Development of a Titanocene-Catalyzed Enyne Cyclization/ Isocyanide Insertion Reaction

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Received March 3, 1994[⊗]

Abstract: The first early transition metal-catalyzed enyne cyclization reaction is described. The system converts enyne substrates to bicyclic iminocyclopentenes through the use of 10 mol % of $Cp_2Ti(PMe_3)_2$ in the presence of a silyl cyanide. Subsequent hydrolysis produces the corresponding bicyclic cyclopentenones in good overall yield. The cyclization reaction is tolerant of polar functional groups such as ethers, amines, and esters and is diastereoselective with certain chiral enyne substrates.

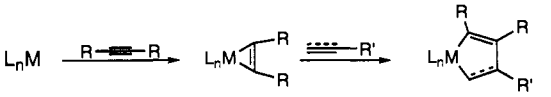
Introduction

One of the more interesting features of organometallic reagents is their ability to mediate reactions which are difficult or impossible using classical methods of organic synthesis. One example is the reductive coupling reaction of simple unsaturated organic fragments (Scheme 1).[2] The zirconocene-mediated intermolecular reductive coupling of diynes,[3] enynes,[4] and dienes[5] was originally explored by Nugent,[5] Negishi,[6] and their co-workers (Scheme 2). The metallacycles **1** behave as 1,2-dianion equivalents and have been shown to react with electrophiles[2,6,7] to furnish a number of highly functionalized organic and organo-main group compounds, as outlined in Scheme 3. More recently, others have applied this and related methodology to the intramolecular cyclization of hydrazone/alkenes (or alkynes),[8] enones, and ynones.[9]

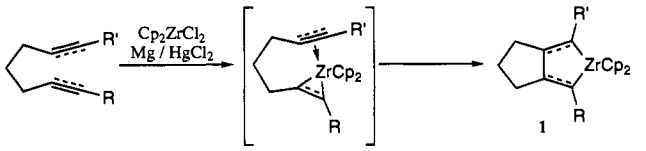
Negishi and co-workers showed that the zirconacycles **1** could be directly carbonylated[6] to produce, in a one-pot procedure, bicyclic cyclopentenones **2** (Scheme 4). This method provides an easy way to prepare cyclopentenone skeletons from simple starting materials through a formal [2 + 2 + 1] process and has been used successfully as the key step of several natural product syntheses.[10]

Several other metal complexes are known to induce the conversion of enynes to bicyclic cyclopentenones. Carbonyl complexes of cobalt[11] (the intramolecular Pauson–Khand reaction) and iron[12] have been shown to effectively mediate this reaction. Additionally, Tamao has used bis(cyclooctadienyl)-nickel in the presence of an isocyanide, a carbon monoxide equivalent, to convert enynes to bicyclic iminocyclopentenes (Scheme 5).[14] Note that, in each of these cases, a stoichiometric amount of the metal species is required to effect the desired transformation.[11d,15]

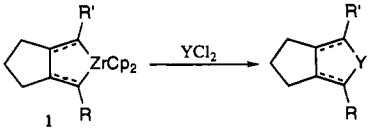
Scheme 1



Scheme 2

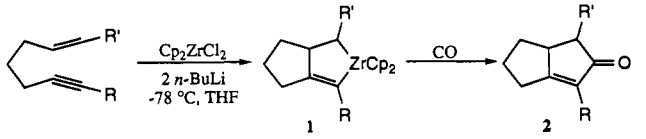


Scheme 3



Y = (H, H), PPh, AsPh, SbPh, BiPh, $GeCl_2$, $InCl_2$, S, Se, $SnMe_2$, S=O, B-R

Scheme 4



[⊗] Abstract published in *Advance ACS Abstracts*, August 15, 1994.

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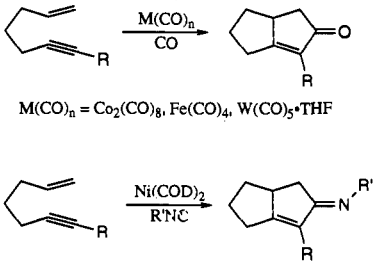
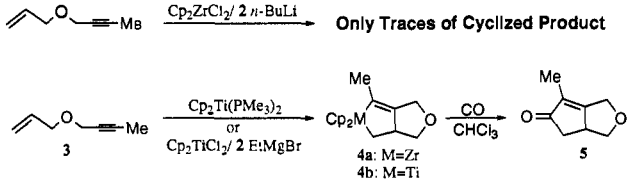
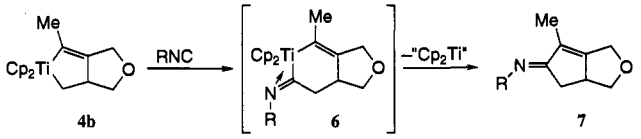
Scheme 5



Scheme 6



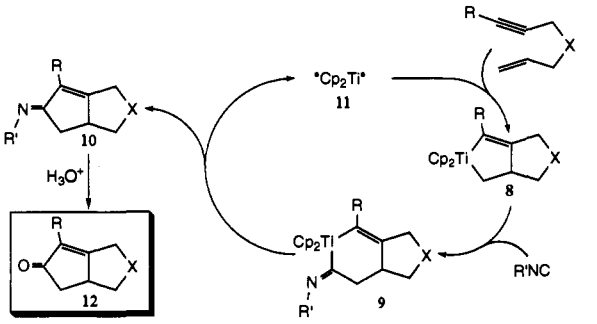
Scheme 7



While attempting to use Negishi's method to synthesize cyclopentenone **5**, we were surprised to find that the cyclization of enyne **3** provided only a trace of the desired zirconacycle **4a** (Scheme 6).[16] We thought that this may be due to an irreversible interaction between the oxygen atom and zirconium. Because titanium–oxygen bonds are substantially weaker than zirconium–oxygen bonds (by about 20 kcal/mol),[17] we attempted the reaction using $Cp_2Ti(PMe_3)_2$[18] and were able to generate the metallacycle **4b** quantitatively. Direct carbonylation in chloroform afforded the desired product **5**. We discovered that the combination of Cp_2TiCl_2 and 2 equiv of EtMgBr (or *n*-BuLi) functioned similarly to the analogous zirconium system[19] as an *in situ*-generated titanocene equivalent. Unlike the zirconium reaction, the titanium-mediated cyclization also tolerated the presence of ester groups.[16,20]

We have also shown that the addition of *tert*-butyl isocyanide to metallacycle **4b** led to the expected 1,1-insertion into the titanium–sp^3 carbon bond, providing iminoacyl compound **6** (Scheme 7).[21] Upon warming, this complex decomposed, presumably *via* the reductive elimination of "titanocene", to form the bicyclic iminocyclopentene **7** in good yield.[16] This result led us to envisionthe catalytic cycle shown in Scheme 8. After

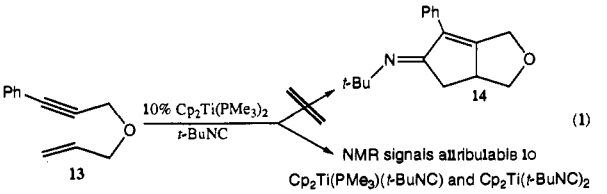
Scheme 8



isocyanide insertion into the bicyclic metallacycle **8** to form iminoacyl complex **9**, a reductive elimination reaction would provide bicyclic iminocy-clopentene **10** and reactive "titanocene" species **11**. If this reactive fragment could be trapped by another equivalent of enyne prior to its decomposition or conversion to "dead end" products, the cycle would be completed. Hydrolysis of imine **10** would then furnish bicyclic cyclopentenone **12**.[22,25]

Results and Discussion

Attempts to cyclize enyne **13** using 10 mol % of $Cp_2Ti(PMe_3)_2$ in the presence of *tert*-butyl isocyanide proved fruitless. ^1H NMR analysis showed no reaction of the enyne and resonances attributable to isocyanide complexes of titanocene (eq 1).[23]



(1)

Evidently, the titanocene reagent reacted much faster with the isocyanide than with the enyne. Efforts to limit the concentration of isocyanide by slow or portion-wise addition resulted in little improvement. Sequential addition of enyne and *tert*-butyl isocyanide to a stoichiometric amount of $Cp_2Ti(PMe_3)_2$, repeated four times, gave a 220% yield (by ^1H NMR analysis) of **14** based on titanium,[16b] suggesting that catalytic turnover was indeed possible.

We saw a potential solution to the "isocyanide delivery" problem in the tautomeric equilibrium which exists between trialkylsilyl cyanides and the corresponding isocyanides (eq 2).[24] The

(2)

equilibrium largely favors the cyano tautomer (~95:5 in the case of trimethylsilyl cyanide). Furthermore, the "normal:iso"

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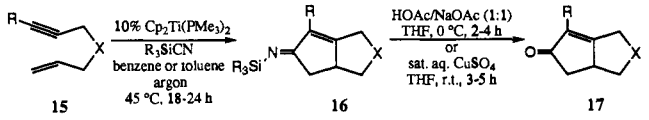
Scheme 9



ratio can be affected by modifying the nature of the groups on the silicon. We hoped that running the reaction in the presence of the appropriately substituted trialkylsilyl cyanide would be an ideal way to conveniently limit the concentration of free isocyanide in the reaction mixture.

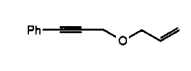
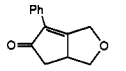
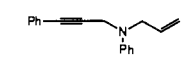
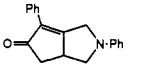
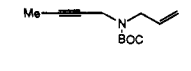
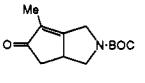
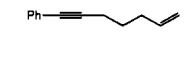
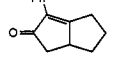
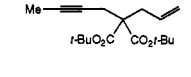
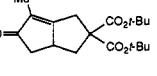
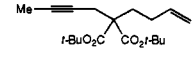
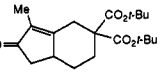
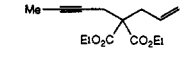
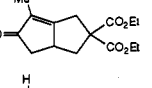
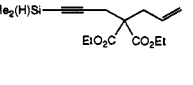
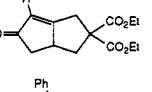
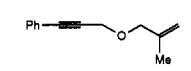
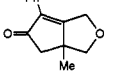
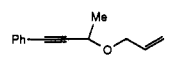
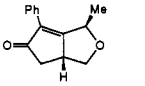
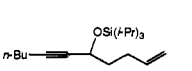
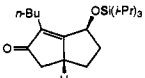
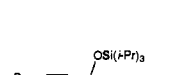
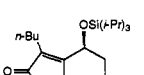
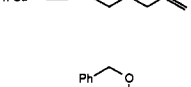
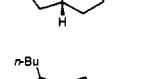
After much experimentation, it was found that 10 mol % of $Cp_2Ti(PMe_3)_2$, under the conditions shown in Scheme 9, would catalytically convert enynes **15** and a slight excess of trialkylsilyl cyanide to the corresponding iminocyclopentenes **16**.[25] Mild hydrolysis then afforded bicyclic cyclopentenones **17**. Use of Me_3SiCN gave variable results, although in some cases complete consumption of the enyne was observed when slow addition of the silyl cyanide was employed (Table 1, entries 1, 2, and 4). Reactions using *i*-Pr_3SiCN went to completion but were too slow to be useful (10 days, room temperature). *t*-$BuMe_2SiCN$ proved to be a good compromise with respect to both reactivity and compatibility. Reactions employing *t*-$BuMe_2SiCN$ were generally run at 45 °C for 18–24 h (Table 1, entries 4–7[10–12]). One drawback of this reagent is that it is a waxy solid and is difficult to prepare in a pure form. More recently, we have found that Et_3SiCN, an easily distillable liquid, works well under the standard reaction conditions (Table 1, entries 3, 7–9, and 13). Another advantage of Et_3SiCN is that reaction times using this reagent are slightly shorter (12–16 h, 45 °C).

For certain substrates (Table 1, entries 9, 11, and 12), greater than 10 mol % of catalyst is required for complete conversion. This effect is probably steric in origin. With these bulkier enynes, binding to the titanocene species **11** is more difficult, and with each turnover of the cycle (see Scheme 8), there is a greater chance that **11** will decompose before metallacycle **8** can form.

In all cases shown in Table 1, conversion of enyne **15** to imine **16** was nearly quantitative (^1H NMR analysis). Hydrolytic workup of **16** was the yield-limiting step, affording cyclopentenones **17** in fair to good yield.[26] The cyclization reaction successfully forms both 5,5- and 5,6-fused ring compounds and tolerates the presence of polar functional groups, such as ethers (Table 1, entries 1 and 9–13), nitrogen-containing compounds (Table 1, entries 2 and 3), and esters (Table 1, entries 5–8). This is similar to the functional group toleration which we have observed in the stoichiometric reactions.[16]

For the cyclization of enynes containing stereogenic centers (Table 1, entries 10–13), levels and sense of diastereoselectivity for this process were similar to those observed in related zirconium-mediated stoichiometric processes reported by Nugent and Livinghouse.[4,27] There is a high degree of 1,3-stereoinduction for the formation of 5,6-fused ring systems (Table 1, entry 12). While ^1H NMR analysis of the intermediate imines shows a small amount (5–10%) of the minor diastereomer, the ketone shown in Table 1, entry 12, was the only diastereomer detected (by GC and TLC analyses) after hydrolysis. This is probably due to selective decomposition of the minor product imine. Livinghouse has rationalized the high diastereoselectivity on the basis of the reduction of allylic 1,3-strain in the precyclization conformers (Figure 1).[27] No explicit explanation was given for the observed selectivity for the formation of 5,5-fused systems. Molecular modeling using an augmented MM2 parameter set for use with metal complexes (packaged with the Tektronix CAChe Molecular Worksystem) shows that the observed selectivity in these cases may be explicable as a result of the reduction of 1,3-diaxial interactions in the precyclization conformers (Figure 2). While high 1,2-stereoinduction is observed (Table 1, entry

Table 1. Titanocene-Catalyzed Conversion of Enynes to Bicyclic Cyclopentenones

entry	starting material	cyanide[a]	product	isolated yield (%)[d]
1		Me_3SiCN		80
2		Me_3SiCN		44[b]
3		Et_3SiCN		43
4		Me_3SiCN *t*-$BuMe_2SiCN$		55 66
5		*t*-$BuMe_2SiCN$		70
6		*t*-$BuMe_2SiCN$		71
7		*t*-$BuMe_2SiCN$ Et_3SiCN		65 71
8		Et_3SiCN		42
9		Et_3SiCN[c]		58
10		*t*-$BuMe_2SiCN$		71 (5 : 1)
11		*t*-$BuMe_2SiCN$[e]		54 (1.6 : 1)
12		*t*-$BuMe_2SiCN$[e]		52[f]
13		Et_3SiCN		45 (12 : 1)

[a] Me_3SiCN was added slowly over a 4–8 h period; *t*-$BuMe_2SiCN$ and Et_3SiCN were added immediately at the beginning of the reaction. See the Experimental Section for full details. [b] 13% of the starting material was also isolated. [c] Required 20 mol % of catalyst for complete reaction. [d] The major isomer, as assigned on the basis of NOE analysis, is shown. Numbers in parentheses indicate the ratio of diastereomers. [e] Required 15 mol % of catalyst for complete reaction. [f] The isomer shown was the only one detected.

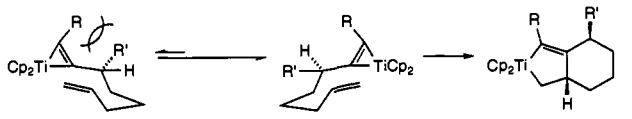


Figure 1.

(25) A portion of this work has been previously communicated. See: Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 4912.

(26) Treating the crude iminocyclopentene with vitride, $Na[H_2Al(OCH_2CH_2OCH_3)_2]$, followed by heating to 50 °C overnight leads to quantitative yield of the corresponding allylic silylamine. Although the crude product is ~98% pure by GC, there are some small impurity peaks by ^1H NMR. Research on exploiting this reduction reaction to provide higher yields of isolable organic products is underway.

(27) Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487.

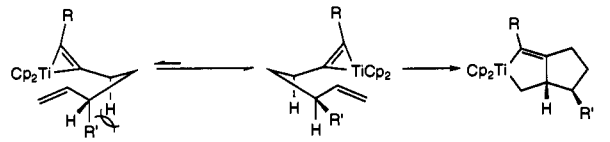


Figure 2.

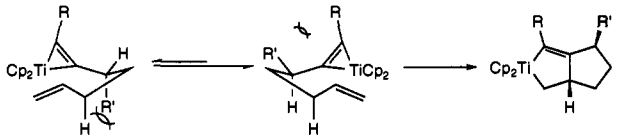
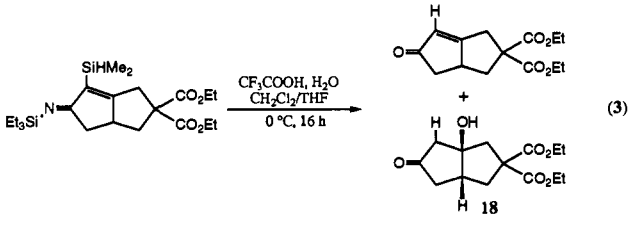


Figure 3.

13), only modest 1,3-stereoinduction is seen (Table 1, entries 10 and 11),[4] perhaps due to competing allylic 1,3-strain (see Figure 3).

Much attention was devoted to the improvement of the hydrolysis procedure, with mixed results. While the Si–N bond is readily cleaved, as evidenced by the formation of Et_3SiOH (GC analysis), several undesirable side reactions can occur during the hydrolysis of the desilylated imine. Under a variety of conditions, ranging from acidic to alkaline, significant amounts of decomposition through tautomerization, enamine formation, and polymerization were observed. For most substrates, traces of the corresponding β-hydroxy ketone, formed by Michael addition of water to the cyclopentenone (or imine), were shown to be present in the crude reaction mixture. For entry 8 of Table 1, this alcohol product **18** was isolated as a pure material in 22% yield (eq 3). The two best hydrolysis procedures to date are shown as part of Scheme 9. For most substrates, slow addition of a pH 5 buffer (1:1 mixture of acetic acid and sodium acetate) to a THF solution of the imine at 0 °C is sufficient to afford the desired ketone in 2–4 h. In an alternative procedure, saturated aqueous $CuSO_4$ is added to the imine solution at room temperature, followed by stirring for 3–5 h. We have found that the $CuSO_4$ protocol is more useful for substrates where the determination of diastereoselectivity is a concern. The acidic conditions of the acetic acid/sodium acetate workup procedure epimerize the stereogenic center at C-5, leading to changes in product diastereomer ratios (this was seen for Table 1, entry 13, where acidic workup led to a decreased diastereomer ratio of 3:1). For the product in Table 1, entry 8, trifluoroacetic acid is required to remove the silyl group through a protodesilylation reaction (eq 3).



(3)

Several substrates which resist catalytic cyclization are listed in Figure 4. Enyne **19** cyclizes to form a 5,6-fused ring system with oxygen in the backbone, but no turnover is seen under standard reaction conditions. However, **19** can be converted to the corresponding iminocyclopentene using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$. Terminal alkyne **20** was also not successfully cyclized under catalytic conditions. This result was not surprising, since it has been shown that enynes containing terminal alkynes do not cyclize using stoichiometric titanium or zirconium reagents, a result attributed to side reactions due to the presence of the acidic alkyne proton.[4] Enynes **21** and **22** each contain a 1,2-disubstituted olefin. These substrates do not cyclize, even under stoichiometric conditions. Examination of molecular models of the corresponding metallacycles shows a severe steric

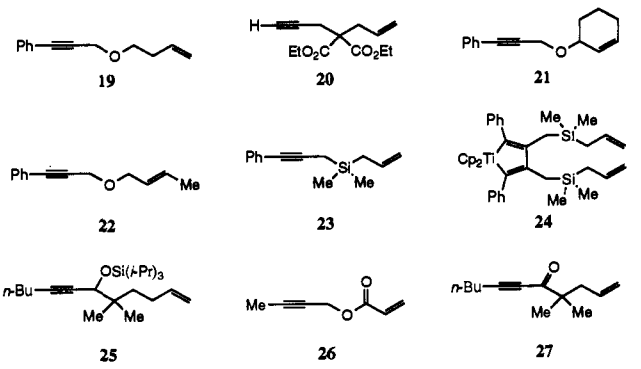
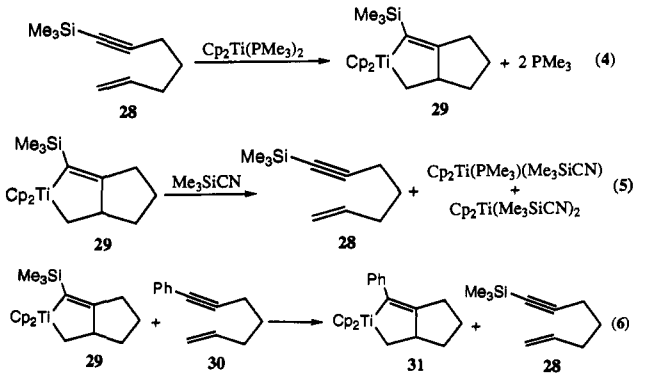


Figure 4.

interaction between the metallacycle substituents and the cyclopentadienyl rings on the titanium. This is in contrast to the stoichiometric zirconocene system, in which these cyclizations readily occur,[6] due to the larger size of the metal coordination site.[3] Silane **23** does not cyclize intramolecularly. Instead, it forms the dimer **24**, implying that the required geometry of the desired 5,5-fused bicyclic species is inaccessible.[6] The enyne in Table 1, entry 12, requires 15 mol % of catalyst to effect complete conversion of the substrate. Thus, enyne **25** was prepared with the hope that the Thorpe–Ingold effect[28] would render the cyclization of this type of substrate more favorable. Unfortunately, **25** was actually a worse substrate for the cyclization reaction. Substrates **26** and **27**, containing carbonyl groups within the tether between the alkyne and olefin units, were converted to a complex mixture of products, as judged by ^1H NMR. We have previously shown that substrates of this type do not cyclize well using the stoichiometric titanium system.[16]

When the trimethylsilyl-substituted enyne **28** failed to cyclize under catalytic conditions, we reasoned that the corresponding titanacycle, **29**, may not be stable. The reaction using a stoichiometric amount of $Cp_2Ti(PMe_3)_2$ produced **29** in high yield, which could be isolated as an air-sensitive solid (eq 4). Treatment of **29** with trimethylsilyl cyanide, *tert*-butyl isocyanide, or even acetonitrile resulted in a retrocyclization reaction to reform **28** (eq 5) along with what we believe are mono- and bis-isocyanide complexes of titanocene.[23] Combining titanacycle **29** with an enyne that is a good substrate under catalytic conditions, such as **30**, led to an enyne exchange reaction to provide the trimethylsilyl enyne and the new metallacycle **31** (eq 6). The rate of this reaction is doubled in the presence of a good donor ligand, such as PMe_3.



Examination of molecular models of **29** shows that the trimethylsilyl group is very close to the cyclopentadienyl ligands (see Figure 5). When a ligand binds to this complex, we believe that the steric environment around the metal becomes severely

(28) (a) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505. (b) Eliel, E. L. *Sterochemistry of Carbon Compounds*: McGraw-Hill: New York, 1962; p 168.

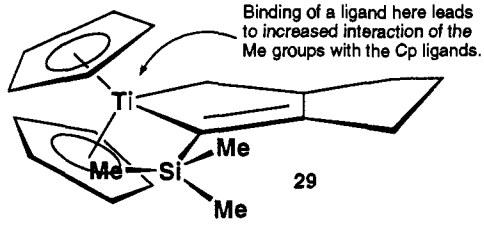
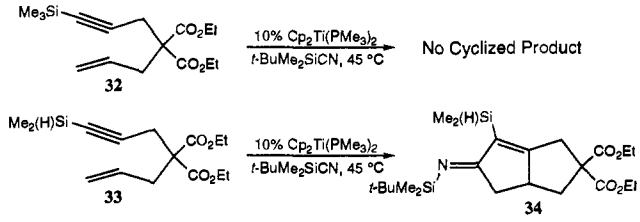


Figure 5.

Scheme 10



crowded and the resulting strain causes the retrocyclization reaction to become favorable. This may explain why the enyne exchange reaction is ligand accelerated. To determine whether this effect is steric in origin, enynes **32** and **33** were subjected to the standard reaction conditions. While the trimethylsilyl-substituted enyne did not react, **33** reacted smoothly to afford bicyclic iminocyclopentene **34** quantitatively (Scheme 10). This result demonstrates the sensitivity of the titanocene system to steric effects. Similar effects have been reported by Nugent and co-workers.[3a]

In conclusion, we have developed the first early transition metal system for the catalytic formation of bicyclic cyclopentenones from enynes and a carbon monoxide equivalent. The reaction is somewhat tolerant of polar functional groups and cyclizes chiral enynes with a moderate degree of diastereoselectivity. While we have made a considerable amount of progress in the development of the reaction, we are continuing our efforts to improve the yields, substrate compatibility, and experimental simplicity. Future work will be directed toward developing an *in situ*-generated catalyst system and toward the development of enantiopure catalysts of titanium and other metals.

Experimental Section

General Considerations. All manipulations involving air-sensitive materials were conducted in a Vacuum Atmospheres drybox or by using standard Schlenk techniques under an atmosphere of argon. THF and benzene were distilled under argon from sodium/benzophenone ketyl before use. Toluene was distilled under argon from molten sodium. Bis(trimethylphosphine)titanocene, $Cp_2Ti(PMe_3)_2$, was prepared from titanocene dichloride (obtained from Boulder Scientific, Boulder, CO) by the procedure of Binger et al.[18b] and was stored in a drybox under argon. *t*-$BuMe_2SiCN$ was prepared from *t*-$BuMe_2SiCl$ and KCN in the presence of 18-crown-6.[29] Et_3SiCN was prepared by the procedure of Becu[30] (Me_3SiCN, Et_3SiCl, trace KF, then removal of Me_3SiCl by distillation). The enynes 3-(allyloxy)-1-phenyl-1-propyne, 3-((2-methyl-2-propenyl)oxy)-1-phenyl-1-propyne, and 3-(allyloxy)-1-phenyl-1-butyne (Table 1, entries 1, 9, and 10) were prepared by the condensation of allyl bromide with the appropriate propargyl alcohol (NaH, dry THF).[31] 1-Phenyl-6-hepten-1-yne[32] (Table 1, entry 4) was synthesized by the reaction of lithium phenylacetylide (prepared *in situ* from *n*-BuLi and phenylacetylene in THF at 0 °C) and 5-bromo-1-pentene in the presence of 2 equiv of *N,N'*-dimethylpropyleneurea (DMPU) (reflux, 3 h). Diethyl 7-octen-2-yne-5,5-dicarboxylate[16] (Table 1, entry 7) was prepared by the alkylation of diethyl allylmalonate with 1-methylpropargyl mesylate (NaI, K_2CO_3, acetone, reflux, 4 days). Syntheses of previously unreported enyne substrates are described below. All other reagents were available from commercial sources and were used without further purification, unless noted otherwise.

Preparative flash chromatography was performed on E. M. Science Kieselgel 60 (230–400 mesh). Yields, unless otherwise stated, refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and/or ^1H NMR analysis. All compounds were characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopies. Previously unreported compounds were also characterized by high-resolution mass spectroscopy. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, a Varian Unity 300, or a Bruker AC 250 Fourier transform spectrometer. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All ^1H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. All ^{13}C NMR spectra are reported in ppm relative to the central line of the 77.0 ppm triplet for deuterochloroform. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 Series Fourier transform spectrometer. High-resolution mass spectra were recorded on a Finnegan MAT System 8200. Gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 gas chromatograph with a 3392A integrator and FID detector using a 25 m capillary column with cross-linked SE-30 as a stationary phase. Melting points were measured on a Haake Buchler melting point apparatus and are uncorrected.

Preparation of Enyne Starting Materials. *N*-Allyl-*N*-(3-phenyl-2-propynyl)aniline (Table 1, Entry 2). Allylaniline (4.1 mL, 30 mmol) and THF (100 mL) were added to a dry Schlenk flask under argon. The solution was cooled to −78 °C (dry ice/acetone bath), and *n*-BuLi (12 mL, 2.5 M in hexanes, 31 mmol) was added dropwise. 1-Phenylpropargyl bromide (6.0 g, 30 mmol) was then added, and the reaction mixture was allowed to warm to room temperature overnight. The next day, the mixture was added to a separatory funnel with 150 mL each of 1 N HCl and ether. The organic layer was separated and washed with 3 × 50 mL of 1 N HCl and 50 mL of brine. After the solution was dried over $MgSO_4$, flash chromatography (CH_2Cl_2:hexane = 1:99) provided 4.3 g (58% yield) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.3–7.4 (m, 2 H), 7.2–7.3 (m, 5 H), 6.91 (d, J = 9 Hz, 2 H), 6.78 (t, J = 9 Hz, 1 H), 5.8–6.0 (m, 1 H), 5.30 (dd, J = 2 Hz, J = 17 Hz, 1 H), 5.20 (dd, J = 2 Hz, J = 10 Hz, 1 H), 4.23 (s, 2 H), 4.03 (d, J = 5.1 Hz, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 134.2, 131.7, 129.1, 128.2, 128.1, 123.1, 118.0, 116.7, 114.3, 85.6, 83.9, 53.9, 40.6. IR (neat): 3297, 3060, 3032, 2979, 2912, 2245, 1642, 1598, 1575, 1503, 1490, 1442, 1417, 1378, 1346, 1287, 1255, 1229, 1192, 1173, 1126, 1255, 1229, 1192, 1173, 990, 911, 755, 733, 691 cm^{-1}. Exact mass calcd for $C_{18}H_{17}N$: 247.1361. Found: 247.1363.

***tert*-Butyl *N*-allyl-*N*-(2-butynyl)carbamate (Table 1, Entry 3).** 1-Methylpropargyl mesylate (7.0 g, 47 mmol, freshly prepared by the reaction of 2-butyn-1-ol and methanesulfonyl chloride in the presence of triethylamine in ether) was added neat to allylamine (17.6 mL, 235 mmol) with stirring at 0 °C (ice bath). The bath was allowed to warm to room temperature at which point GC analysis showed the complete disappearance of the mesylate. The reaction mixture was added to 150 mL of ether, and the white precipitate which formed was filtered away. Distillation (130 °C, 760 mmHg) provided the desired *N*-allyl-*N*-(2-butynyl)amine. This material (2.0 g, 18 mmol) was then added to ether (50 mL) in a 250 mL Schlenk flask under argon. Pyridine (1.54 mL, 19 mmol) was added, and the solution was cooled to 0 °C (ice bath). Di-*tert*-butyl carbonate (4.37 mL, 19 mmol) was then added dropwise, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then diluted with ether (75 mL) and washed with 3 × 50 mL of 1 N NaOH. The organic layer was dried over $MgSO_4$ and purified by vacuum distillation (47 °C, 0.02 mmHg) to afford the desired product as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 5.7–5.85 (m, 1 H), 5.17 (d, J = 7.4 Hz, 1 H), 5.14 (d, J = 11 Hz, 1 H), 3.97 (s, 2 H), 3.92 (d, J = 5.7 Hz, 2 H), 1.81 (t, J = 2.3 Hz, 3 H), 1.46 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8, 133.5, 116.6, 79.8, 78.9, 74.6, 48.2, 35.5, 28.2, 3.3. IR (neat): 3082, 2977, 2922, 2226, 1699, 1455, 1406, 1366, 1246, 1173, 1146, 924, 872, 769 cm^{-1}. Exact mass calcd for $C_{12}H_{19}NO_2$: 209.1416. Found: 209.1414.

Di-*tert*-butyl 2-Pentyne-5,5-dicarboxylate. Sodium hydride (3.71 g, 155 mmol) was slurried in dry *tert*-butyl alcohol (100 mL) and cooled to 0 °C under an atmosphere of argon. After 15 min, di-*tert*-butyl malonate (46.1 mL, 206 mmol) was added dropwise. The mixture was then warmed to room temperature, and 1-methylpropargyl mesylate (15.3 g, 103 mmol, freshly prepared by the reaction of 2-butyn-1-ol and methanesulfonyl chloride in the presence of triethylamine in ether) was added. Additional *tert*-butyl alcohol (50 mL) was added, and the mixture

(29) Gassman, P. G.; Haberman, L. M. *J. Org. Chem.* **1986**, *51*, 5010.
(30) Becu, C.; Anteunis, M. J. O. *Bull. Soc. Chem. Belg.* **1987**, *96*, 115.
(31) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315.
(32) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

was heated to 65 °C. After 1 h, the mixture was cooled to room temperature and added to a separatory funnel with 100 mL of H_2O. The aqueous layer was then separated and extracted with 3 × 100 mL of ether. The combined organic layers were dried over K_2CO_3, filtered, and concentrated under reduced pressure. A trace amount of magnesium oxide was added to prevent decomposition. Vacuum distillation (100 °C, 0.15 mmHg) in base-washed glassware afforded the desired product (18.89 g, 70.5 mmol, 69% yield), which was used immediately in the following two preparations.

Di-*tert*-butyl 7-Octen-2-yne-5,5-dicarboxylate[33] (Table 1, Entry 5). Sodium hydride (0.85 g, 35.3 mmol) was placed under an atmosphere of argon and slurried in toluene (120 mL). Di-*tert*-butyl 2-pentyne-5,5-dicarboxylate (6.3 g, 23.5 mmol) and additional toluene (20 mL) were added, and the mixture was heated to 85 °C. After 2.5 h, the mixture was cooled to room temperature. Allyl bromide (2.45 mL, 28.2 mmol) in toluene (20 mL) was added, and the mixture was again heated to 85 °C. The mixture was stirred overnight and then cooled to room temperature. *p*-Toluenesulfonic acid (2.03 g, 11.8 mmol) was added slowly, and the reaction mixture was stirred for 5 min. The mixture was filtered, concentrated under reduced pressure, and vacuum distilled (108 °C, 0.15 mmHg) in base-washed glassware, yielding the desired product (2.66 g, 8.6 mmol, 38% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.5–5.7 (m, 1 H), 5.0–5.2 (m, 2 H), 2.66 (d, J = 7.4 Hz, 2 H), 2.59 (q, J = 2.6 Hz, 2 H), 1.72 (t, J = 2.6 Hz, 3 H), 1.42 (s, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3, 132.5, 119.0, 81.4, 78.3, 73.9, 57.6, 36.3, 27.8, 22.7, 3.4. IR (neat): 3079, 3004, 2931, 2250, 1731, 1642, 1477, 1456, 1437, 1393, 1369, 1298, 1250, 1227, 1153, 1068, 993, 921, 847, 747 cm^{-1}. Exact mass calcd for $C_{14}H_{20}O_4$ [M − C_4H_8]$^+$: 252.1361. Found: 252.1360.

Di-*tert*-butyl 8-Nonen-2-yne-5,5-dicarboxylate[33] (Table 1, Entry 6). Sodium hydride (0.85 g, 35.3 mmol) was placed under an atmosphere of argon and slurried in toluene (120 mL). Di-*tert*-butyl 2-pentyne-5,5-dicarboxylate (6.3 g, 23.5 mmol) and additional toluene (20 mL) were added, and the mixture was heated to 80 °C. After 2.5 h, the mixture was cooled to room temperature. 4-Bromo-1-butene (2.45 mL, 28.2 mmol) in toluene (20 mL) was added, and the mixture was again heated to 80 °C. After 1 day, sodium iodide (0.70 g, 4.7 mmol) was added. After an additional 2 days, the reaction was cooled to room temperature, *p*-toluenesulfonic acid (2.03 g, 11.8 mmol) was added slowly, and the reaction mixture was stirred for 5 min. The mixture was filtered, concentrated under reduced pressure and vacuum distilled (115 °C, 0.15 mmHg) in base-washed glassware. The crude product obtained was then purified by flash chromatography (92:8 hexane:diethyl ether), yielding the desired product (2.28 g, 7.07 mmol, 30% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.7–5.9 (m, 1 H), 4.9–5.1 (m, 2 H), 2.62 (q, J = 2.4 Hz, 2 H), 1.85–2.05 (m, 4 H), 1.70 (t, J = 2.4 Hz, 3 H), 1.41 (s, 18 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 138.0, 114.7, 81.3, 78.2, 73.8, 57.7, 30.9, 28.3, 27.8, 22.9, 3.1. IR (neat): 3078, 2977, 2933, 2275, 1729, 1642, 1477, 1451, 1393, 1359, 1280, 1245, 1216, 1160, 912, 849 cm^{-1}. Exact mass calcd for $C_{15}H_{22}O_4$ [M − C_4H_8]$^+$: 266.1518. Found: 266.1520.

Diethyl 1-(Dimethylsilyl)-6-hepten-1-yne-5,5-dicarboxylate (Table 1, Entry 8). To a solution of *i*-Pr_2NH (12.9 mL, 92.5 mmol) in THF (75 mL) was added *n*-BuLi (35.6 mL, 2.6 M in hexanes, 92.5 mmol) at 0 °C (ice bath) under argon. The solution was transferred by cannula into a solution of diethyl allylmalonate (13.6 mL, 69 mmol) in THF (150 mL) at −78 °C (dry ice/acetone bath) with stirring. After the addition was complete, propargyl bromide (10.7 mL, 80 wt % in toluene, 96.2 mmol) was added and the cold bath was allowed to warm to room temperature overnight. The next day, the reaction was quenched by slow addition of saturated aqueous NH_4Cl (~50 mL) and added to a separatory funnel with 150 mL each of ether and H_2O. The organic layer was separated off, washed with 2 × 100 mL of 1 N HCl and 100 mL of brine, and then dried over $MgSO_4$. Vacuum distillation afforded 10.7 g (65% yield) of diethyl 6-hepten-1-yne-4,4-dicarboxylate. To a solution of this material (9.25 g, 39 mmol) in THF (70 mL) at −78 °C (dry ice/acetone bath) was added a freshly prepared solution (see above) of lithium diisopropylamide (46 mmol in 70 mL of THF) by cannula. When the addition was complete, the reaction mixture was stirred for 10 min. Dimethylsilyl chloride (5.1 mL, 56 mmol) was then added, and the mixture was stirred at −78 °C for 1 h. The reaction was then quenched by slow addition of 40 mL of saturated aqueous NH_4Cl at low temperature. Upon warming to room temperature, the mixture was added to 100 mL each of ether and H_2O. The aqueous layer was separated off and extracted with 25 mL of ether, and the combined organic layers were washed with 2 × 50 mL of saturated aqueous $CuSO_4$ and 50 mL of brine. The solution was dried over $MgSO_4$ and purified by vacuum distillation (87–90 °C, 0.02 mmHg) followed by flash chromatography[34] (ether:hexane = 5:95) to afford the desired product as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.5–5.7 (m, 1 H), 5.17 (dd, J = 2.0 Hz, J = 20 Hz, 1 H), 5.13 (dd, J = 2.0 Hz, J = 9.3 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 4 H), 4.08 (m, 1 H), 2.83 (s, 2 H), 2.80 (d, J = 7.5 Hz, 2 H), 1.26 (t, J = 7.1 Hz, 6 H), 0.20 (d, J = 3.7 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 131.8, 119.6, 102.8, 85.0, 61.5, 56.7, 36.4, 23.9, 14.0, −3.0. IR (neat): 3080, 2981, 2181, 2137, 1736, 1444, 1367, 1322, 1286, 1251, 1215, 1190, 1145, 1096, 1032, 885, 841, 772, 742 cm^{-1}. Exact mass calcd for $C_{14}H_{21}O_4Si$ [M − CH_3]$^+$: 281.1209. Found: 281.1208.

5-((Triisopropylsilyl)oxy)-1-undecen-6-yne (Table 1, Entry 11). Undec-1-en-6-yn-5-ol was prepared by a method adapted from Ireland[35] by the addition of 1-hexynyllithium to the crude aldehyde product generated by the Swern oxidation of 4-penten-1-ol. To a 50-mL two-necked flask under nitrogen were added imidazole (2.7 g, 40 mmol) and DMF (20 mL). After the imidazole had dissolved, undec-1-en-6-yn-5-ol (3.3 g, 20 mmol) was added to the solution. Triisopropylsilyl chloride (4.2 mL, 20 mmol) was then added dropwise, and the mixture was stirred at room temperature. After 4 h, the reaction mixture was poured into a separatory funnel with 75 mL each of ether and saturated aqueous $CuSO_4$. The organic layer was separated off and washed with 30 mL each of saturated aqueous $CuSO_4$, H_2O, and brine. The solution was then dried over $MgSO_4$ and purified by vacuum distillation to afford 1.9 g (30% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.8–5.9 (m, 1 H), 5.03 (dd, J = 2.0 Hz, J = 1.8 Hz, 1 H), 4.96 (dd, J = 2.0 Hz, J = 10 Hz, 1 H), 4.4–4.5 (m, 1 H), 2.15–2.3 (m, 4 H), 1.75 (dd, J = 7.9 Hz, J = 14 Hz, 2 H), 1.3–1.5 (m, 4 H), 1.0–1.1 (m, 21 H), 0.90 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 114.5, 84.6, 81.7, 62.7, 38.5, 30.8, 29.5, 22.0, 18.5, 18.2 (two overlapping signals), 13.7, 12.4. IR (neat): 3078, 2942, 2866, 2262, 1641, 1464, 1340, 1248, 1092, 1014, 996, 912, 883, 681 cm^{-1}. Exact mass calcd. for $C_{17}H_{31}OSi$ [M − C_3H_7]$^+$: 279.2144. Found: 279.2143.

6-((Triisopropylsilyl)oxy)-1-dodecen-7-yne (Table 1, Entry 12). Dodec-1-en-7-yn-6-ol was prepared by a method adapted from Ireland[35] by the addition of 1-hexynyllithium to the crude aldehyde product generated by the Swern oxidation of 5-hexen-1-ol. To a 100 mL three-necked flask under argon were added imidazole (3.95 g, 58 mmol) and DMF (30 mL). After the imidazole had dissolved, dodec-1-en-7-yn-6-ol (5.23 g, 29 mmol, made by the addition of 1-hexynyllithium (prepared *in situ* from *n*-BuLi and 1-hexyne in THF at 0 °C) to 5-hexen-1-al (generated from the Swern oxidation of 5-hexen-1-ol[35]), was added to the solution. The reaction vessel was placed in a room temperature water bath, and triisopropylsilyl triflate (8.6 mL, 32 mmol) was then added dropwise. The mixture was stirred at room temperature for 4 h, then diluted with 75 mL of ether and washed with 2 × 75 mL of saturated aqueous $CuSO_4$. The aqueous washings were then extracted with 2 × 50 mL of ether, and the combined organic layers were washed with 2 × 50 mL each of H_2O and brine. The solution was dried over $MgSO_4$ and purified by vacuum distillation (155 °C, 0.02 mmHg) to afford 5.69 g (58% yield) of a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.7–5.9 (m, 1 H), 4.9–5.05 (m, 2 H), 4.4–4.5 (m, 1 H), 2.18 (td, J = 6.9 Hz, J = 1.8 Hz, 2 H), 2.08 (q, J = 6.9 Hz, 2 H), 1.3–1.7 (m, 8 H), 1.0–1.2 (m, 21 H), 0.90 (t, J = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 114.3, 84.4, 81.9, 63.1, 38.7, 33.6, 30.8, 24.5, 22.0, 18.5, 18.2, 18.1, 13.7, 12.4. IR (Nujol): 3077, 2942, 2866, 2250, 1641, 1464, 1382, 1339, 1248, 1149, 1093, 1066, 1014, 996, 910, 883, 681 cm^{-1}. Exact mass calcd for $C_{18}H_{33}OSi$ [M − C_3H_7]$^+$: 293.2301. Found: 293.2299.

3-(Benzyloxy)-1-undecen-6-yne (Table 1, Entry 13). To a slurry of NaH (1.72 g, 72 mmol) in THF (100 mL) in a 500 mL round-bottom Schlenk flask under argon were added undec-1-en-6-yn-3-ol[36] (10.4 g, 63 mmol) and benzyl bromide (8.55 mL, 72 mmol). The reaction mixture was heated to reflux for 5 h, then the reaction was quenched by addition of ~40 mL of NH_4Cl. The mixture was then added to a separatory funnel with 80 mL each of H_2O and ether. The aqueous layer was

(33) Prepared by a procedure adapted from the following: Fonken, G. S.; Johnson, W. S. *J. Am. Chem. Soc.* **1952**, *74*, 831.

(34) Rigorous purification is necessary to remove a trace impurity which is responsible for catalyst deactivation.

(35) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198.

(36) Prepared by the addition of vinylmagnesium bromide to 4-nonyn-1-al. The aldehyde was synthesized by the reaction of 1-hexynyllithium (prepared *in situ* from *n*-BuLi and 1-hexyne in THF at 0 °C) with 2-(2-bromoethyl)-1,3-dioxolane in the presence of DMPU (2 equiv), followed by hydrolysis (PPTS, acetone, H_2O, reflux).

separated off and extracted with 2 × 75 mL of ether. The combined organic extracts were then washed with 2 × 80 mL of brine and dried over $MgSO_4$. Purification by vacuum distillation (150 °C, 0.02 mmHg) afforded 7.2 g (45% yield) of a colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.2–7.4 (m, 5 H), 5.6–5.8 (m, 1 H), 5.26 (dd, J = 1.9 Hz, J = 8.0 Hz, 1 H), 5.21 (s, 1 H), 4.59 (d, J = 12 Hz, 1 H), 4.36 (d, J = 12 Hz, 1 H), 3.89 (q, J = 5.5 Hz, 1 H), 2.2–2.3 (m, 2 H), 2.0–2.2 (m, 2 H), 1.75–1.9 (m, 1 H), 1.6–1.75 (m, 1 H), 1.3–1.5 (m, 4 H), 0.89 (t, J = 7.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.5, 128.2, 127.7, 127.3, 117.2, 80.5, 79.4, 79.2, 70.3, 34.9, 31.2, 21.8, 18.3, 14.9, 13.5; IR (neat): 3065, 3030, 2956, 2930, 2861, 1642, 1496, 1454, 1432, 1329, 1098, 1071, 1028, 993, 927, 735, 697 cm^{-1}. Exact mass calcd for $C_{18}H_{23}O$ [M = H]$^+$: 255.1749. Found: 255.1750.

Conversion of Enynes to Bicyclic Cyclopentenones. General Procedure A. $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) and the enyne (2.0 mmol) were added to a dry Schlenk tube in a drybox under argon. The mixture was stirred for 5 min, and the tube was fitted with an addition funnel. The funnel was charged with a solution of Me_3SiCN (293 μL, 2.2 mmol) in benzene (2 mL), and this was added dropwise to the reaction mixture over a period of 4–8 h. After the addition of Me_3SiCN was complete, the flask was removed from the drybox and attached to a vacuum/argon manifold. The benzene was then removed *in vacuo*, the residue was placed under an atmosphere of argon, and THF (10 mL) and 1 N HCl (4 mL) were added. The mixture was stirred vigorously for 12–16 h, then poured into a separatory funnel with 50 mL each of ether and H_2O. The aqueous layer was separated off and extracted with 2 × 30 mL of ether, and the combined organic extracts were washed with brine and dried over $MgSO_4$ to afford the crude product.

General Procedure B. $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) was added to a dry, sealable Schlenk tube in a drybox under argon. Benzene (1 mL) and the enyne (2.0 mmol) were then added with stirring. After 2–3 min, a solution of *t*-$BuMe_2SiCN$ (326 mg, 2.3 mmol) in benzene (1 mL) was added. The tube was then sealed, removed from the drybox, and immersed in an oil bath heated to 45 °C for 20–24 h, after which time the starting material had been completely converted to the corresponding bicyclic iminocyclopentene (^1H NMR analysis vs anisole, added as an internal standard). The vessel was removed from the oil bath, and the reaction mixture was transferred by cannula to a 250 mL Schlenk flash under argon. The benzene was removed *in vacuo*, and THF (30 mL) was added. The solution was cooled in an ice bath, and 30 mL of a 1:1 mixture of 1.0 M acetic acid and 1.0 M sodium acetate (the pH of this buffered solution was ~5) was added dropwise over a period of 5 min with vigorous stirring. After 2–4 h, hydrolysis to the cyclopentenone was judged to be complete[37] and the mixture was allowed to separate into two layers. The aqueous layer was extracted with 3 × 30 mL of ether, and the combined organic layers were washed with 30 mL each of 1 N NH_4F, H_2O, and brine and then dried over $MgSO_4$ to afford the crude product.

General Procedure C. To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) under argon was added benzene or toluene (2 mL) and the enyne (2.0 mmol). Et_3SiCN (390 μL, 2.3 mmol) was then added, the tube was sealed, and the reaction vessel was immersed in an oil bath heated to 45 °C. After the mixture was stirred for 16–24 h, the starting material was completely converted to the corresponding bicyclic iminocyclopentene (^1H NMR analysis vs anisole, added as an internal standard). The vessel was removed from the oil bath, and the reaction mixture was transferred by cannula to a 250 mL Schlenk flask under argon. The solvent was then removed *in vacuo*, and THF (40 mL) was added, followed by dropwise addition of 3 mL of saturated aqueous $CuSO_4$. After vigorous stirring of the mixture for 3–6 h, hydrolysis to the cyclopentenone was judged to be complete[37] and the reaction mixture was poured into a separatory funnel with 50 mL each of 0.5 N HCl and ether. The aqueous layer was separated off and extracted with two additional 50 mL portions of ether. The combined organic layers were washed with 50 mL portions of 0.5 N HCl and brine and then dried over $MgSO_4$ to afford the crude product.

2-Phenyl-7-oxabicyclo[3.3.0]oct-1-en-3-one[16] (Table 1, Entry 1). Procedure A was used to convert 3-(allyloxy)-1-phenyl-1-propyne[31] (344 μL, 2.0 mmol) to the desired product. Purification by Kugelrohr vacuum distillation afforded 319 mg (80% yield) of pure product as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.25–7.55 (m, 5 H), 4.95 (d, J = 16 Hz, 1 H), 4.44 (d, J = 16 Hz, 1 H), 4.38 (t, J = 7.3 Hz, 1 H), 3.2–3.4 (m, 2 H), 2.85 (dd, J = 6.1 Hz, J = 18 Hz, 1 H), 2.35 (dd, J = 2.8 Hz, J = 18 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 177.3, 134.2, 130.4, 128.3 (two overlapping signals), 127.7, 71.0, 66.0, 43.0, 40.0. IR (neat): 3058, 2976, 2853, 1744, 1707, 1497, 1446, 1408, 1356, 1301, 1165, 1120, 1027, 908, 890, 767, 732, 697 cm^{-1}.

2,7-Diphenyl-7-azabicyclo[3.3.0]oct-1-en-3-one (Table 1, Entry 2). Procedure A was used to convert *N*-(3-phenyl-2-propynyl)-*N*-allylaniline (494 mg, 2.0 mmol) to the desired product. Purification by recrystallization from ethyl acetate afforded 240 mg (44% yield) of pure product as yellow crystals. Mp: 204–206 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 7.56 (d, J = 7.0 Hz, 2 H), 7.2–7.45 (m, 5 H), 6.74 (t, J = 7.3 Hz, 1 H), 6.63 (d, J = 8.1 Hz, 2 H), 4.62 (d, J = 16 Hz, 1 H), 4.07 (d, J = 16 Hz, 1 H), 3.95 (t, J = 8.5 Hz, 1 H), 3.3–3.5 (m, 1 H), 2.89 (dd, J = 6.5 Hz, J = 18 Hz, 1 H), 2.76 (t, J = 9.3 Hz, 1 H), 2.44 (dd, J = 3.6 Hz, J = 18 Hz, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 206.3, 174.9, 163.6, 147.2, 135.2, 130.7, 129.3, 128.5, 128.2, 117.1, 112.0, 51.8, 49.4, 41.3, 31.0. IR (Nujol): 1688, 1645, 1598, 1506, 1468, 1444, 1379, 1358, 1158, 994, 905, 752, 699 cm^{-1}. Exact mass calcd for $C_{19}H_{17}NO$: 275.1310. Found: 275.1308. Flash chromatography (ethyl acetate:hexane = 15:85) of the residue obtained by removal of the solvent from the mother liquor afforded 63 mg (13%) of the starting enyne.

***tert*-Butyl 2-Methyl-3-oxo-7-azabicyclo[3.3.0]oct-1-ene-7-carboxylate (Table 1, Entry 3).** Procedure C was followed to convert *tert*-butyl *N*-allyl-*N*-(2-butynyl)carbamate (416 mg, 2.0 mmol) to the corresponding bicyclic iminocyclopentene. After the $CuSO_4$-mediated hydrolysis was judged to be complete (6 h), the reaction mixture was poured into a separatory funnel with 50 mL each of ether and H_2O. The aqueous layer was separated off and extracted with 50 mL of ether and 2 × 30 mL of ethyl acetate. The combined organic extracts were then washed with brine and dried over $MgSO_4$ to afford, after purification by flash chromatography (ether:hexane = 7:3), 203 mg (43% yield) of the product as a light yellow solid. Mp: 113–115 °C. NMR spectroscopy showed the product to be a slowly equilibrating mixture of two rotamers (R1 and R2) as a result of restricted rotation about the carbon–nitrogen amide bond. ^1H NMR (300 MHz, $CDCl_3$): δ 4.11 (s, 2 H, R1), 4.08 (s, 2 H, R2), 3.98 (t, J = 9.4 Hz, 1 H, R1), 3.90 (t, J = 9.4 Hz, 1 H, R2), 3.07 (s, 1 H, R1 + R2), 2.72 (t, J = 8.1 Hz, 1 H, R1), 2.69 (t, J = 8.1 Hz, 1 H, R2), 2.61 (t, J = 6.5 Hz, 1 H, R1), 2.55 (t, J = 6.5 Hz, 1 H, R2), 2.09 (s, 1 H, R1), 2.03 (s, 1 H, R2), 1.68 (s, 3 H, R1), 1.67 (s, 3 H, R2), 1.41 (s, 9 H, R1), 1.40 (s, 9 H, R2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0 (R1 + R2), 172.4 (R1), 171.9 (R2), 153.8 (R1), 153.6 (R2), 132.8 (R1), 132.7 (R2), 79.4 (R1 + R2), 50.5 (R1), 49.8 (R2), 45.1 (R1), 44.7 (R2), 41.1 (R1), 40.4 (R2), 39.1 (R1), 39.0 (R2), 27.9 (R1 + R2), 8.2 (R1 + R2). IR (Nujol): 1707, 1683, 1308, 1291, 1166, 1109, 1049, 967, 870, 771, 722 cm^{-1}. Exact mass calcd for $C_{13}H_{19}NO_3$: 237.1365. Found: 237.1363.

2-Phenylbicyclo[3.3.0]oct-1-en-3-one[32] (Table 1, Entry 4). Both procedure A and procedure B were used to convert 1-phenyl-6-hepten-1-yne[32] (340 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 3:7) afforded 218 mg (55% yield) of a pale yellow powder using procedure A and 262 mg (66% yield) using procedure B. Mp: 62–63 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, J = 7.0 Hz, 2 H), 7.15–7.35 (m, 3 H), 2.65–2.9 (m, 3 H), 2.45–2.6 (m, 1 H), 2.05–2.2 (m, 2 H), 1.95–2.05 (m, 2 H), 1.04 (quint, J = 9.7 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.0, 184.8, 133.7, 131.2, 127.6, 127.5, 127.0, 44.0, 42.3, 30.3, 26.7, 25.3. IR (Nujol): 1710, 1690, 1625, 1314, 1297, 1132, 926, 763, 695 cm^{-1}.

Di-*tert*-Butyl 2-Methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Table 1, Entry 5). Procedure B was used to convert di-*tert*-butyl 7-octen-2-yne-4,4-dicarboxylate (616 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 1:4) afforded 474 mg (70% yield) of a white solid. Mp: 67–69 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 2 H), 2.8–2.9 (m, 1 H), 2.45–2.6 (m, 2 H), 1.96 (dd, J = 3.0 Hz, J = 17 Hz, 1 H), 1.62 (t, J = 1.1 Hz, 3 H), 1.46 (t, J = 12 Hz, 1 H), 1.39 (s, 9 H), 1.37 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 178.4, 170.7, 170.1, 132.6, 81.8, 81.7, 62.2, 42.5, 41.3, 38.9, 33.7, 27.7 (two overlapping signals), 8.4. IR (Nujol): 1725, 1672, 1457, 1369, 1284, 1256, 1169, 1141, 1062, 1029, 845 cm^{-1}. Exact mass calcd for $C_{15}H_{20}O_5$ [M − C_4H_8]$^+$: 294.1467. Found: 294.1465.

Di-*tert*-butyl 2-Methyl-3-oxobicyclo[3.4.0]non-1-en-8,8-dicarboxylate (Table 1, Entry 6). Procedure B was used to convert di-*tert*-butyl 8-nonen-2-yne-4,4-dicarboxylate (644 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 3:7) afforded 497 mg (71% yield) of a colorless viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ 3.42 (dd, J = 2.2 Hz, J = 14 Hz, 1 H), 2.35–2.6 (m, 4 H), 2.05–2.15

(37) The hydrolysis reaction was conveniently monitored by the addition of a small quantity of tridecane or cyclooctane to the reaction mixture as an internal standard. The hydrolysis was complete when GC analysis showed that the signal corresponding to the cyclopentenone stopped increasing relative to that of the internal standard.

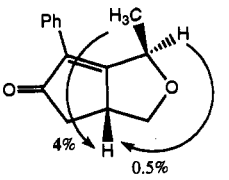
(m, 1 H), 1.8–2.0 (m, 2 H), 1.76 (s, 3 H), 1.48 (s, 9 H), 1.41 (s, 9 H), 1.2–1.35 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 170.7, 170.5, 168.8, 135.4, 82.0, 81.4, 57.2, 40.8, 39.2, 33.1, 30.9, 30.5, 27.8 (two overlapping signals), 7.8. IR (neat): 3056, 2976, 2931, 2862, 1709, 1656, 1496, 1445, 1295, 1270, 1132, 1046, 988, 904, 834, 767, 711, 696, 606 cm^{-1}. Exact mass calcd for $C_{16}H_{22}O_5$ [M − C_4H_8]$^+$: 280.1311. Found: 280.1312.

Diethyl 2-Methyl-3-oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate[16] (Table 1, Entry 7). Procedure B was used to convert diethyl 7-octen-2-yne-4,4-dicarboxylate[16] (504 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 2:3) afforded 366 mg (65% yield) of a white waxy solid. A modification of procedure B where Et_3SiCN (390 μL, 2.3 mmol) was used in place of *t*-$BuMe_2SiCN$ provided, after purification, 400 mg (71% yield) of the same material. Mp: 33–36 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (q, *J* = 7.1 Hz, 2 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 3.24 (d, *J* = 12 Hz, 1 H), 3.20 (d, *J* = 12 Hz, 1 H), 2.99 (m, 1 H), 2.79 (dd, *J* = 7.2 Hz, *J* = 12 Hz, 1 H), 2.65 (dd, *J* = 6.5 Hz, *J* = 18 Hz, 1 H), 2.10 (dd, *J* = 3.5 Hz, *J* = 18 Hz, 1 H), 1.72 (t, *J* = 1.0 Hz, 3 H), 1.66 (t, *J* = 12 Hz, 1 H), 1.30 (t, *J* = 6.8 Hz, 3 H), 1.27 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.5, 178.0, 171.8, 171.2, 133.1, 62.3, 62.1, 61.2, 42.9, 41.6, 39.4, 34.2, 14.2 (two overlapping signals), 8.7. IR (Nujol): 1736, 1675, 1460, 1424, 1384, 1256, 1177, 1084, 1063, 1023 cm^{-1}.

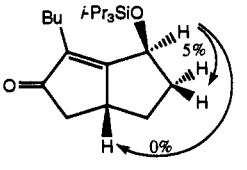
Diethyl 3-Oxobicyclo[3.3.0]oct-1-ene-7,7-dicarboxylate (Table 1, Entry 8). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (66 mg, 0.2 mmol, 10 mol %) under argon was added benzene (2 mL) and diethyl 1-(dimethylsilyl)-6-hepten-1-yne-4,4-dicarboxylate (592 mg, 2.0 mmol). Et_3SiCN (390 μL, 2.3 mmol) was then added, the tube was sealed, and the reaction mixture was stirred at room temperature for 27 h. The solution was transferred by cannula to a 250 mL Schlenk flask under argon, and the solvent was removed *in vacuo*. THF (15 mL) and CH_2Cl_2 (15 mL) were then added, and the reaction vessel was cooled to 0 °C (ice bath). Trifluoroacetic acid (5 mL) and H_2O (0.5 mL) were then added slowly, and the reaction mixture was stirred vigorously as the ice bath warmed to room temperature. After 16 h, 60 mL of saturated aqueous $NaHCO_3$ was added *slowly* to avoid bubbling over. When the bubbling ceased, the mixture was added to a separatory funnel with 80 mL each of ether and H_2O. The aqueous layer was separated off and extracted with 30 mL portions of ether and ethyl acetate. The combined organic layers were then washed with brine and dried over $MgSO_4$. Purification by flash chromatography (ether:hexane = 1:1, then 100% ether) afforded 280 mg (53% yield) of the desired cyclopentenone and 125 mg (22% yield) of the corresponding β-hydroxy ketone **18**. Data for the cyclopentenone are the following. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 1 H), 4.26 (q, *J* = 6.9 Hz, 2 H), 4.22 (q, *J* = 6.8 Hz, 2 H), 3.36 (d, *J* = 19 Hz, 1 H), 3.26 (d, *J* = 19 Hz, 1 H), 3.12 (m, 1 H), 2.81 (dd, *J* = 7.8 Hz, *J* = 1.3 Hz, 1 H), 2.64 (dd, *J* = 6.4 Hz, *J* = 18 Hz, 1 H), 2.14 (dd, *J* = 3.1 Hz, *J* = 18 Hz, 1 H), 1.75 (t, *J* = 13 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.27 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 185.3, 171.1, 170.4, 125.3, 62.0, 61.9, 60.7, 44.9, 42.0, 38.8, 35.1, 14.0 (two overlapping signals). IR (neat): 2882, 2938, 1733, 1634, 1464, 1447, 1413, 1390, 1367, 1254, 1178, 1096, 1064, 1039, 1017, 901, 860, 821 cm^{-1}. Exact mass calcd for $C_{14}H_{18}O_5$: 266.1154. Found: 266.1155. Data for the β-hydroxy ketone 18 are the following. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.1–4.3 (m, 4 H), 3.28 (s, 1 H), 2.6–2.8 (m, 4 H), 2.56 (s, 2 H), 2.36 (d, *J* = 15 Hz, 1 H), 2.0–2.2 (m, 2 H), 1.2–1.3 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 215.7, 173.2, 171.1, 85.4, 62.2, 61.8, 59.9, 51.3, 48.0, 46.8, 44.0, 39.5, 13.9 (two overlapping signals). IR (neat): 3468 (br), 2982, 2940, 1740, 1465, 1446, 1392, 1368, 1258, 1187, 1097, 1044, 916, 860, 733 cm^{-1}. Exact mass calcd for $C_{14}H_{20}O_6$: 284.1260. Found: 284.1258.

2-Phenyl-5-methyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (Table 1, Entry 9). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (132 mg, 0.4 mmol, 20 mol %) under argon were added benzene (2 mL) and 3-((2-methyl-2-propenyl)oxy)-1-phenyl-1-propyne[31] (372 mg, 2.0 mmol). Et_3SiCN (407 μL, 2.4 mmol) was then added, the tube was sealed, and the reaction vessel was immersed in an oil bath heated to 45 °C. After the mixture was stirred for 24 h, the vessel was removed from the oil bath and the reaction mixture was transferred by cannula to a 250 mL Schlenk flash under argon. The solvent was then removed *in vacuo*, and THF (40 mL) was added, followed by dropwise addition of 5 mL of saturated aqueous $CuSO_4$. After vigorous stirring of the mixture for 28 h, hydrolysis was judged to be complete[37] and the reaction was worked up according to procedure C. Purification by flash chromatography (ether:hexane = 3:7) afforded 253 mg (59% yield) of a viscous yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3–7.6 (m, 5 H), 4.99 (d, *J* = 16 Hz, 1 H), 4.61 (d, *J* = 16 Hz, 1 H), 4.04 (d, *J* = 7.9 Hz, 1 H), 3.43 (d, *J* = 7.9 Hz, 1 H), 2.61 (d, *J* = 15 Hz, 1 H), 2.54 (d, *J* = 15 Hz, 1 H), 1.39 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 180.5, 133.1, 130.5, 128.6, 128.5, 128.1, 76.5, 65.3, 48.7, 47.8, 24.7. IR (Nujol): 3056, 2967, 2852, 1712, 1654, 1496, 1446, 1345, 1295, 1151, 1072, 1025, 918, 896, 766, 697, 597 cm^{-1}. Exact mass calcd for $C_{14}H_{14}O_2$: 214.0994. Found: 214.0996.

2-Phenyl-8-methyl-7-oxabicyclo[3.3.0]oct-1-en-3-one (Table 1, Entry 10). Procedure B was used to convert 3-(allyloxy)-1-phenyl-1-butyne (372 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 3:7) afforded 305 mg (71% yield) of a pale yellow viscous oil, a 5:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.0 Hz, 2 H), 7.3–7.45 (m, 3 H), 4.85 (q, *J* = 6.5 Hz, 1 H), 4.35 (t, *J* = 7.8 Hz, 1 H), 3.35–3.45 (m, 1 H), 3.25 (dd, *J* = 7.8 Hz, *J* = 11 Hz, 1 H), 2.79 (dd, *J* = 6.4 Hz, *J* = 18 Hz, 1 H), 2.28 (dd, *J* = 3.5, *J* = 18 Hz, 1 H), 1.56 (d, *J* = 6.5 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 179.5, 134.1, 130.2, 128.5, 127.8, 127.7, 71.7, 70.6, 41.2, 39.0, 20.7. Data for the minor isomer are the following. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 2 H), 7.3–7.45 (m, 3 H), 5.23 (q, 1 H), 4.27 (s, 1 H), 3.35–3.45 (m, 1 H), 3.25 (dd, 1 H), 2.78 (dd, 1 H), 2.34 (dd, 1 H), 1.14 (d, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 181.6, 135.3, 129.5, 127.9, 127.8, 127.6, 72.2, 68.9, 44.5, 39.5, 16.7. IR (neat): 2977, 2933, 2869, 1727, 1659, 1456, 1393, 1369, 1287, 1257, 1166, 1139, 1072, 847, 734 cm^{-1}. Exact mass calcd for $C_{14}H_{14}O_2$: 214.0994. Found: 214.0995. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the methyl group at δ 1.56 gave a 4% NOE of the C-5 hydrogen at δ 3.4. Irradiation of the C-8 hydrogen at δ 4.85 gave about 0.5% enhancement of the same hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:

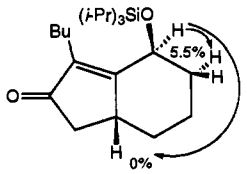


2-Butyl-8-((triisopropylsilyl)oxy)bicyclo[3.3.0]oct-1-en-3-one (Table 1, Entry 11). $Cp_2Ti(PMe_3)_2$ (99 mg, 0.3 mmol, 15 mol %) was added to a dry, sealable Schlenk tube in a drybox under argon. Benzene (1.5 mL) and 5-((triisopropylsilyl)oxy)-1-undecen-6-yne (648 mg, 2.0 mmol) were then added with stirring. After 2–3 min, a solution of *t*-$BuMe_2$-SiCN (340 mg, 2.3 mmol) in benzene (0.5 mL) was added. The tube was then sealed, removed from the drybox, and immersed in an oil bath heated to 45 °C for 16 h. General procedure C was followed for the hydrolysis and workup to provide the desired product. Purification by flash chromatography (ether:hexane = 5:95) afforded 399 mg (57% yield) of a pale yellow oil as a 1.6:1 mixture of diastereomers. A pure sample of the major diastereomer was obtained from the chromatography for analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.8–4.9 (m, 1 H), 3.0–3.1 (m, 1 H), 2.61 (dd, *J* = 6.4 Hz, *J* = 18 Hz, 1 H), 2.1–2.2 (m, 4 H), 1.94 (dd, *J* = 2.8 Hz, *J* = 18 Hz, 1 H), 1.8–2.0 (m, 1 H), 1.2–1.4 (m, 4 H), 0.9–1.1 (m, 22 H), 0.82 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 179.8, 135.9, 68.0, 42.4, 39.7, 37.4, 30.3, 28.3, 23.8, 22.8, 17.9 (two overlapping signals), 13.7, 12.3. IR (neat): 2943, 2866, 1709, 1668, 1464, 1138, 1082, 1065, 917, 883, 734, 681, 648 cm^{-1}. Exact mass calcd for $C_{21}H_{38}O_2Si$: 350.2641. Found: 350.2643. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-8 hydrogen at δ 4.87 gave a 5% enhancement of the adjacent at δ 2.15 and no enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:

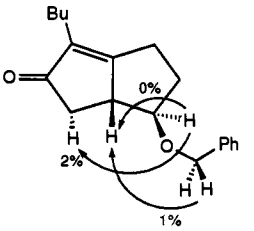


2-Butyl-9-((triisopropylsilyl)oxy)bicyclo[3.4.0]non-1-en-3-one (Table 1, Entry 12). To a dry, sealable Schlenk tube charged with $Cp_2Ti(PMe_3)_2$ (99 mg, 0.3 mmol, 15 mol %) under argon was added benzene (1.5 mL) and 6-((triisopropylsilyl)oxy)-1-dodecen-7-yne (672 mg, 2.0 mmol). A

solution of *t*-BuMe$_2$SiCN (340 mg, 2.3 mmol) in toluene (0.5 mL) was then added, and the tube was sealed and immersed in an oil bath heated to 45 °C for 22 h. General procedure C was followed for the hydrolysis and workup to provide the desired product as a single diastereomer. Purification by flash chromatography (ether:hexane = 7:93) afforded 390 mg (54% yield) of a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.94 (t, J = 2.3 Hz, 1 H), 3.0–3.1 (m, 1 H), 2.52 (dd, J = 6.5 Hz, J = 19 Hz, 1 H), 1.9–2.3 (m, 5 H), 1.91 (d, J = 19 Hz, 1 H), 1.2–1.6 (m, 6 H), 0.9–1.1 (m, 22 H), 0.90 (t, J = 7.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 175.1, 135.9, 65.0, 41.4, 36.3, 35.8, 35.7, 30.9, 22.8, 22.7, 19.4, 18.0, 17.9, 13.8, 12.3. IR (Nujol): 2939, 2865, 1706, 1653, 1464, 1179, 1118, 1083, 1027, 882, 681 cm^{-1}. Exact mass calcd for $C_{22}H_{40}SiO_2$: 364.2797. Found: 364.2801. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-9 hydrogen at δ 4.94 gave a 5.5% enhancement of the adjacent hydrogens at δ 1.43 and no enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



2-Butyl-6-(benzyloxy)bicyclo[3.3.0]oct-1-en-3-one (Table 1, Entry 13). Procedure C was followed to convert 3-(benzyloxy)-1-undecen-6-yne (512 mg, 2.0 mmol) to the desired product. Purification by flash chromatography (ether:hexane = 1:4) afforded 239 mg (42% yield) of a pale yellow oil as a 12:1 mixture of diastereomers. A pure sample of the major diastereomer was obtained from the chromatography for analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.2–7.4 (m, 5 H), 4.56 (s, 2 H), 3.54 (q, J = 7.4 Hz, 1 H), 2.92 (m, 1 H), 2.0–2.8 (m, 8 H), 1.2–1.5 (m, 4 H), 0.88 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.2, 178.0, 138.1, 137.9, 128.3, 127.6, 127.4, 83.2, 71.7, 49.5, 41.1, 32.0, 30.0, 23.9, 23.2, 22.5, 13.7. IR (neat): 2956, 2931, 2870, 1705, 1662, 1454, 1358, 1117, 912, 734, 696 cm^{-1}. Exact mass calcd for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1772. A nuclear Overhauser enhancement study was undertaken to determine the relative configuration of the major isomer. Irradiation of the C-6 hydrogen at δ 3.54 gave a 2% enhancement of the C-4 hydrogen at δ 2.15 and no enhancement of the C-5 hydrogen. Also, irradiation of the benzyl protons at δ 4.56 gave a 1% enhancement of the C-5 hydrogen. The stereochemistry of the major isomer was therefore assigned as shown:



Acknowledgment. We thank the National Institutes of Health (GM 34917) for support of this research. S.L.B. acknowledges additional support as an Alfred P. Sloan Fellow and a Camille & Henry Dreyfus Teacher-Scholar. S.C.B. thanks the National Science Foundation for a predoctoral fellowship. We acknowledge Ms. Lori Yerkey for the preparation of the substrates used in entries 5, 6, and 7 and Mr. Andrew Tseng for the preparation of the substrates used in entries 9, 11, 12, and 13.