** occurs with enones tethered to alkynes. Instead, reductive elimination and β-hydride elimination are the modes of decomposition of **55** (in alkyne cyclizations) that are consistent with the experimental results. In the absence of added ligands, alkylative cyclization product **58**, which likely is derived from reductive elimination of **55**, is observed. When the catalyst is pretreated with triphenylphosphine, reductive cyclization product **57**, which is likely derived from β-hydride elimination of **55**, is observed. Deuterium labeling studies in reductive cyclizations of alkynyl enones demonstrated that the major reaction pathway proceeded by a mechanism in which the hydrogen substituent on atom Y of product **57** was derived from the organozinc; a result that is consistent with the β-hydride elimination mechanism.[7a] The potential involvement of two pathways to reductive cyclization product **57** is consistent with the observation that bis-enone reductive cyclizations do not require a β-hydrogen on the organozinc (Table 3), whereas alkynylenone reductive cyclizations do require a β-hydrogen on the organozinc (eq 3).

Reductive elimination of dialkylpalladium and aryl(allyl) palladium complexes is well established to be facilitated by the coordination of electron-deficient alkenes by virtue of their ability to serve as potent π-acceptor ligands.[30] To explain the reductive elimination/β-hydride elimination crossover in reactions of alkynyl enones, we speculate that unreacted substrate may coordinate to intermediate **55** in the absence of triphenylphosphine to promote reductive elimination. The presence of triphenylphosphine, however, could suppress enone coordination, generate a more electron-rich nickel species, and allow β-H elimination to occur through a dissociative process. The dramatically different reduction:alkylation ratios observed for alkynylenones compared with alkynes tethered to nitroalkenes clearly demonstrates that the structure of the electron-deficient alkene plays an important role in governing selectivities between reductive and alkylative cyclization products (compare method B of entries 1 and 6, Table 1). Knochel recently reported a similar phenomenon in nickel-promoted couplings of sp^3-hybridized centers.[31]

Finally, the possibility exists that alkynyl enone alkylative cyclizations proceed by alkyne carbometalation followed by conjugate addition, but a direct regiochemical comparison of the above cyclizations with intermolecular coupling data from Ikeda[23] and from us[21] suggests that such a mechanism is not consistent with the experimental data. Cyclizations involving terminal alkynes are highly selective for the exocyclic mode, with the organozinc substituent adding to the terminal carbon (Table 1). However, in intermolecular three-component couplings involving terminal alkynes, the organozinc substituent adds predominantly to the substituted position of the alkyne.[21,23] Such a regiochemical reversal is not consistent with a mechanism that involves irreversible alkyne carbometalation without the direct influence of the electron-deficient alkene (eq 6).

Conclusions

A general and efficient nickel-catalyzed, organozinc-promoted cyclization of electron-deficient alkenes with tethered unsaturation has been developed. Considerable flexibility is tolerated

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(31) Devasagayaraj, A.; Südemann, T.; Knochel, P. *Angew Chem. Int. Ed. Engl.* **1995**, *34*, 2723.

$$\text{(6)}$$

in each of the reactive functionalities. The most stringent limitation lies in the requirement for a highly electrophilic double bond, with enones, alkylidene malonates, and nitroalkenes being the most efficient examined to date. Although many important mechanistic questions remain unresolved, a detailed set of empirical rules has been established that provides a high degree of predictability within each substrate class examined. Our laboratory is actively pursuing more complex methodological and mechanistic studies as well as applications in the total synthesis of complex molecules.

Experimental Section

Unless otherwise noted, reagents were commercially available and were used without purification. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium/benzophenone ketyl. Dichloromethane and DMSO were distilled from calcium hydride. All organolithium reagents were freshly titrated with 2,5-dimethoxybenzyl alcohol. Zinc chloride was dried at 150 °C at 0.1 mm overnight, then thoroughly ground by mortar and pestle in an inert atmosphere glovebox, and then dried again overnight at 150 °C at 0.1 mm. Ni(COD)$_2$ and anhydrous ZnCl$_2$ were stored and weighed in an inert atmosphere glovebox. All reactions were conducted in flame-dried glassware under a nitrogen or argon atmosphere.

General Procedure A for Alkylative Cyclization. A 0.3−0.5 M solution of ZnCl$_2$ (2.5−3.0 equiv) in THF was stirred at 0 °C, and the organolithium or Grignard reagent (3.7−4.5 equiv) was added by syringe followed by stirring for 0.25−1 h at 0 °C. A 0.02−0.04 M THF solution of Ni(COD)$_2$ (0.04−0.06 equiv) was added, and the resultant mixture was immediately transferred by cannula to a 0.1−0.2 M solution of the unsaturated substrate (1.0 equiv). After consumption of starting material by TLC analysis (typically 0.25−2.0 h at 0 °C), the reaction mixture was subjected to an extractive workup (NaHCO$_3$/EtOAc or NH$_4$Cl/NH$_4$OH pH = 8 buffer/Et$_2$O) followed by flash chromatography on SiO$_2$. Although the above procedure was typically used, commercial diorganozincs performed comparably.

General Procedure B for Reductive Cyclization. A 0.03−0.06 M solution of triphenylphosphine (0.2−0.3 equiv) in THF was added to Ni(COD)$_2$ (0.04−0.06 equiv) at 25 °C and stirred for 3−5 min. The nickel solution was transferred to a 0.5−0.6 M solution of Et$_2$Zn in THF at 0 °C, and the resultant mixture was immediately transferred by cannula to a 0.10−0.50 M 0 °C THF solution of the unsaturated substrate (1.0 equiv). After consumption of starting material by TLC analysis (typically 0.25−2.0 h at 0 °C), the reaction mixture was subjected to an extractive workup (NaHCO$_3$/EtOAc or NH$_4$Cl/NH$_4$-OH pH = 8 buffer/Et$_2$O) followed by flash chromatography on SiO$_2$. Slightly lower yields were obtained using organolithium-derived diorganozinc reagents prepared by addition of n-BuLi (3.75 equiv) to a 0.3−0.6 M solution of ZnCl$_2$ (2.5 equiv) in THF at 0 °C. The experiments reported with BuLi/ZnCl$_2$ were not optimized.

(Z)-1-Ethylidene-2-(2-oxo-2-phenylethyl)cyclopentane (2a). Following general procedure A, (2E)-1-phenyloct-2-en-7-yn-1-one (**1**)[7a] (60 mg, 0.30 mmol), MeLi (0.92 mL, 1.10 mmol of a 1.2 M ethyl ether solution), zinc chloride (99 mg, 0.73 mmol), and Ni(COD)$_2$ (7 mg, 0.025 mmol) were employed to produce, after flash chromatography (35:1 hexanes:EtOAc), 53 mg (82%) of **2a** as a colorless oil that was contaminated with <5% of **2b**. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.96 (m, 2H), 7.40−7.60 (m, 3H), 5.35 (m, 1H), 3.26 (s, 1H), 3.09 (dd, J = 3.9, 16.5 Hz, 1H), 2.92 (dd, J = 10.2, 16.2 Hz, 1H), 2.15−2.45 (m, 2H), 1.93 (m, 1H), 1.62 (d, J = 6.6 Hz, 3H), 1.42−1.75 (m, 3H); ^{13}C

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NMR (75 MHz) δ 199.7, 146.7, 137.3, 132.9, 128.5, 128.0, 115.5, 43.1, 35.9, 33.3, 32.8, 24.1, 14.6; IR (film) 1687, 1597 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{15}$H$_{18}$O 214.1358, found 214.1358 (M$^+$).

1-Methylidene-2-(2-oxo-2-phenylethyl)cyclopentane (2b). Following general procedure B, (2*E*)-1-phenyloct-2-en-7-yn-1-one (**1**)[7a] (51 mg, 0.26 mmol), Et$_2$Zn (74 mg, 0.061 mL, 0.60 mmol), zinc chloride (27 mg, 0.20 mmol), PPh$_3$ (37 mg, 0.14 mmol), and Ni(COD)$_2$ (6 mg, 0.021 mmol) were employed to produce, after flash chromatography (20:1 pentane:Et$_2$O), 48 mg (92%) of **2b** as a colorless oil that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.56 (m, 1H), 7.47 (m, 2H), 4.93 (d, *J* = 2.0 Hz, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 3.24 (dd, *J* = 3.5, 15.5 Hz, 1H), 2.93−3.04 (m, 2H), 2.30−2.47 (m, 2H), 2.05 (dq, *J* = 4.5, 12.0, Hz, 1H), 1.73 (m, 1H), 1.61 (m, 1H), 1.31 (m, 1H); ^{13}C NMR (125 MHz) δ 199.8, 155.9, 137.2, 133.0, 128.6, 128.1, 104.7, 43.6, 39.8, 33.4, 33.0, 24.1; IR (film) 1686, 1652, 1595, 1580 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{14}$H$_{16}$O: 200.1201, found: 200.1207 (M$^+$).

(Z)-1-Ethylidenespiro[4.5]decane-7-one (4a). Following procedure A, 3-(4-pentynyl)-2-cyclohexen-1-one (**3**)[32] (70 mg, 0.43 mmol), MeLi (1.72 mL, 1.5 mmol of a 0.87 M ethyl ether solution), zinc chloride (0.136 g, 1.0 mmol), and Ni(COD)$_2$ (11.5 mg, 0.042 mmol) were employed to produce, after flash chromatography (4:1 hexanes:EtOAc), 55.5 mg (72%) of **4a** as a pale-yellow liquid that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.39 (tq, *J* = 2.0, 7.5 Hz, 1H), 2.78 (d, *J* = 14.0 Hz, 1H), 2.25−2.38 (m, 5H), 2.17 (dt, *J* = 14.0, 2.0 Hz, 1H), 1.95−2.03 (m, 1H), 1.76 (dt, *J* = 7.5, 2.0 Hz, 3H), 1.70−1.80 (m, 1H), 1.44−1.64 (m, 5H); ^{13}C NMR (125 MHz) δ 211.7, 148.0, 116.5, 50.1, 48.6, 41.3, 39.5, 36.3, 34.2, 23.3, 23.2, 13.9; IR (film) 1713, 1435 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{12}$H$_{18}$O 178.1358, found 178.1354 (M$^+$).

(Z)-1-Ethylidene-2-(methylmalonyl)cyclopentane (8a). Following general procedure A, alkylidene malonate **7**[33] (112 mg, 0.53 mmol), MeLi (2.2 mL, 3.0 mmol of a 1.4 M ethyl ether solution), ZnCl$_2$ (272 mg, 2.0 mmol), and Ni(COD)$_2$ (8 mg, 0.03 mmol) were employed to produce, after flash chromatography (85:15 hexanes:EtOAc), 89 mg (74%) of **8a** as a colorless oil that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.32−5.36 (m, 1H), 3.70 (s, 3H) 3.67 (s, 3H), 3.52 (d, *J* = 9 Hz, 1H), 3.30−3.38 (m, 1H), 2.26−2.36 (m, 1H), 2.10−2.20 (m, 1H), 1.82−1.9 (m, 1H), 1.63−1.73 (m, 2H), 1.48−1.58 (m, 4H); ^{13}C NMR (125 MHz) δ 169.1, 169.0, 142.9, 117.8, 54.1, 52.3, 52.2, 39.7, 32.6, 30.3, 22.8, 14.5; IR (film) 1755, 1739 cm^{-1}; MS (EI) *m/e* calcd for C$_{12}$H$_{18}$O$_4$ 226.1205, found 226.1200 (M$^+$).

1-Methylidene-2-(methylmalonyl)cyclopentane (8b). Following general procedure B, alkylidene malonate **7**[33] (120 mg, 0.57 mmol), Et$_2$Zn (1.8 mL, 1.7 mmol of a 15 wt % hexane solution), PPh$_3$ (32 mg, 0.12 mmol), and Ni(COD)$_2$ (8 mg, 0.03 mmol) were employed to produce, after flash chromatography (85:15 hexanes:EtOAc), 100 mg (83%) of **8b** as a colorless oil that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.88 (q, *J* = 2.0 Hz, 1H), 4.73 (q, *J* = 2.0 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.49 (d, *J* = 8.5 Hz, 1H), 3.09 (q, *J* = 7.7 Hz, 1H), 2.30−2.34 (m, 2H), 1.87 (m, 1H), 1.72 (m, 1H). 1.50−1.65 (m, 2H); ^{13}C NMR (125 MHz) δ 169.1, 168.8, 152.6, 106.5, 55.1, 52.33, 52.26, 43.3, 32.9, 30.4, 23.8; IR (film) 3074, 1737, 1653.5 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{11}$H$_{16}$O$_4$ 212.1048, found 212.1049 (M$^+$).

2-[(Z)-2-Ethylidenecyclopentyl]-3-oxobutyric Acid Methyl Ester (10a). Following general procedure A, ketoester **9**[33] (107 mg, 0.55 mmol), MeLi (1.9 mL, 2.5 mmol of a 1.4 M ethyl ether solution), ZnCl$_2$ (187 mg, 1.4 mmol), and Ni(COD)$_2$ (8 mg, 0.03 mmol) were employed to produce, after flash chromatography (9:1 hexanes:EtOAc), 78 mg (68%) of **10a** (1:1 mixture of diastereomers) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.35 (m, 2H), 3.69 (s, 3H) 3.63−3.66 (m, 4H), 3.52 (d, *J* = 9 Hz, 1H), 3.30−3.40 (m, 2H), 2.30 (m, 2H), 2.23 (s, 3H), 2.19 (s, 3H), 2.17 (m, 1H), 1.77−1.86 (m, 2H), 1.60−1.67 (m, 4H), 1.50−1.58 (m, 9H); ^{13}C NMR (125 MHz) δ 203.1, 203.0, 169.7, 169.6, 143.0, 142.9, 117.9, 117.8, 61.9, 61.2, 52.2, 52.1, 39.7, 39.5, 32.7, 32.2, 30.6, 30.3, 30.2, 29.9, 22.9, 22.4, 14.7; IR (film) 1738, 1720 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{12}$H$_{18}$O$_3$ 210.1256, found 210.1260 (M$^+$).

(32) Sidduri, A.; Rozema, M. J.; Knochel, P. *J. Org. Chem.* **1993**, *58*, 2694.

(33) Alkylidene malonate **7** and *β*-ketoester **9** were prepared from hex-5-ynal and dimethyl malonate by the Lehnert modification of the Knoevenagel condensation. Lehnert, W. *Tetrahedron Lett.* **1970**, 4723

2-(2-Methylidenecyclopentyl)-3-oxobutyric Acid Methyl Ester (10b). Following general procedure B, ketoester **9**[33] (105 mg, 0.54 mmol), Et$_2$Zn (170 μL, 1.66 mmol), PPh$_3$ (32 mg, 0.12 mmol), and Ni(COD)$_2$ (8mg, 0.03 mmol) were employed to produce, after flash chromatography (4:1 hexanes:EtOAc), 84 mg (79%) of **10b** (1:1 mixture of diastereomers) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 4.87 (m, 2H), 4.72 (q, *J* = 2.0 Hz, 1H), 4.65 (q, *J* = 2.1 Hz, 2H), 3.69 (s, 3H), 3.68 (s, 3H), 3.61 (d, *J* = 9.0 Hz, 1H), 3.51 (d, *J* = 9.0 Hz, 1H), 3.11 (m, 2H), 2.31 (m, 4H), 2.23 (s, 3H), 2.21 (s, 3H), 1.83−1.89 (m, 2H), 1.66−1.76 (m, 2H), 1.50−1.60 (m, 3H), 1.34−1.41 (m, 1H); ^{13}C NMR (125 MHz) δ 202.8, 202.5, 169.5, 169.2, 152.9, 152.8, 106.6, 106.5, 63.8, 62.9, 52.2, 52.1, 43.1, 43.0, 32.9, 32.7, 30.5, 30.3, 29.9, 29.7, 23.8, 23.7; IR (film) 1744, 1717 cm^{-1}; HRMS (EI) *m/e* calcd for C$_9$H$_{14}$O$_2$ 154.0994, found 154.0997 ((M−CH$_2$=C=O)$^+$).

(Z)-1-Ethylidene-2-(nitromethyl)cyclopentane (12a). Following general procedure A, nitroalkene **11**[34] (99 mg, 0.71 mmol), MeLi (2.3 mL, 3.2 mmol of a 1.4 M ethyl ether solution), ZnCl$_2$ (242 mg, 1.8 mmol), and Ni(COD)$_2$ (10 mg, 0.04 mmol) were employed to produce, after flash chromatography (9:1 hexanes:Et$_2$O), 44 mg (39%) of **12a** and 50 mg (45%) of the acyclic conjugate addition product **12c** as yellow oils. The purified sample of **12a** was contaminated with < 5% of **12c**. For **12a**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.48 (m, 1H), 4.40 (dd, *J* = 11.7, 5.0 Hz, 1H), 4.14 (t, *J* = 11.5 Hz, 1H), 3.42 (m, 1H), 2.20−2.34 (m, 2H), 1.85−1.93 (m, 1H), 1.61−1.73 (m, 6H); ^{13}C NMR (125 MHz) 141.2, 119.1, 77.7, 39.3, 32.8, 30.4, 23.7, 14.5; IR (film) 1551, 1378 cm^{-1}; HRMS (EI) *m/e* calcd for C$_8$H$_{12}$ 108.0939, found 108.0942 ((M − HNO$_2$)$^+$). For **12c**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 4.31 (dd, *J* = 11.8, 6.3 Hz, 1H), 4.19 (dd, *J* = 11.8, 7.8 Hz, 1H), 2.33 (m, 1H), 2.19 (m, 2H), 1.95 (t, *J* = 2.8 Hz, 1H), 1.46−1.65 (m, 3H), 1.32−1.40 (m, 1H), 1.01 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 83.7, 81.5, 68.8, 32.7, 32.3, 25.4, 18.4, 17.1; IR (film) 1551, 1383 cm^{-1}. Yields were variable for this particular example (40−85% combined), but product ratios were consistent irrespective of yield.

(Z)-1-(1-Propylidene)-2-(nitromethyl)cyclopentane (12b). Following general procedure B, nitroalkene **11**[34] (104 mg, 0.75 mmol), Et$_2$Zn (230 μl, 2.25 mmol), PPh$_3$ (42 mg, 0.16 mmol), and Ni(COD)$_2$ (11 mg, 0.04 mmol) were employed to produce, after flash chromatography (49:1 hexanes:EtOAc), 106 mg of an inseparable mixture of **12b** (47%) and **12d** (13%) as a yellow oil contaminated with 16% triphenylphosphine. For **12b**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.38 (m, 1H), 4.36 (dd, *J* = 12.0, 4.5 Hz, 1H), 4.15 (t, *J* = 11.3 Hz, 1H), 3.42 (m, 1H), 1.60−2.40 (m, 8H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 139.5, 127.0, 78.1, 39.5, 32.8, 30.4, 23.6, 22.6, 14.4; IR (film) 1551, 1378 cm^{-1}; MS(EI) *m/e* calcd for C$_9$H$_{14}$ 122.1096, found 122.1095 ((M − HNO$_2$)$^+$). Distinct ^{1}H NMR signals for **12d**: 5.03 (m, 1H), 4.86 (m, 1H), 4.48 (dd, *J* = 12.0, 5.5 Hz, 1H), 4.27 (dd, *J* = 12.0, 9.5 Hz, 1H) 3.20 (m, 1H). HRMS(EI) *m/e* calcd for C$_7$H$_{10}$ 94.0783, found 94.0785 ((M − HNO$_2$)$^+$).

(E)-1-Ethylidene-2-(methylmalonyl)cyclopentane (14b). Following general procedure B, alkylidene malonate **13**[33] (94 mg, 0.42 mmol), Et$_2$Zn (130 μl, 1.27 mmol), PPh$_3$ (29 mg, 0.11 mmol), and Ni(COD)$_2$ (6 mg, 0.02 mmol) were employed to produce, after flash chromatography (4:1 hexanes:Et$_2$O), 84 mg (83%) of **14b** as a colorless oil that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 5.19 (m, 1H), 3.69 (s, 3H), 3.42 (d, *J* = 9.3 Hz, 1H), 3.07 (m,1H), 2.22 (m, 2H), 1.63−1.82 (m, 2H), 1.51−1.61 (m, 5H); ^{13}C NMR (125 MHz) δ 169.2, 168.9, 143.4, 116.3, 55.2, 52.2, 43.9, 30.4, 28.3, 23.3, 14.7; IR (film) 1759, 1738 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{12}$H$_{18}$O$_4$ 226.1205, found 226.1208 (M$^+$). Anal. Calcd for C$_{12}$H$_{18}$O$_4$: C, 63.70; H, 8.02. Found: C, 63.94; H, 8.19.

2-(2-Oxo-2-phenylethyl)-(E)-1-(1-phenylpentylidene)cyclopentane (16a). Following general procedure A, (2*E*)-1,8-diphenyloct-2-en-7-yne-1-one (**15**)[7a] (53 mg, 0.19 mmol), *n*-BuLi (0.41 mL, 0.83 mmol of a 2.03 M hexane solution), zinc chloride (68 mg, 0.50 mmol), and Ni(COD)$_2$ (6.9 mg, 0.025 mmol) were employed to produce, after flash chromatography (49:1 hexanes:EtOAc), in order of elution, 43 mg (68%) of **16a** as a colorless oil and 4.0 mg (8%) of **16b** as a white solid that were both homogeneous by TLC analysis. For **16a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00−8.20 (m, 2H), 7.57−7.60 (m, 1H), 7.48−7.51 (m, 2H), 7.30−7.33 (m, 2H), 7.19−7.23 (m, 1H), 7.13−7.14 (m,

(34) Nitroalkene **11** was prepared from nitromethane and 5-hexyn-1-al by a nitroaldol condensation, acylation, and elimination sequence. Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579.

2H), 3.46 (m, 1H), 3.13 (dd, *J* = 4.0, 16.5 Hz, 1H), 3.07 (dd, *J* = 10.0, 16.5 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.16−2.24 (m, 1H), 2.08−2.14 (m, 1H), 1.87−1.94 (m, 1H), 1.52−1.71 (m, 3H), 1.16−1.28 (m, 4H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz) δ 199.7, 143.6, 142.3, 137.4, 133.7, 133.0, 128.6, 128.3, 128.1, 127.9, 125.9, 43.7, 37.7, 34.6, 32.4, 31.4, 30.8, 24.0, 22.8, 14.0; IR (film) 1686, 1598, 1580 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{24}$H$_{28}$O 332.2140, found 332.2135 (M$^+$). Anal. Calcd for C$_{24}$H$_{28}$O: C, 86.70; H, 8.49. Found: C, 86.69; H, 8.51. The alkene stereochemistry was assigned by observation of 7.6% NOE of the cyclopentyl ring methine proton (δ 3.46) and 2.9% and 0.8% NOEs of the two diastereotopic protons α to the carbonyl (δ 3.13 and 3.07, respectively) upon irradiation of the allylic protons in the butyl group (δ 2.38). Assignments were confirmed by homonuclear decoupling experiments.

(*E*)-1-Benzylidene-2-(2-oxo-2-phenylethyl)cyclopentane (16b). Following general procedure B, (2*E*)-1,8-diphenyloct-2-en-7-yne-1-one (**15**)[7a] (157 mg, 0.57 mmol), Et$_2$Zn (0.17 mL, 1.65 mmol), Ni(COD)$_2$ (30 mg, 0.11 mmol), and triphenylphosphine (115 mg, 0.44 mmol) were employed to produce, after flash chromatography (24:1 hexanes:EtOAc), in order of elution, 108 mg (69%) of **16b** as a white solid that was homogeneous by TLC analysis. For **16b**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.01 (m, 2H), 7.59 (m, 1H), 7.48 (m, 2H), 7.32 (m, 4H), 7.19 (m, 1H), 6.31 (q, *J* = 2.5 Hz, 1H), 3.34 (dd, *J* = 4.8, 16.3 Hz, 1H), 3.24 (m, 1H), 3.08 (dd, *J* = 8.75, 16.3 Hz, 1H), 2.58−2.74 (m, 2H), 2.05 (m, 1H), 1.88 (m, 1H), 1.71 (m, 1H), 1.37 (m, 1H); ^{13}C NMR (75 MHz) δ 199.7, 149.4, 138.5, 137.3, 133.0, 128.6, 128.20, 128.17, 128.14, 126.0, 121.1, 44.1, 42.0, 32.5, 31.5, 24.9; IR (KBr) 1681, 1644, 1594, 1578 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{20}$H$_{20}$O 276.1514, found 276.1517 (M$^+$). Anal. Calcd for C$_{20}$H$_{20}$O: C, 86.92; H, 7.29. Found: C, 86.60; H, 7.48.

2-(2-Oxo-2-phenylethyl)-(*Z*)-1-(1-phenylpentylidene)cyclopentane (18a). Following general procedure A, (2*E*)-1-phenyldodec-2-en-7-yn-1-one (**17**)[7a] (69 mg, 0.27 mmol), PhMgBr (1.05 mL, 1.05 mmol of a 1.0 M THF solution), zinc chloride (95 mg, 0.70 mmol), and Ni(COD)$_2$ (6 mg, 0.021 mmol) were employed to produce, after flash chromatography (50:1 pentane:Et$_2$O) 34 mg (38%) of **18a** as colorless glass that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.18−7.46 (m, 10H), 3.09 (m, 1H), 2.83 (dd, *J* = 4.0, 14.5 Hz, 1H), 2.45−2.54 (m, 1H), 2.35−2.45 (m, 2H), 2.33 (dd, *J* = 12.0, 14.0 Hz, 1H), 2.26 (m, 1H), 1.76−1.87 (m, 1H), 1.62−1.76 (m, 2H), 1.49−1.57 (m, 1H), 1.22−1.35 (m, 4H), 0.86 (m, 3H); ^{13}C NMR (125 MHz) δ 200.1, 143.6, 142.2, 136.4, 134.3, 132.5, 128.8, 128.6, 128.4, 128.2, 126.2, 42.8, 39.0, 36.1, 31.1, 30.2, 29.8, 23.6, 22.6, 14.1; IR (film) 1678, 1597, 1580 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{24}$H$_{28}$O 332.2140, found 332.2139 (M$^+$).

2-(2-Oxo-2-phenylethyl)-(*E*)-1-(1-pentylidene)cyclopentane (18b). Following general procedure B, (2*E*)-1-phenyldodec-2-en-7-yn-1-one (**17**)[7a] (70 mg, 0.28 mmol), *n*-BuLi (0.42 mL, 1.05 mmol of a 2.5 M hexanes solution), zinc chloride (95 mg, 0.70 mmol), PPh$_3$ (34 mg, 0.13 mmol), and Ni(COD)$_2$ (6 mg, 0.021 mmol) were employed to produce, after flash chromatography (42:1 pentane:Et$_2$O), in order of elution, 14 mg (16%) of **18c** (R = Bu) and 41 mg (58%) of **18b** (R = H), both as colorless oils that were homogeneous by TLC analysis. For **18b**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.55 (tt, *J* = 1.5, 7.5 Hz, 1H), 7.46 (m, 2H), 5.18 (m, 1H), 3.19 (dd, *J* = 4.5, 16.0 Hz, 1H), 2.94 (m, 1H), 2.88 (dd, *J* = 9.0, 15.5 Hz, 1H), 2.16-2.36 (m, 2H), 1.92−2.02 (m, 3H), 1.75 (m, 1H), 1.53−1.63 (m, 1H), 1.20−1.35 (m, 5H), 0.89 (m, 3H); ^{13}C NMR (125 MHz) δ 200.2, 145.3, 137.4, 132.9, 128.5, 128.1, 120.6, 43.9, 40.2, 33.3, 31.8, 29.2, 28.9, 24.0, 22.4, 14.0; IR (film) 1688, 1597, 1581 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{18}$H$_{24}$O 256.1827, found 256.1823 (M$^+$).

2-(Methylmalonyl)-(*E*)-1-[(1-trimethylsilyl)ethylidene]cyclopentane (20a). Following general procedure A, alkylidene malonate **19**[35] (100 mg, 0.35 mmol), MeLi (1.6 mL, 2.1 mmol of a 1.3 M ethyl ether solution), ZnCl$_2$ (190 mg, 1.4 mmol), and Ni(COD)$_2$ (5 mg, 0.02 mmol) were employed to produce, after flash chromatography (93:7 hexanes:EtOAc), 73 mg (70%) of **20a** as a colorless oil that was homogeneous by TLC analysis. ^{1}H NMR (500 MHz, CDCl$_3$) δ 3.69

(s, 3H) 3.67 (s, 3H), 3.62 (d, *J* = 9 Hz, 1H), 3.50 (m, 1H), 2.20−2.36 (m, 2H), 1.85 (m, 1H), 1.75 (m, 2H), 1.68 (s, 3H), 1.54 (m, 1H), 0.08 (s, 9H); ^{13}C NMR (125 MHz) δ 169.3, 169.2, 152.7, 127.9, 53.6, 52.2, 52.1, 41.8, 32.5, 29.2, 23.6, 18.9, −0.4; IR (film) 1757, 1739 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{15}$H$_{26}$O$_4$Si 298.1600, found 298.1597 (M$^+$). Anal. Calcd for C$_{15}$H$_{26}$O$_4$Si: C, 60.37; H, 8.78. Found: C, 60.49; H, 8.82.

2-(Methylmalonyl)-(*E*)-1-[(1-trimethylsilyl)-1-propylidene]cyclopentane (20b). Following general procedure B, alkylidene malonate **19**[35] (564 mg, 2.0 mmol), Et$_2$Zn (7.0 mL, 7.7 mmol, PPh$_3$ (105 mg, 0.4 mmol), and Ni(COD)$_2$ (28 mg, 0.1 mmol) were employed to produce, after flash chromatography (9:1 hexanes:EtOAc), 100 mg (75%) of a 5:1 mixture of **20b** (R = H) and **20c** (R = Et) as a colorless oil that was homogeneous by TLC analysis. For **20b**: ^{1}H NMR (CDCl$_3$, 500 MHz) δ 5.12 (m, 1H), 3.69 (s, 3H), 3.67 (s, 3H), 3.55 (d, *J* = 8.0 Hz, 1H), 3.05 (q, *J*=7.5 Hz, 1H), 2.23 (m, 3H), 1.55−1.87 (m, 4H), 0.04 (m, 9H); ^{13}C NMR (125 MHz) δ 169.3, 168.8, 161.4, 119.7, 54.8, 52.2, 52.1, 46.6, 32.3, 29.4, 24.1, −0.5; IR 1759, 1740 cm^{-1}; HRMS (EI) *m/e* calcd for **20b** C$_{14}$H$_{24}$O$_4$Si 284.1444, found 284.1442 (M$^+$). Diagnostic ^{1}H NMR signals for **20c**: δ 0.87 (t, *J* = 7.3 Hz, 3H), 0.09 (s, 9H).

3-Butyl-1-phenyl-7-hepten-1-one (22a). Following general procedure A, enone **21**[36] (90 mg, 0.45 mmol), *n*-BuLi (0.62 mL of a 2.43 M hexane solution, 1.5 mmol), ZnCl$_2$ (1.0 mL of a 1.0 M ether solution, 1.0 mmol), and Ni(COD)$_2$ (3 mg, 0.01 mmol) were employed to produce, after flash chromatography (6:1 hexanes:EtOAc), 87 mg (75%) of **22a** as a colorless oil that was homogeneous by TLC analysis. The product was identical to authentic material prepared by addition of Bu$_2$CuLi to enone **21**. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.90−8.00 (m, 2H), 7.40−7.60 (m, 3H), 5.70−5.85 (m, 1H), 4.90−5.05 (m, 2H), 2.88 (d, *J* = 6.6 Hz, 2H), 2.00−2.15 (m, 3H), 1.20−1.50 (m, 10H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz) δ 200.5, 138.8, 137.5, 132.7, 128.5, 128.0, 114.3, 43.4, 34.1, 34.0, 33.8, 33.6, 28.8, 26.0, 22.9, 14.0; IR (film) 1685 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{18}$H$_{26}$O: 258.1984, found: 258.1982 (M$^+$).

1*S,2*R**,3*S**,5*S**2-Benzoyl-3-hydroxy-3-phenylbicyclo[3.3.0] octane (24).** Following general procedure A, bis-enone **23**[36] (91 mg, 0.30 mmol), *n*-BuLi (0.43 mL of a 2.44 M hexane solution, 1.05 mmol), ZnCl$_2$ (0.70 mL of a 1.0 M ether solution, 0.70 mmol), and Ni(COD)$_2$ (3 mg, 0.01 mmol) were employed to produce, after flash chromatography, in order of elution, 56 mg (60%) of **24** as a white crystalline solid and 12 mg (13%) of **36**. Spectral data of **36** were identical to that previously reported.[14a] For **24**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.10−7.80 (m, 10H), 5.53 (d, *J* = 2.0 Hz, 1H), 3.87 (d, *J* = 9.5 Hz, 1H), 3.08 (quintet of doublets, *J* = 9.0, 2.5 Hz, 1H), 2.95−3.05 (m, 1H), 2.38 (dd, *J* = 8.0, 13.5 Hz, 1H), 1.65−1.85 (m, 4H), 1.50−1.60 (m, 3H); ^{13}C NMR (75 MHz) δ 207.2, 144.5, 137.7, 133.6, 128.6, 128.3, 128.1, 126.8, 124.7, 87.1, 59.6, 50.2, 49.6, 42.6, 32.7, 31.9, 25.6; IR (KBr) 3412, 1646 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{21}$H$_{22}$O$_2$: 306.1619, found: 306.1614 (M$^+$). Anal. Calcd for C$_{21}$H$_{22}$O$_2$: C, 82.32; H, 7.24. Found: C, 82.63; H, 7.37. The structure was proven by single crystal X-ray analysis.[37]

Compound 37. Following general procedure A, bis-enone **23**[36] (190 mg, 0.62 mmol), MeLi (1.85 mL of a 1.20 M ether solution, 2.20 mmol), ZnCl$_2$ (1.50 mL of a 1.0 M ether solution, 1.50 mmol), and Ni(COD)$_2$ (10 mg, 0.04 mmol) were employed to produce, after flash chromatography (5:1 hexanes:EtOAc), in order of elution, 110 mg of the mixture of **24** and **36** (2:1 ratio based on ^{1}H NMR) as a white solid and 62 mg (32%) of **37** as a white solid that was homogeneous by TLC analysis. For **37**: ^{1}H NMR (500 MHz, C$_6$D$_6$) d 7.60 (d, *J* = 7.5 Hz, 2H), 7.50−7.55 (m, 2H), 7.45−7.50 (m, 2H), 7.38 (d, *J* = 6.5 Hz, 2H), 7.03 (tt, *J* = 1.5, 7.0 Hz, 1H), 6.84−6.98 (m, 9H), 6.75 (t, *J* = 8.0 Hz, 2H), 5.79 (d, *J* = 1.0 Hz, 1H), 3.67 (d, *J* = 10.0 Hz, 1H), 2.95−3.02 (m, 1H), 2.97 (t, *J* = 10.5 Hz, 1H), 2.83 (dq, *J* = 2.5, 9.5 Hz, 1H), 2.63 (d, *J* = 14.0 Hz, 1H), 2.55 (dd, *J*=3.2, 15.2 Hz, 1H), 2.50−2.58 (m, 1H), 2.34−2.43 (m, 1H), 2.21 (dd, *J* = 9.5, 15.0 Hz, 1H), 2.02−2.10 (m, 1H), 1.82−1.95 (m, 1H), 1.85 (d, *J* = 10.5 Hz,

(35) 6-Trimethylsilylhex-5-ynal was employed as the aldehyde component in the Knoevenagel condensation (see ref 32) to prepare alkynyl silane **19**. 6-Trimethylsilanylhex-5-yn-1-al was prepared from hex-5-yn-1-ol by bis-silylation, monodesilylation, and PCC oxidation. Harris, G. D.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1993**, *52*, 5452.

(36) Montgomery, J.; Savchenko, A. V.; Zhao, Y. *J. Org. Chem.* **1995**, *60*, 5699.

(37) The author has deposited atomic coordinates for **24** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

1H), 1.71−1.73 (m, 2H), 1.48−1.68 (m, 3H), 0.97−1.27 (m, 4H); ^{13}C NMR (125 MHz, CDCl$_3$) d 206.9, 205.9, 199.2, 144.1, 138.8, 137.8, 136.5, 133.5, 133.0, 132.8, 128.7, 128.6, 128.5, 128.4, 128.2, 128.0, 126.5, 125.3, 87.3, 60.8, 59.3, 53.4, 48.1, 46.6, 44.9, 42.5, 40.8, 31.9, 31.7, 30.4, 28.5, 26.3, 25.1; IR (KBr) 3360, 1680, 1670, 1648 cm^{-1}; MS (FAB, thioglycerol matrix) *m/e* (% rel intensity) 611 (1%, (M + 1)$^+$), 593 (7%), 305 (3%), 217 (19%), 181 (11%), 91 (100%). Stereochemical assignments were made on the basis of coupling constants and on homonuclear decoupling and NOE experiments.[7b]

1*S*,2*R*,3*R*,5*S*-2-Acetyl-3-hydroxy-3-methylbicyclo[3.3.0]-octane (26a). Following general procedure A, bis-enone 25[36] (200 mg, 1.11 mmol), *n*-BuLi (1.40 mL of a 2.43 M hexane solution, 3.40 mmol), ZnCl$_2$ (2.25 mL of a 1.0 M ether solution, 2.25 mmol), and Ni(COD)$_2$ (12 mg, 0.04 mmol) were employed to produce, after flash chromatography (5:1 hexanes:EtOAc), in order of elution, 35 mg (17%) of 26b as a white crystalline solid, 11 mg (5%) of trans isomer 36b[14a] as a colorless oil, and 109 mg (54%) of 26a as a pale yellow solid that all were homogeneous by TLC analysis. Spectral data of 26b and 36b were identical to that previously reported.[14a] For 26a: ^1H NMR (300 MHz, CDCl$_3$) d 2.70−2.85 (m, 1H), 2.54 (s, 1H), 2.50 (d, *J* = 9.8 Hz, 1H), 2.25−2.45 (m, 1H), 2.21 (s, 3H), 1.96 (dd, *J* = 8.3, 12.0 Hz, 1H), 1.50−1.65 (m, 4H), 1.45 (t, *J* = 11.0 Hz, 1H), 1.30−1.40 (m, 2H), 1.10 (s, 3H); ^{13}C NMR (75 MHz) d 210.7, 80.7, 68.1, 49.6, 41.7, 37.9, 33.0, 32.9, 31.3, 24.8, 23.2; IR (KBr) 3372, 1682 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{10}$H$_{15}$O$_2$: 167.1072, found: 167.1068 ((M − CH$_3$)$^+$). Anal. Calcd for C$_{11}$H$_{18}$O$_2$: C, 72.49; H, 9.95. Found: C, 72.66; H, 10.13. Stereochemical assignments were made on the basis of NOE data.

3-Methyl-1-phenyl-(*E*)-7,9-decadien-1-one (28a). Following general procedure A, enone 27[38] (114 mg, 0.5 mmol), MeLi (1.5 mL, 2.1 mmol of a 1.4 M ethyl ether solution), ZnCl$_2$ (136 mg, 1.2 mmol), and Ni(COD)$_2$ (7 mg, 0.03 mmol), were employed to produce, after flash chromatography (95:5 hexanes:EtOAc), 80 mg (66%) of 28a as a colorless oil that was >97% pure by capillary GC analysis. ^1H NMR (CDCl$_3$, 500 MHz) δ 7.94 (m, 2H), 7.54 (m, 1H), 7.45 (m, 2H), 6.30 (dt, *J* = 17.0, 10.3 Hz, 1H), 6.04 (dd, *J* = 15.3, 10.3, 1H), 5.69 (dt, *J* = 15.0, 7.3 Hz, 1H), 5.08 (dd, *J* = 17.0, 1.0 Hz, 1H), 4.96 (d, *J* = 10.0 Hz, 1H), 2.94 (dd, *J* = 16.0, 5.5 Hz, 1 H), 2.76 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.05−2.21 (m, 3H), 1.36−1.52 (m, 3H), 1.22−1.30 (m, 1H), 0.96 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz) δ 200.3, 137.4, 137.3, 135.2, 132.9, 131.1, 128.5, 128.1, 114.8, 45.9, 36.7, 32.7, 29.6, 26.6, 20.0; IR 3085, 3061, 1686 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{17}$H$_{22}$O 242.1671, found 242.1667 (M$^+$).

1-(2-Oxo-2-phenylethyl)-(*E*)-2-(1-propenyl)cyclopentane (28b). Following general procedure B, enone 27[38] (115 mg, 0.51 mmol), Et$_2$Zn (150 μL, 1.46 mmol), PPh$_3$ (20 mg, 0.08 mmol), and Ni(COD)$_2$ (7 mg, 0.03 mmol) were employed to produce, after flash chromatography (9:1 hexanes:EtOAc), 81 mg (70%) of 28b as a colorless oil contaminated with 5−10% of a diastereomer. ^1H NMR (500 MHz, CDCl$_3$) δ 7.93 (m, 2H), 7.53 (m, 1H), 7.44 (m, 2H), 5.44 dq, *J* = 15 Hz, 6.5 Hz, 1H), 5.29 (m, 1H), 3.17 (dd, *J* = 16.0, 3.0 Hz, 1H), 2.71 (dd, *J* = 16.0, 9.0 Hz, 1H), 1.96−2.06 (m, 3H), 1.79−1.87 (m, 1H), 1.64 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.56−1.66 (m, 2H), 1.33−1.42 (m, 1H), 1.14−1.24 (m, 1H); ^{13}C NMR (125 MHz) δ 200.6, 137.3 134.7, 132.8, 128.5, 128.1, 125.3, 50.4, 43.1, 42.3, 32.7, 32.1, 23.4, 17.9 ; IR (film) 3060, 3026, 2954, 2869, 1687 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{16}$H$_{20}$O 228.1514, found 228.1510 (M$^+$).

2-(2-Oxo-2-phenylethyl)-cyclopentan-1-ol (30). A mixture of *n*-BuLi (1.5 mL of a 2.4 M hexane solution, 3.6 mmol) and ZnCl$_2$ (2.0 mL of a 1 M ether solution, 2.0 mmol) in 40 mL of THF was stirred for 20 min at 0 °C. A 4 mL THF solution of triphenylphosphine (68 mg, 0.26 mmol) was added to Ni(COD)$_2$ (7 mg, 0.03 mmol) and stirred 5 min at 25 °C. The nickel solution was transferred by cannula to the organozinc reagent and stirred at 0 °C. A 10 mL THF solution of 29 (107 mg, 0.50 mmol) was added to the nickel/organozinc mixture, and the reaction mixture was stirred at 0 °C. After stirring 30 min at 0 °C, the reaction mixture was subjected to an extractive workup (NH$_4$-

Cl/NH$_4$OH pH = 8 buffer, Et$_2$O), followed by flash chromatography (7:3 hexanes: EtOAc) on silica gel to afford 52 mg (47%) of 30 (1.5:1 mixture of diastereomers) as a colorless oil. For the major diastereomer: ^1H NMR (300 MHz, CDCl$_3$) δ 7.99 (m, 2H), 7.57 (m, 1H), 7.45 (m, 2H), 3.86 (q, *J* = 6.2 Hz, 1H), 3.48 (s, 1H), 3.21 (dd, *J* = 17.7, 5.4 Hz, 1H), 3.04 (dd, *J* = 17.7, 8.4 Hz, 1H), 2.20−2.34 (m, 1H), 1.90−2.06 (m, 2H), 1.56−1.80 (m, 3H), 1.20−1.34 (m, 1H); ^{13}C NMR (75 MHz) δ 201.4, 136.8, 133.2, 128.6, 128.1, 79.0, 44.2, 43.3, 34.5, 31.2, 22.4; IR (film) 3417, 1680 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{13}$H$_{16}$O$_2$ 204.1150 found 218.1147 M$^+$).

2-(2-Oxo-2-phenylethyl)cyclohexan-1-ol (32). A mixture of *n*-BuLi (1.2ml of a 2.5 M hexane solution, 3.0 mmol) and ZnCl$_2$ (2.0 mL of a 1 M ethyl ether solution, 2.0 mmol) in 40 mL THF was stirred for 20 minutes at 0 °C. A 5 mL THF solution of triphenylphosphine (21 mg, 0.08 mmol) was added to Ni(COD)$_2$ (12 mg, 0.04 mmol) and stirred 5 min at 25 °C. The nickel solution was transferred by cannula to the organozinc reagent and stirred at 0 °C. A 10 mL THF solution of 31 (107 mg, 0.50 mmol) was added to the nickel/organozinc mixture at 0 °C by syringe drive addition over a 1.5 h period. After stirring 30 min at 0 °C, the reaction mixture was subjected to an extractive workup (NH$_4$Cl/NH$_4$OH pH = 8 buffer, Et$_2$O), followed by flash chromatography (7:3 hexanes:EtOAc) on silica gel to afford 62 mg (57%) of 32 (2:1 mixture of diastereomers) as a colorless oil. For the major diastereomer: ^1H NMR (300 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.54 (m, 1H). 7.44 (m, 2H), 3.45 (dd, *J* = 16.4, 5.6 Hz, 1H) 3.26 (dt, *J* = 10.0, 4.3 Hz, 1H), 2.78 (dd, *J* = 16.5, 6.8 Hz, 1H), 2.18−2.30 (br s, 1H), 1.90−2.06 (m, 2H), 1.72−1.85 (m, 2H), 1.59−1.66 (m, 1H), 0.90−1.36 (m, 4H); ^{13}C NMR (75 MHz) δ 201.3, 137.2, 133.0, 128.5, 128.2, 75.1, 43.0, 41.9, 36.1, 31.8, 25.5, 24.9; IR (film) 3426, 3061, 1679 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{14}$H$_{18}$O$_2$ 218.1307, found 218.1300 (M$^+$). Anal. Calcd for C$_{14}$H$_{18}$O$_2$: C, 77.03; H, 8.31. Found: C, 76.29; H, 8.28.

6-Cyano-3-methyl-1-phenylhexan-1-one (34a): Following general procedure A, enone 33[39] (110 mg, 0.55 mmol), MeLi (2.0 mL, 2.3 mmol of a 1.1 M ethyl ether solution), ZnCl$_2$ (170 mg, 1.3 mmol), and Ni(COD)$_2$ (7 mg, 0.03 mmol) were employed to produce, after flash chromatography (4:1 hexanes:EtOAc), 86 mg (73%) of 34a as a yellow oil that was homogeneous by TLC analysis. ^1H NMR (500 MHz, CDCl$_3$) δ 7.93 (m, 2H), 7.55 (m, 1H) 7.46 (m, 2H), 2.92 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.83 (dd, *J* = 16.2, 6.2 Hz, 1H), 2.34 (m, 2H), 2.22 (octet, *J* = 6.5 Hz, 1H), 1.61−1.78 (m, 2H), 1.50−1.58 (m, 1H), 1.34−1.43 (m, 1H) , 0.99 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 199.6, 137.2, 133.1, 128.6, 128.0, 119.7, 45.6, 35.9, 28.8, 23.1, 19.8, 17.3; IR (film) 3060, 2244, 1684 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{14}$H$_{17}$NO 215.1310, found 215.1306 (M$^+$).

6-Cyano-1-phenylhexan-1-one (34b) and 6-Cyano-1-phenyl-2-hexen-1-ol (35b). General procedure B was followed except that trimethylsilyl chloride (115 μL, 0.9 mmol) was added as the last reagent dropwise by syringe. Enone 33[39] (120 mg, 0.6 mmol), Et$_2$Zn (185 μL, 1.8 mmol), PPh$_3$ (16 mg, 0.06 mmol), and Ni(COD)$_2$ (9 mg, 0.03 mmol) were employed to produce, after flash chromatography (3:2 hexanes:EtOAc), 70 mg (58%) of 34b and 30 mg (25%) of 35b as colorless oils that were both homogeneous by TLC analysis. For 34b: ^1H NMR (500 MHz, CDCl$_3$) δ 7.95 (m, 2H), 7.56 (m, 1H), 7.46 (m, 2H), 3.00 (t, *J* = 7.3 Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.79 (quintet, 7.5 Hz, 2H), 1.73 (quintet, *J* = 7.5 Hz, 2H), 1.55 (m, 2H); ^{13}C NMR (125 MHz) δ 199.7, 136.8, 133.1 128.6, 128.0, 119.6, 38.0, 28.3, 25.3, 23.2, 17.0; IR (film) 2244, 1683 cm^{-1}; MS (EI) *m/e* calcd for C$_{13}$H$_{15}$-NO 201.1154, found 201.1151 (M$^+$). For 35b: ^1H NMR (500 MHz, CDCl$_3$) δ 7.35 (m, 4H), 7.28 (m, 1H), 5.66−5.79 (m, 2H), 5.17 (d, *J* = 6.0 Hz, 1H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.22 (q, 7.3 Hz, 2H), 2.13 (br s, 1H), 1.76 (quintet, *J* = 7.2 Hz, 2H); ^{13}C NMR (125 MHz) δ 143.0, 134.5, 129.1, 128.6, 127.7, 126.1, 119.6, 74.8, 30.9, 24.7, 16.5; IR (film) 3424.6, 3025.0, 2931.0, 2249.4, 1666.5 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{13}$H$_{15}$NO 201.1154, found 201.1149 (M$^+$).

1*R*,2*R*,6*R*-1-Benzoyl-6-(2-oxo-2-phenylethyl)-2-phenylcyclo-hexane (38a). General procedure A was followed except that PhLi

(38) Diene 27 was prepared by Wittig olefination of (*E*)-5,7-octadienal. (E)-5,7-Octadienal was prepared from 2,3-dihydropyran by α-alkylation (a), ring-opening (b), and Taber modified swern oxidation (c). (a) Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411. (b) Viola, A.; Collins, J. J.; Fillip, N.; Locke, J. S. *J. Org. Chem.* **1993**, *58*, 5067. (c) Taber, D. F., Amedio Jr., J. C.; Jung, K-Y. *J. Org. Chem.* **1987**, *52*, 5621.

(39) Nitrile 33 was prepared by Wittig olefination of 4-cyano-butanal. 4-Cyanobutanal was prepared from THF by ZnCl$_2$-mediated ring opening and acylation, ester hydrolysis, and Taber-modified Swern oxidation (see ref 38c). (a) Synerholm, M. E. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol III, p 187. (b) Earl, H. A., Sterling, J. M. *J. Chem. Soc., Perkin Trans. II* **1987**, 1273.

was freshly prepared as follows: *t*-BuLi (1.55 mL of a 1.44 M pentane solution, 2.23 mmol) was added dropwise to a 5 mL −78 °C solution of phenyl iodide (0.225 g, 0.125 mL, 1.10 mmol). After stirring for 30 min at −78 °C, the mixture was allowed to warm to 0 °C, and $ZnCl_2$ (0.70 mL of a 1.0 M ether solution, 0.70 mmol) was added dropwise by syringe. Bis-enone **23**[36] (91 mg, 0.30 mmol) and Ni-(COD)$_2$ (3 mg, 0.01 mmol) were employed to produce, after flash chromatography (7:1 hexanes:EtOAc), 74 mg (65%) of **38a** as a pale-yellow solid which was homogeneous by TLC analysis: mp 118−118.5 °C (recrystallized from Et$_2$O/hexane); ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.90−7.90 (m, 15H), 3.65 (t, J = 10.5 Hz, 1H), 2.90−3.10 (m, 2H), 2.50−2.70 (m, 2H), 1.85−2.00 (m, 3H), 1.65−1.85 (m, 1H), 1.45−1.65 (m, 1H), 1.25−1.45 (m, 1H); ^{13}C NMR (75 MHz) δ 205.5, 199.1, 143.4, 138.9, 136.7, 133.0, 132.5, 128.5, 128.2, 128.0, 127.8, 127.6, 126.3, 56.2, 48.7, 43.9, 38.6, 33.5, 31.3, 25.6; IR (KBr) 1681, 1667 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{27}$H$_{26}$O$_2$: 382.1933, found: 382.1926 (M$^+$). Anal. Calcd for C$_{27}$H$_{26}$O$_2$: C, 84.78; H, 6.85. Found: C, 84.78; H, 6.96.

1*R**,2*R**,6*R**-1-Acetyl-6-(2-oxopropyl)-2-phenylcyclohexane (39a) and 1*R**,2*R**,6*S**-1-Acetyl-6-(2-oxopropyl)-2-phenylcyclohexane (39b). The procedure for compound **38a** was followed, employing bis-enone **25**[36] (72 mg, 0.40 mmol), *t*-BuLi (1.7 mL of a 1.59 mmol pentane solution, 2.7 mmol), phenyl iodide (0.273 g, 0.150 mL, 1.34 mmol), ZnCl$_2$ (0.90 mL of a 1.0 M ether solution, 0.90 mmol), and Ni(COD)$_2$ (5 mg, 0.018 mmol) to afford, after flash chromatography (5:1 hexanes:EtOAc), 12 mg (12%) of **39b** as a pale yellow oil and 60 mg (58%) of **39a** as a white solid that were both homogeneous by TLC analysis. For **39a**: mp 92−93 °C (recrystallized Et$_2$O/hexane); ^{1}H NMR (300 MHz, CDCl$_3$) d 7.10−7.35 (m, 5H), 2.72 (dt, J = 3.3, 11.4 Hz, 1H), 2.55 (t, J = 10.8 Hz, 1H), 2.15−2.40 (m, 3H), 2.10 (s, 3H), 1.80−1.95 (m, 3H), 1.68 (s, 3H), 1.40−1.65 (m, 2H), 1.05−1.25 (m, 1H); ^{13}C NMR (75 MHz) d 212.7, 207.5, 143.6, 128.6, 127.3, 126.7, 62.7, 48.6, 47.8, 35.8, 34.2, 31.7, 30.9, 30.3, 25.6; IR (KBr) 1707, 1698 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{17}$H$_{22}$O$_2$: 258.1620, found: 258.1614 (M$^+$). Anal. Calcd for C$_{17}$H$_{22}$O$_2$: C, 79.03; H, 8.58. Found: C, 79.22; H, 8.64. For (**39b**): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.10−7.30 (m, 5H), 3.11 (dd, J = 4.2, 11.7 Hz, 1H), 2.86−3.00 (m, 2H), 2.80 (dd, J = 6.3, 18.0 Hz, 1H), 2.40 (dd, J = 6.3, 18.0 Hz, 1H), 2.12 (s, 3H), 1.92 (s, 3H), 1.80−1.90 (m, 1H), 1.55−1.80 (m, 3H), 1.35−1.55 (m, 2H); ^{13}C NMR (75 MHz) δ 210.9, 207.3, 145.1, 128.3, 127.2, 126.1, 58.0, 42.2, 40.3, 34.6, 31.4, 31.2, 30.4, 29.7, 21.1; IR (film) 1705, 1700 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{17}$H$_{22}$O$_2$: 258.1620, found: 258.1615 (M$^+$).

1*S**,2*R**,3*S**-2-Benzoyl-3-phenylcyclohexanol (40). PhMgBr (3.0 mL of a 1.0 M THF solution, 3.0 mmol) was added to ZnCl$_2$ (278 mg, 2.0 mmol) in 40 mL of THF at 0 °C. After stirring 30 min the solution was added by syringe drive addition over a 2 h period to a mixture of enone **29**[36] (102 mg, 0.50 mmol) and Ni(COD)$_2$ (9 mg, 0.03 mmol) in 15 mL of THF at 0 °C. After stirring 15 min at 0 °C, the reaction mixture was subjected to aqueous workup (NH$_4$Cl/NH$_4$OH pH = 8 buffer, Et$_2$O) followed by flash chromatography on silica gel to afford 58 mg (41%) of **40** as a white crystalline solid (mp 119−120 °C) that was >97% pure by capillary GC analysis. ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.00−7.70 (m, 10H), 4.24 (br s, 1H) 3.82 (dd, 2.0, 11.7 Hz, 1H), 3.53 (br s, 1H), 3.47 (dt, 3.7, 11.8 Hz, 1H), 1.96−2.10 (m, 3H), 1.58−1.76 (m, 3H); ^{13}C NMR (125 MHz) δ 205.3, 143.8, 137.0, 133.2, 128.4, 128.3, 128.1, 127.5, 126.4, 66.7, 54.0, 40.8, 33.7, 31.8, 19.7; IR (film) 3468, 1645 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{19}$H$_{20}$O$_2$ 280.1463, found 280.1464 (M$^+$).

2-(2-Oxo-2-phenylethyl)-(*Z*)-1-(1-pentylidene)cyclopentane (41a). Following general procedure A, (2*E*)-1-phenyloct-2-en-7-yn-1-one (**1**)[7a] (0.10 g, 0.50 mmol), *n*-BuLi (0.58 mL, 1.4 mmol of a 2.43 M hexane solution), zinc chloride (0.75 mL, 0.75 mmol of a 1.0 M ether solution), and Ni(COD)$_2$ (6.9 mg, 0.025 mmol) were employed to produce, after flash chromatography (24:1 to 9:1 hexanes:EtOAc), in order of elution, 65 mg (51%) of **41a** and 11 mg (11%) of **2b**, both as colorless oils

that were homogeneous by TLC analysis. For **41a**: ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.97 (m, 2H), 7.40−7.60 (m, 3H), 5.27 (tq, J = 7.3, 1.9 Hz, 1H), 3.24 (m, 1H), 3.06 (dd, J = 3.8, 16.6 Hz, 1H), 2.94 (dd, J = 10.5, 16.6 Hz, 1H), 2.34 (m, 1H), 2.25 (m, 1H), 1.86−2.06 (m, 3H), 1.41−1.76 (m, 3H), 1.32 (m, 4H), 0.88 (m, 3H); ^{13}C NMR (75 MHz) δ 199.7, 145.5, 137.3, 132.9, 128.5, 128.0, 121.8, 43.6, 36.1, 33.2, 32.8, 32.2, 29.0, 24.0, 22.4, 14.0; IR (film) 1684, 1596, 1579; cm^{-1}; HRMS (EI) *m/e* calcd for C$_{18}$H$_{24}$O 256.1827, found 256.1822 (M$^+$). Anal. Calcd for C$_{18}$H$_{24}$O: C, 84.32; H, 9.44. Found: C, 84.16; H, 9.57. The alkene stereochemistry was assigned by observation of 1.3% and 1.0% NOE of the allylic ring methylene protons (δ 2.25 and 2.34) that are syn to the alkene proton upon irradiation of that alkene proton at δ 5.27. Assignments were confirmed by homonuclear decoupling experiments.

(*Z*)-1-Benzylidene-2-(2-oxo-2-phenylethyl)cyclopentane (42). Following general procedure A, (2*E*)-1-phenyloct-2-en-7-yn-1-one (**1**)[7a] (43.5 mg, 0.22 mmol), PhMgBr (1.10 mL, 1.10 mmol of a 1.0 M THF solution), zinc chloride (98 mg, 0.72 mmol), and Ni(COD)$_2$ (5.5 mg, 0.020 mmol) were employed to produce, after flash chromatography (21:1 hexanes:EtOAc), 37 mg (61%) of **42** as a white crystalline solid that was recrystallized from hexanes/ether: mp 96−97 °C, ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.80 (m, 2H), 7.55 (m, 1H), 7.38 (m, 2H), 7.28 (m, 4H), 7.15 (m, 1H), 6.44 (m, 1H), 3.76 (m, 1H), 3.07 (dd, J = 3.0, 17.0 Hz, 1H), 2.86 (dd, J = 11.5, 17.0 Hz, 1H), 2.59 (m, 1H), 2.53 (m, 1H), 2.05 (dq, J = 12.8, 7.8 Hz, 1H), 1.71 (m, 2H), 1.58 (m, 1H); ^{13}C NMR (125 MHz) δ 199.7, 149.8, 138.0, 137.1, 132.9, 128.5, 128.03, 128.01, 126.1, 121.6, 41.7, 36.5, 36.0, 33.5, 23.4; IR (KBr) 1673, 1593 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{20}$H$_{20}$O: 276.1514, found: 276.1510 (M$^+$). Anal. Calcd for C$_{20}$H$_{20}$O: C, 86.92; H, 7.29. Found: C, 87.12; H, 7.48. The alkene stereochemistry was assigned by observation of 1.4% and 1.3% NOE of the allylic ring methylene protons (δ 2.53 and 2.59) that are syn to the alkene proton upon irradiation of that alkene proton at δ 6.44. Assignments were confirmed by homonuclear decoupling experiments.

(*Z*)-1-(3-Butenylidene)-2-(2-oxo-2-phenylethyl)cyclopentane (43a). Following general procedure A, (2*E*)-1-phenyloct-2-en-7-yn-1-one (**1**)[7a] (60 mg, 0.30 mmol), vinylmagnesium bromide (1.05 mL, 1.05 mmol of a 1.0 M THF solution), zinc chloride (95 mg, 0.70 mmol), and Ni-(COD)$_2$ (6 mg, 0.021 mmol) were employed to produce, after flash chromatography (25:1 pentane:Et$_2$O), in order of elution, 10.5 mg of **43a** as a yellow oil and 35 mg of mixture of **43a** and **2b** (6:1 molar ratio based on ^{1}H NMR integration.) Total combined yield of **43a**: 41 mg, 59%. For **43a**: ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.96 (m, 2H), 7.56 (tt, J = 1.5, 7.5 Hz, 1H), 7.46 (m, 2H), 6.46 (dt, J = 10.5, 17.0 Hz, 1H), 5.99 (dd, J = 2.0, 11.0 Hz, 1H), 5.07 (dd, J = 1.0, 17.0 Hz, 1H), 4.97 (d, J = 10.0 Hz, 1H), 3.45 (m, 1H), 3.00−3.10 (m, 2H), 2.42−2.52 (m, 1H), 2.28−2.38 (m, 1H), 1.95 (m, 1H), 1.67 (m, 2H), 1.49−1.55 (m, 1H); ^{13}C NMR (125 MHz) δ 199.3, 150.7, 137.1, 133.9, 133.0, 128.6, 128.1, 122.0, 114.9, 43.9, 36.5, 33.6, 32.8, 23.8; IR (film) 1685, 1652, 1597, 1581 cm^{-1}; HRMS (EI) *m/e* calcd for C$_{16}$H$_{18}$O 226.1358, found 226.1354 (M$^+$).

Supporting Information Available: Copies of ^{1}H NMR spectra of representative compounds (25 pages). See any current masthead page for ordering and Internet access instructions.

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