On Inventing Reactions for Atom Economy

BARRY M. TROST

*Department of Chemistry, Stanford University,
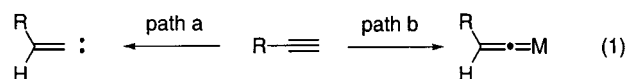Stanford, California 94305-5080*

Received August 23, 2001

ABSTRACT
An important first step in making organic reactions more environmentally benign by design requires processes that are, to a first approximation, simple additions with anything else needed only catalytically. Since so few of the existing reactions are additions, synthesis of complex molecules requires the development of new atom-economic methodology. The prospect for such developments is probed in the context of ruthenium-catalyzed reactions. Using mechanistic reasoning, over 20 new processes of varying complexity have been designed and implemented. While some involved oxidation–reduction processes, most involved C–C bond-forming reactions.

A significant goal of green chemistry must be to maximize the efficiency of use of raw materials and to minimize the creation of waste. Thus, it is fundamental that chemical reactions of the form A + B → C + D by necessity generate two products even though only one, let us say C, is desired. By definition D is a byproduct. To maximize the efficiency of such processes, either a use can be found for D or D must be as small and innocuous as possible. In the ideal circumstance, D would vanish and the reaction would become A + B → C, i.e., an addition, with anything else only needed catalytically. Thus, as a first step in making chemical manufacturing more efficient, more use of reactions that are simple additions must be emphasized.[1] It is important to note that there are such reactions. The Diels–Alder reaction is noteworthy since it comes close to being almost the truly ideal reaction for forming C–C bonds—it can be chemo-, regio-, diastereo-, and enantioselective as well as being atom economic.[2] Surprisingly, few industrial processes make use of such a reaction, although it is an extremely important research tool for the synthesis of complex molecules. Hydro-

Barry M. Trost was born in Philadelphia, Pennsylvania, in 1941, where, in 1959, he began his university training at the University of Pennsylvania (BA, 1962). He obtained a Ph.D. degree in chemistry just three years later at the Massachusetts Institute of Technology (1965). He directly moved to the University of Wisconsin, where he was promoted to Professor of Chemistry in 1969 and subsequently became the Vilas Research Professor in 1982. He joined the faculty at Stanford as Professor of Chemistry in 1987 and became Tamaki Professor of Humanities and Sciences in 1990. In recognition of his many contributions, Professor Trost has received numerous awards, a few of which are the ACS Award in Pure Chemistry (1977), the ACS Award for Creative Work in Synthetic Organic Chemistry (1981), Guenther Award in the Chemistry of Essential Oils and Related Products (1990), the Dr. Paul Janssen Prize (1990), the ACS Roger Adams Award (1995), the Presidential Green Chemistry Challenge Award (1998), the Herbert C. Brown Award for Creative Research in Synthetic Methods (1999), the Yamada Prize (2001), and the ACS Nobel Laureate Signature Award for Graduate Education in Chemistry (2002). Professor Trost's research interest include the invention and development of new synthetic reactions largely based upon catalysis using transition metal complexes and their use to define strategies that result in the total synthesis of complex molecules largely of biological significance.

formylation, on the other hand, represents an atom-economic reaction that has gained important use industrially and only limited use in complex molecule synthesis in a typical research laboratory.[3] Catalytic hydrogenation comes the closest to being an ideal reaction that is extensively practiced both industrially and academically.[4] Unfortunately, in multistep syntheses, very few of the reactions used, if any, are additions because so few such reactions really exist. Increasing the number of such reactions in our toolbox undoubtedly can change that picture. With this goal in mind, we set out to see if we can participate in this first-stage endeavor by, to a first approximation, deliberating inventing addition reactions wherein anything else is needed only catalytically. In this Account, I outline the development of our program in Ru-catalyzed reactions.
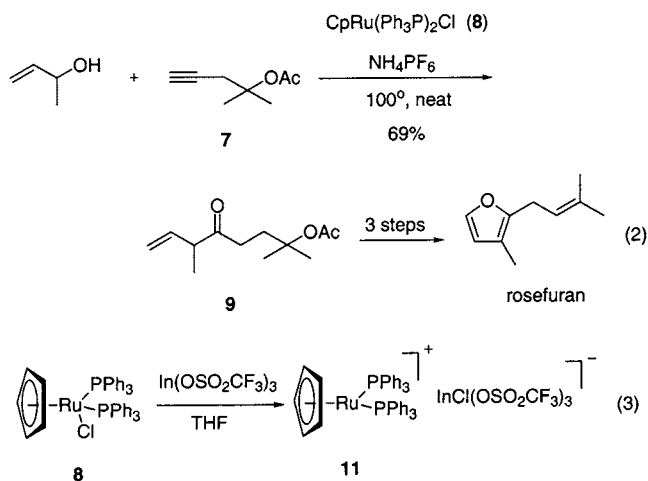
Additions via Vinylidene Complexes

In the 1980s, I was struck by a number of reactions in which terminal alkynes were reported to be converted either thermally (eq 1, path a), albeit at very high temperature,[4] or in the presence of metals[5] to the corresponding carbene or metal complexed carbene. While a cyclo-

$$ \underset{H}{\overset{R}{{\Large\diagdown}}}{=}: \quad \xleftarrow{\text{path a}} \quad R{-}{\equiv}{\equiv} \quad \xrightarrow{\text{path b}} \quad \underset{H}{\overset{R}{{\Large\diagdown}}}{=}{\bullet}{=}M \qquad (1) $$
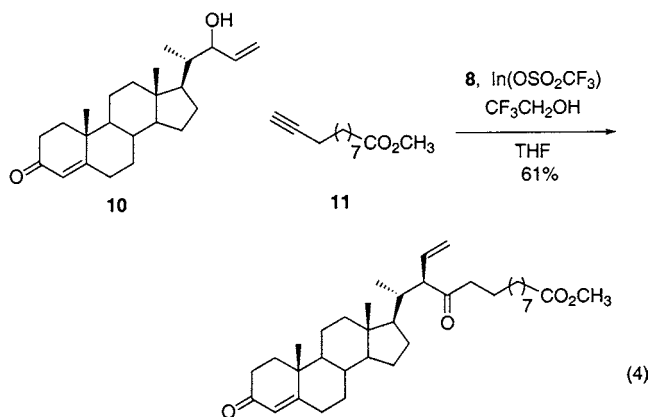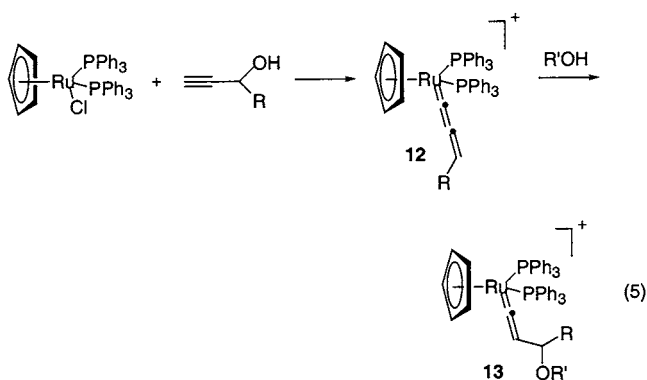
pentenone synthesis evolved from the former, the extraordinarily high temperatures required made it dubious that this strategy might lend itself to new reaction development. On the other hand, vinylidene metal complexes formed under very mild conditions, but the resulting complexes normally proved to be too stable and therefore devoid of reactivity. We were attracted to the facile room-temperature formation of vinylideneruthenium complexes **2** by the interaction of terminal alkynes with a complex like **1** (see Scheme 1).[6] The low reactivity of such carbenes led us to speculate about the possibility of precoordinating a potential nucleophilic alcohol partner by prior alkene coordination, as might happen with an allyl alcohol substrate (i.e., **2** → **3** → **4**). This addition creates a metalla analogue of a 1,5-diene **4** that should undergo a sigmatropic rearrangement to **5** and a reductive elimination to form **6**.[7] Indeed, heating a neat mixture of 3-hydroxy-1-butene (excess) and a terminal alkyne **7** in the presence of catalyst **8** gave the 1:1 adduct **9** as predicted by Scheme 1 and shown in eq 2.[8] The latter, after dihydroxylation which spontaneously creates a tetrahydrofuran and dehydration, produces a short synthesis of the fragrance rosefuran.

The requirement for use of excess allyl alcohol led to the development of a second-generation catalyst. Examination of the catalytic cycle suggested that a cationic complex bearing only one phosphine ligand might be more reactive and allow reactions to proceed at lower temperatures. As shown in eq 3, addition of an In(3+) salt to promote C1 dissociation would open a coordination as well as create a positive charge. Indeed, now more

$$(2)$$

$$(3)$$

nearly stoichiometric amounts of allyl alcohol **10** and alkyne **11** suffice to give satisfactory yields of the β,γ-unsaturated ketones (eq 4).[9]


$$(4)$$

Propargyl alcohols are known to form allenylidene complexes **12** with these types of ruthenium complexes

(eq 5).[10] Such species are subject to nucleophilic addition

$$(5)$$

to give adducts such as **13** if an alcohol is the nucleophile—a vinylidene complex that can enter the catalytic cycle of Scheme 1.[11] In a synthesis directed toward the spirocyclic core of the calyculins, a tandem cyclization—reconstitutive addition was developed (eq 6) in which the only stoichiometric byproduct was water.[12]


$$(6)$$
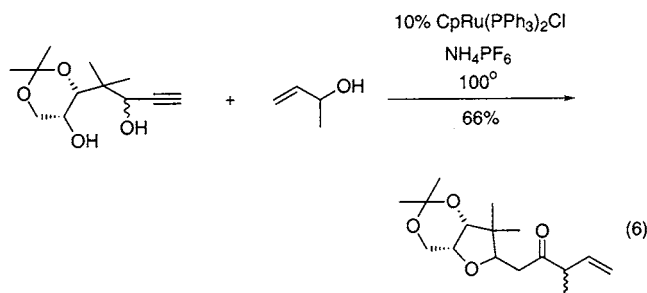
Redox Isomerization

The initial studies of the reconstitutive addition revealed that the allyl alcohols were being isomerized to saturated ketones. Indeed, the chemoselectivity of the process

Scheme 1. A Rationale for Reconstitutive Addition
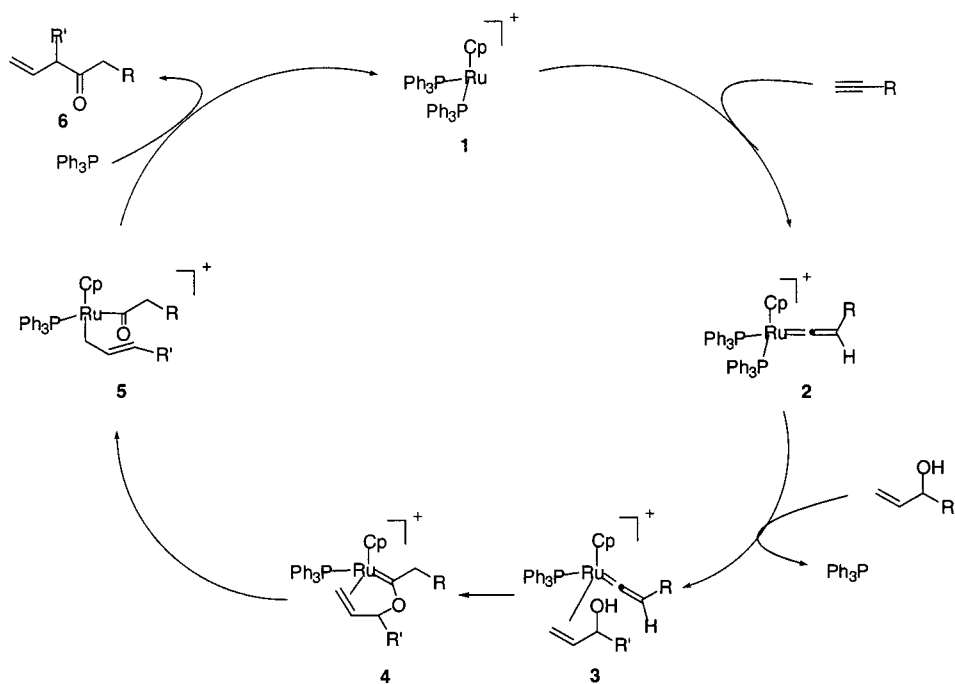
makes this process a synthetically useful reaction, as shown in eq 7.[13] Particularly noteworthy is the compat-


$$(7)$$

93%
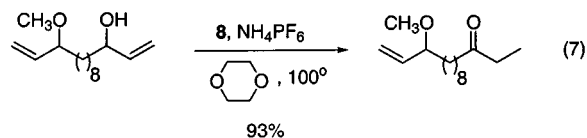
ibility of isolated double and triple bonds. A potentially even more powerful process is the related redox isomerization of propargyl alcohols to α,β-unsaturated carbonyl compounds. The preferred catalyst for this process is the indenyl complex **14**.[14] The example of eq 8 highlights the utility of the reaction.[15a] Previously, the transformation


$$(8)$$
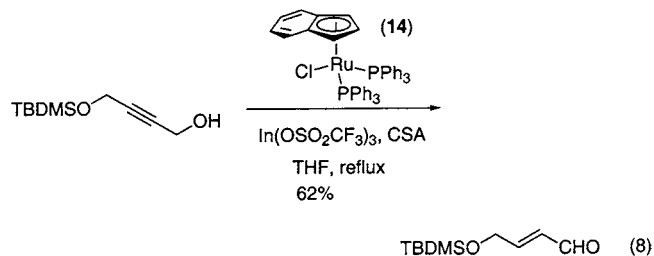
required first a stoichiometric reduction followed by a stoichiometric oxidation.[15b] A one-step isomerization accomplishes the same transformation!

Mechanistic work reveals that the two processes are quite distinct. Scheme 2, cycle A, outlines a proposed mechanism for the case of allyl alcohols. The requirement for allyl alcohols (the corresponding ethers are unreactive as in eq 7) and the observation of α,β-unsaturated carbonyl compounds as minor products in a few cases support this proposal.[13] Redox isomerization of the propargyl alcohol differs in that an intramolecular 1,2-hydride migration as shown in eq 9 is the critical step.[14]


$$(9)$$
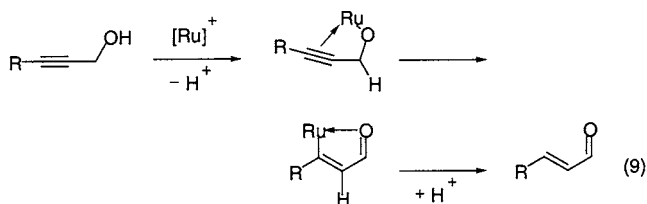
An Ene—Yne Addition

The proposal outlined in Scheme 2 invokes a ruthenium hydride intermediate **15**. Such a species might be diverted by a hydrometalation of an alkyne to follow cycle B. Indeed, using a more coordinatively unsaturated complex **16**, a simple addition results in the formation of γ,δ-unsaturated ketones (eq 10).[16-18]

$$(10)$$
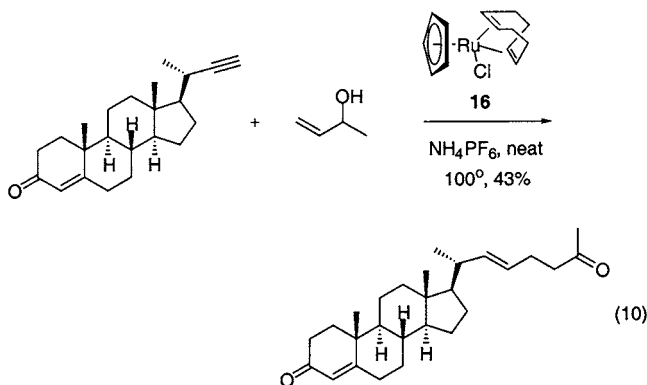
During these studies using complex **16**, a very minor byproduct was observed that proved to be an adduct of COD and the alkyne. Indeed, a general [2 + 2 + 2] cycloaddition was developed, as shown in eq 11.[19] Thus, the COD does not simply serve as a readily exchangeable ligand, thereby providing the open coordination sites, but it literally reacts off of the Ru to open the two coordination

Scheme 2. Mechanistic Rationale for Redox Isomerization of Allyl Alcohols and Its Implication for Creating a Related Process

(11)

(14)

b/l >25 : 1
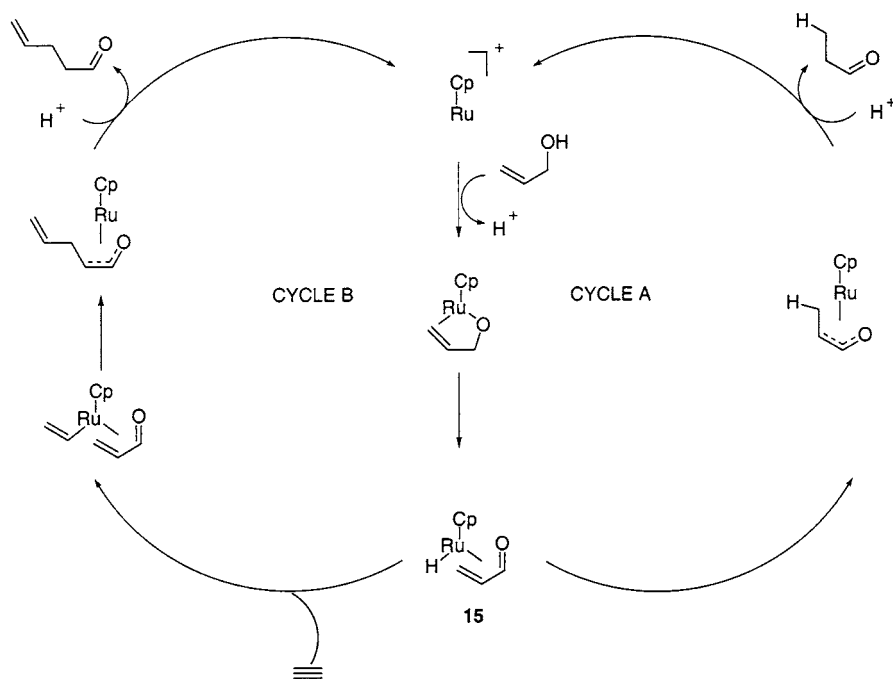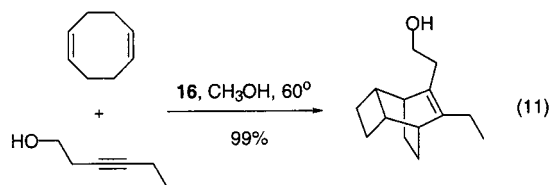
sites. The ability to generate such a complex tricycle by this unprecedented bis-homo-Diels−Alder-type reaction becomes even more impressive as an atom-economical process when it is realized that both substrates also derive by addition reactions, COD by the nickel-catalyzed dimerization of 1,3-butadiene and the alkyne by addition of the terminal acetylene and ethylene oxide.

If the mechanism of Scheme 2, cycle B, is operative, an allyl alcohol is required as a substrate. To test this hypothesis, a simple alkene was employed as a substrate, as shown in eq 12. Using our first-generation catalyst 16,


(12)

| 16, CH$_3$OH, reflux | 50% | 4 : 1 |
| (18), CSA, acetone, r.t. | 67% | 25 : 1 |
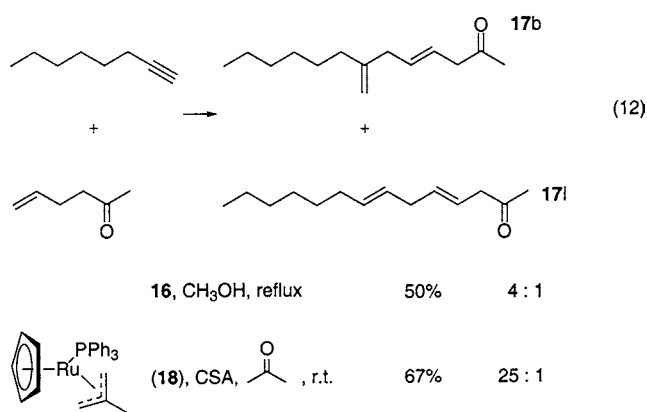
the reaction proceeded to form the expected branched (17b) and linear (17l) adducts in a 4:1 ratio.[20] With alkene 19, the regioselectivity with 16 as catalyst was 12.5:1 (eq 13)—a key reaction in a short synthesis of alternaric acid.[21]


(13)

b/l 12.5 : 1
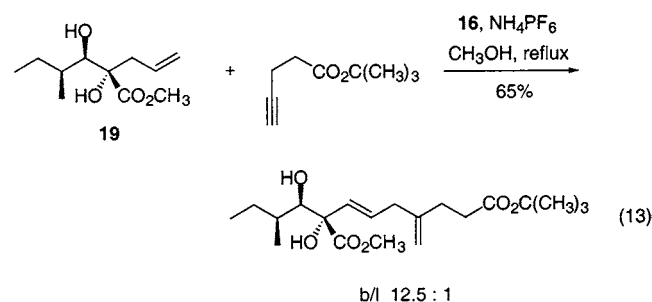
This example also illustrates the excellent chemoselectivity of the process. Since only two open coordination sites were anticipated to be needed, complex 18 in the presence of CSA was examined in the reaction of eq 12. Gratifyingly, the enhanced steric bulk at the Ru increased the b/l selectivity to 25/1.[22] A third-generation catalyst 20 also effected reaction at ambient temperature to give good to excellent regioselectivity (eq 14).[23] The ease of access of this complex and its great generality make it the catalyst of choice.[23]

Disubstituted alkynes also may give excellent regioselectivity. For example, silyl-substituted alkynes gave only
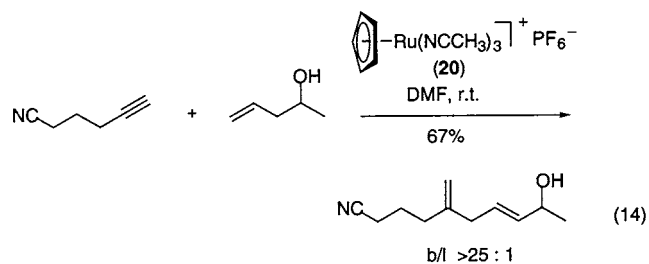
single regioisomers wherein the new C−C bond formed at the less hindered alkyne carbon (eq 15).[25] Alkynoates


(15)

ONLY
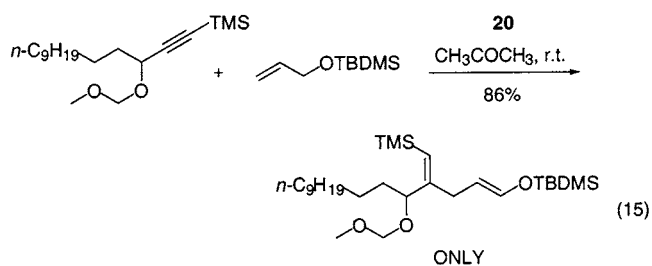
showed a rather unexpected regioselectivity wherein the new C−C bond formed at the α alkyne carbon.[26] Thus, this reaction provides a heretofore unavailable complement to the common conjugate addition-type processes normally expected with α,β-alkynoates. This unorthodox regioselectivity served as a key aspect in a novel strategy to the acetogenins, as illustrated in the synthesis of squamocins using our first-generation catalyst (parviflorin) (eq 16).[27] Even unsymmetrical internal alkynes bearing

(16)
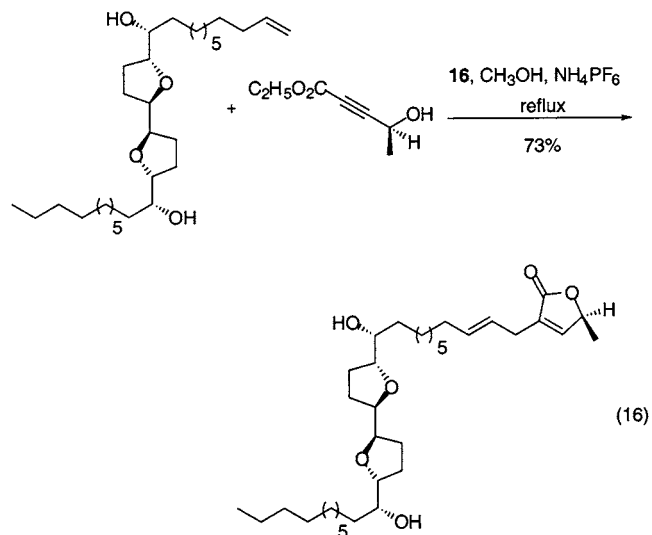
only alkyl-type substituents may give rise to excellent regioselectivity and thus constitute a geometrically controlled trisubstituted olefin synthesis. As illustrated in eq 17, a building block for the total synthesis of callipeltoside A and its analogues became available by a simple addition.[28] The third-generation catalyst allowed the extension of this addition to disubstituted alkenes (eq 18).[17]

These results with simple alkenes are inconsistent with the mechanism outlined in cycle B of Scheme 2. All of the results are consistent with a metallacycle mechanism[29] as outlined in Scheme 3. While metallacyclopentenes are

(17)

(18)

α/β 9/1
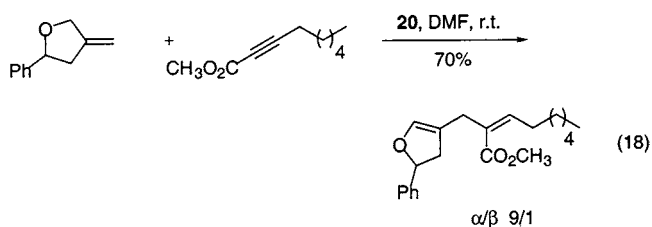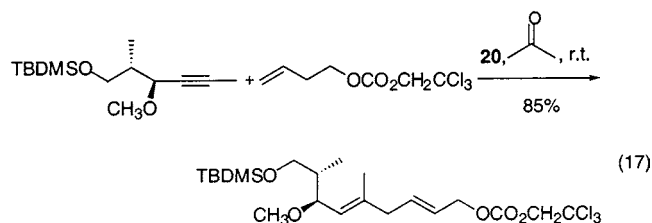
geometrically ill-disposed to undergo endocyclic β-hydrogen elimination which accounts for exclusive formation of the 1,4-dienes, such eliminations have been reported when exocyclic processes are precluded (eq 19).[29]


(19)
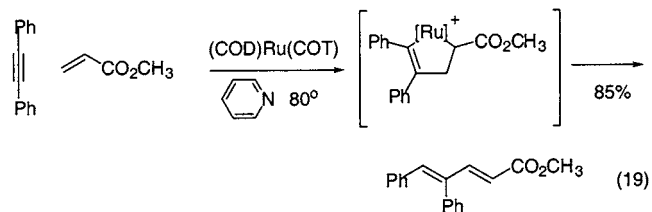
The metallacycle mechanism predicts that when monosubstituted alkenes are employed, cyclization processes to form "normal" ring sizes (e.g., 5, 6, 7) cannot proceed since they require a 1,3-bridge in the metallacycle. However, if the tether is long enough to allow such 1,3-bridging, then intramolecular processes become possible. Indeed, macrocyclizations to form 18-membered or larger rings proceed readily, as illustrated by the formation of a 25-membered ring in good yield in eq 20.[30] The ability to employ more substituted double bonds with the third-generation catalyst **20** also allows the normal-sized rings to form (eq 21, path a).[31] This example illustrates the complementary regioselectivity between the Ru- versus the Pd (eq 21, path b)-catalyzed cycloisomerizations.[32]

(20)
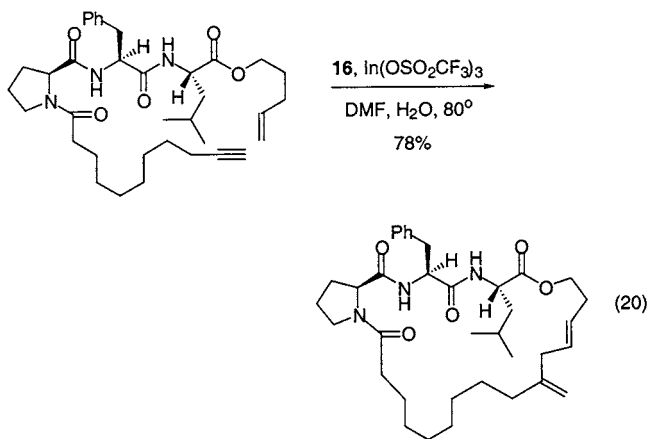
Cycloisomerizations to form 1,3-dienes, in cases where 1,4-diene formation is precluded, have also been observed.

(21)
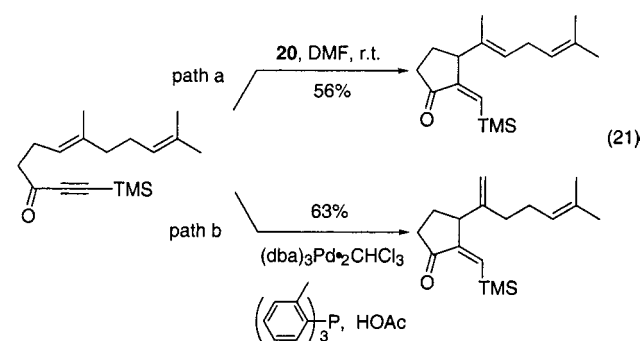
A Three-Component Coupling

Employing an alkene partner incapable of exocyclic β-hydrogen elimination has not led to endocyclic β-hydrogen elimination, in contrast to the results of eq 19. However, the vinylruthenium unit appears to be polarized, as suggested by the depicted resonance structure **21**. Such

21
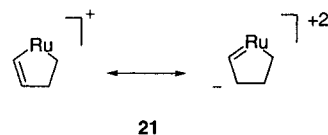
a resonance structure reactionalizes the α regioselectivity with conjugated alkynoates. This depiction suggests the

Scheme 3. A Metallacycle Mechanism for Alkene–Alkyne Addition
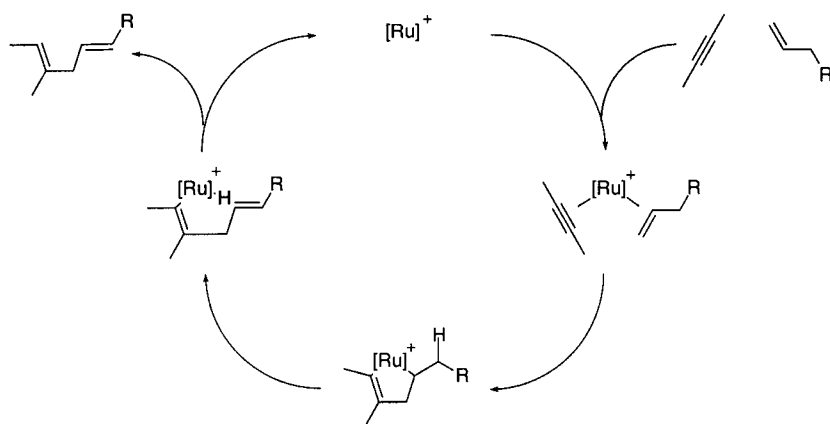
Scheme 4. A Rationale for Hydrative Three-Component Coupling

ability to add HX across such a double bond if a facile β-hydrogen elimination is excluded. Indeed, utilization of a vinyl ketone as the alkene partner in aqueous DMF effects a useful three-component coupling, as illustrated in eq 22 and rationalized in Scheme 4.[34,35]

Utilizing complex **20** as the catalyst allows an intramolecular version of the reaction. Thus, the 1,7-enyne **22** produced the diketone **23** at room temperature (eq 23, path a).[36] While the diketone can be easily isolated, direct
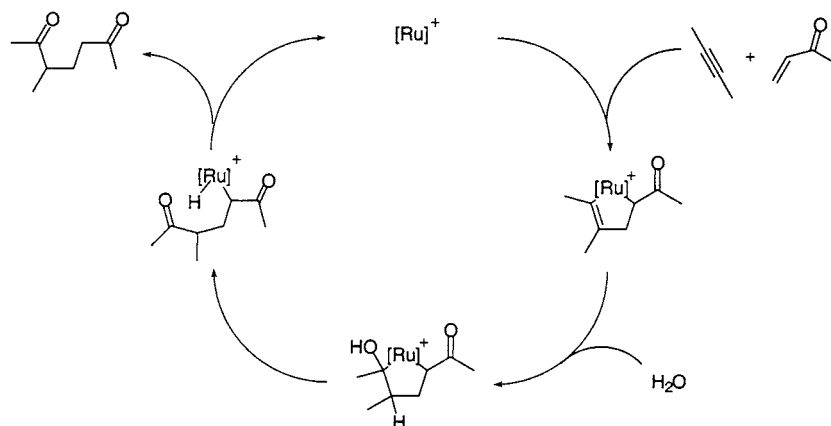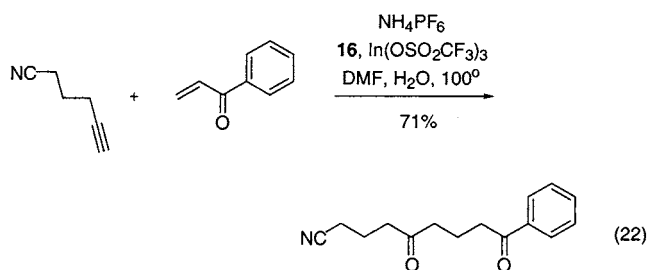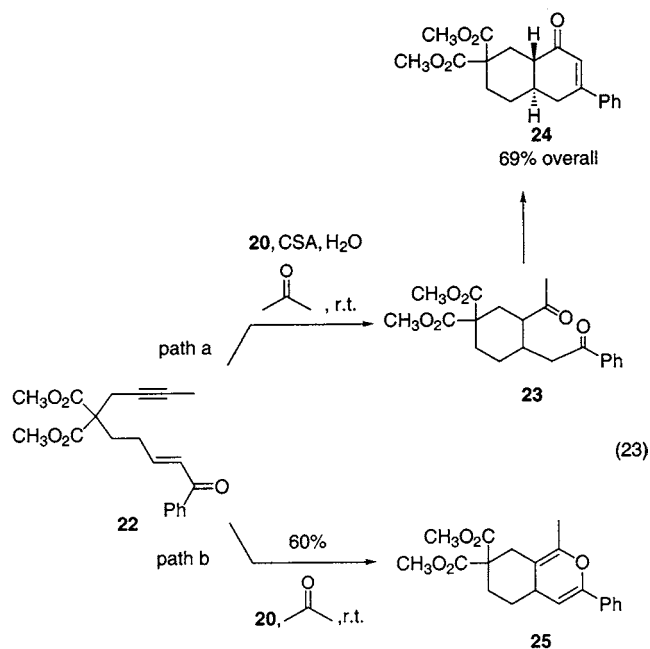

base-catalyzed intramolecular aldol condensation completes a facile bicycloannulation sequence. Performing the

same reaction under anhydrous conditions produced the 4*H*-pyran **25** exclusively. The somewhat reduced yield derived from the sensitivity of this product. It is possible that pyran **25** is the precursor of the diketone **23** by simple acid-catalyzed hydrolysis.

Another consequence of the resonance considerations of the metallacycle is the ionization of propargylic substituents that can function as leaving groups. For example, if a propargylic alcohol is employed, a reorganization of the type predicted in eq 24 would be predicted. As shown in eq 25, such a process indeed occurs.[37] The exclusive formation of enone **26** eliminates consideration of diol **27** (formed as in Scheme 4) as an intermediate followed by dehydration. Such an intermediate should produce enone **28** to some extent.
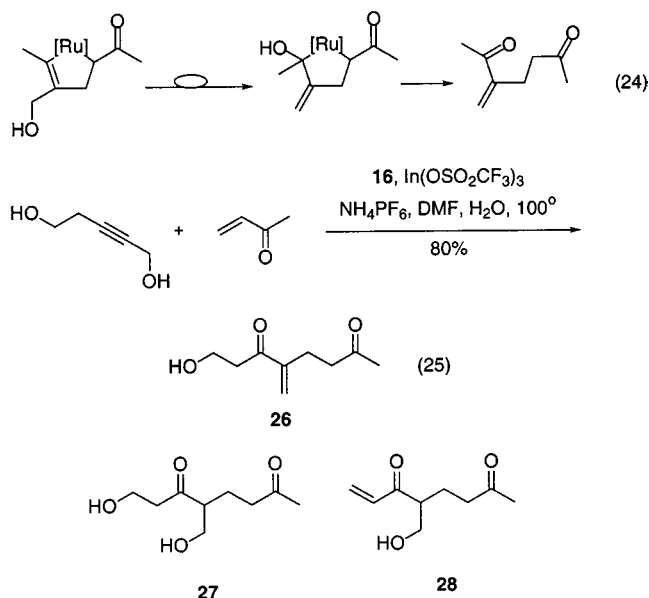
This three-component coupling led to examination of alternatives to water. Hydrogen halides, specifically HCl and HBr in the form of aqueous chloride and bromide salts, might behave analogously to water in Scheme 4. In the event (eq 26), reaction of an aqueous chloride solution with an alkyne and enone gave selectively the *E*-vinyl chloride **29**, not the *Z*-isomer expected via the mechanism

$$(26)$$

29

$$(28)$$
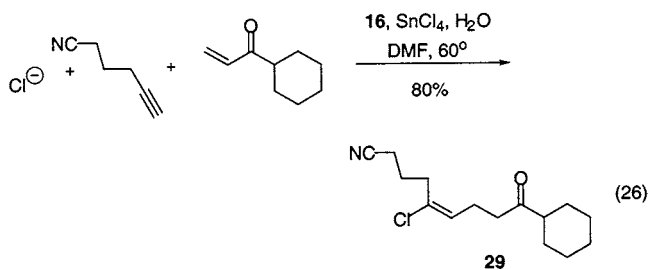
of Scheme 4.[38] Scheme 5, cycle A, outlines a rationale wherein the process is initiated by a typical type of electrophilically promoted trans addition to the alkyne.[35] The affinity of halides for ruthenium suggests that a cis addition pathway may also be accessible (Scheme 5, cycle B). Indeed, upon switching to bromide with acetone as solvent, excellent *Z*-selectivity was obtained.[39] Equation 27 illustrates the evolution of a facile cyclopentenone synthesis from this three-component coupling to produce a selective COX-2 inhibitor, **30**.[40]

$$(27)$$

30

a) X = S
b) X = SO$_2$
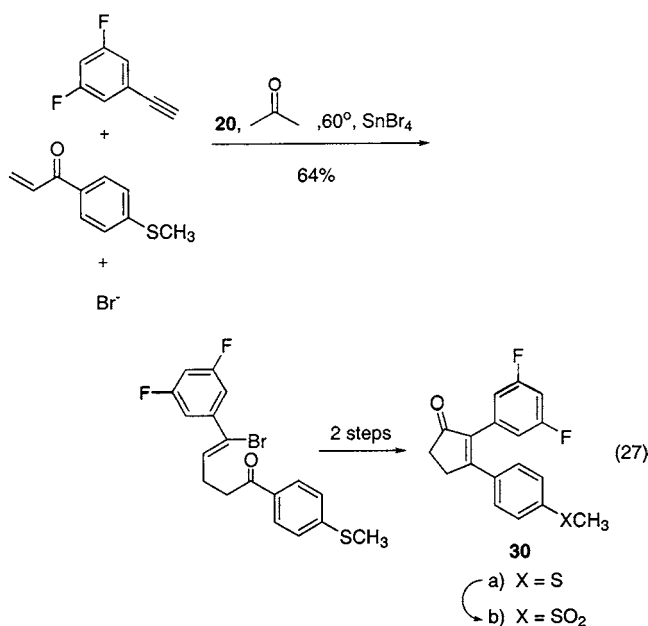
The working hypothesis of Scheme 5 invokes the intermediacy of an enolate which is simply protonated. Can such a species be intercepted by an alternative electrophile faster than protonation?[41] Equation 28 demonstrates the realization of this prediction in both the trans chlororuthenation (path a) and cis bromoruthenation (path b) processes, respectively.[42] This four-component coupling creates a great deal of molecular complexity in one step in highly atom-economic fashion.

An Allene—Alkene Addition

The uniqueness of the alkyne as a reaction partner was probed by considering alternative functional groups retaining an sp-hybridized carbon such as an allene.[43] To avoid issues of chemoselectivity in the β-hydrogen elimination, an enone was considered as the alkene partner. Scheme 6 proposes a catalytic cycle to form a 1,3-diene,
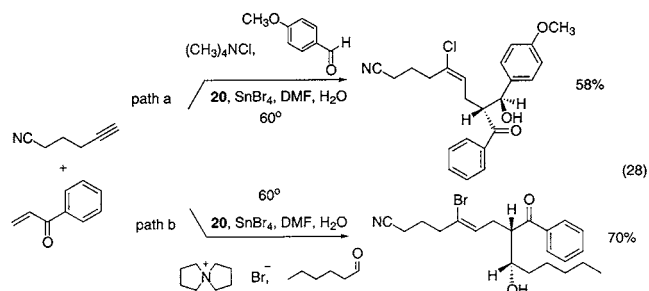
a useful functionality for further atom-economical additions. Equation 29 demonstrates the viability of this proposal.[44] The formed 1,3-diene **31** participates well in

31

$$(29)$$

32
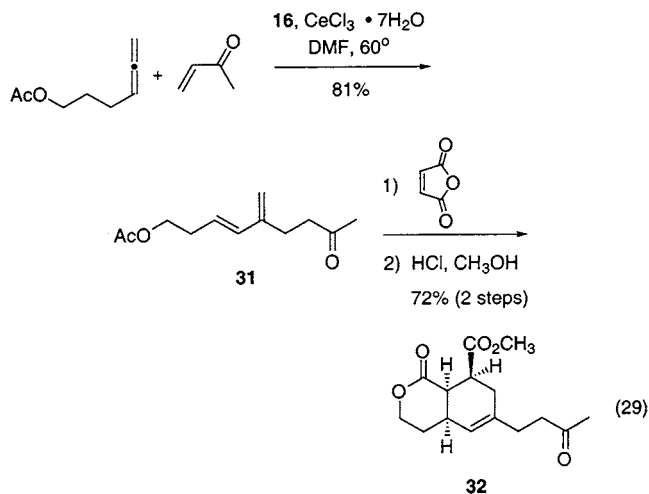
a subsequent Diels—Alder reaction with maleic anhydride, which solvolyzes selectively to form lactone **32** in highly atom-economic fashion wherein the only stoichiometric byproduct is methyl acetate.

Scheme 6 proposes a σ-allylruthenium intermediate. The well-known susceptibility of allylmetal complexes toward nucleophiles, including ruthenium,[45] suggested that a properly disposed nucleophile might capture the allylruthenium moiety faster than it underwent β-hydrogen elimination. Equation 30 reveals that an alcohol can, indeed, function as such a nucleophile to form a cyclic ether concomitant with addition of the enone.[46] The

$$(30)$$

R = CH$_3$ 90%
Ph   74%

$$(31)$$
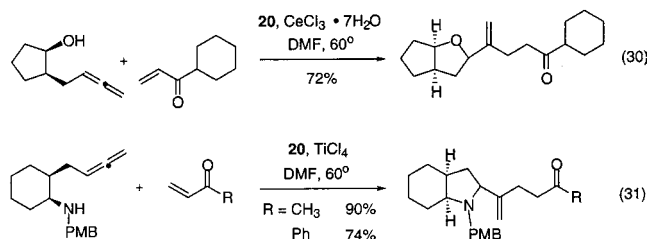
observation that amines normally served as catalyst poisons for the ruthenium-catalyzed alkene—alkyne addition led us to believe that amines could not function as a suitable nucleophile. In complete contrast to that expectation, secondary amines function extremely well to form nitrogen heterocycles, as illustrated in eq 31.[47]

Scheme 5. A Working Hypothesis for Three-Component Coupling Involving Hydrogen Halide

CYCLE A   CYCLE B
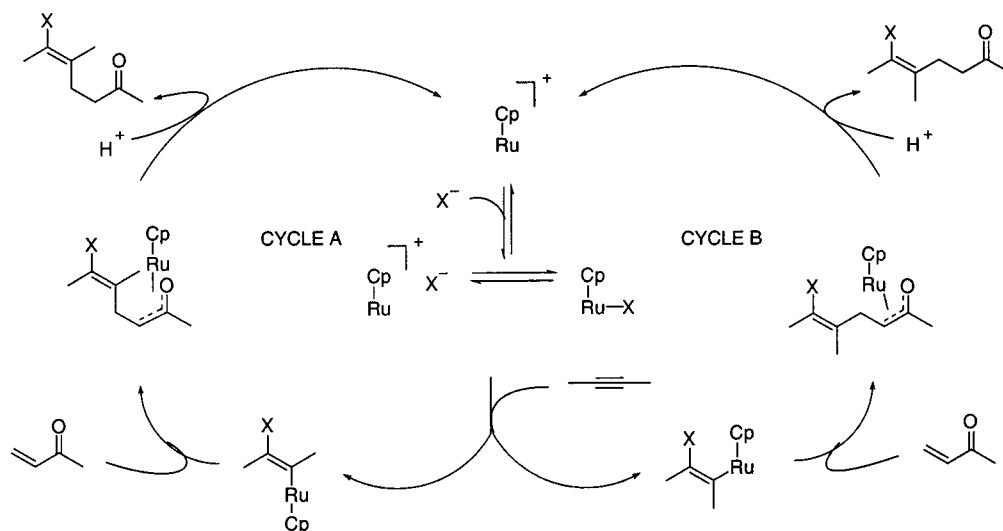
Scheme 6. An Allene—Enone Addition
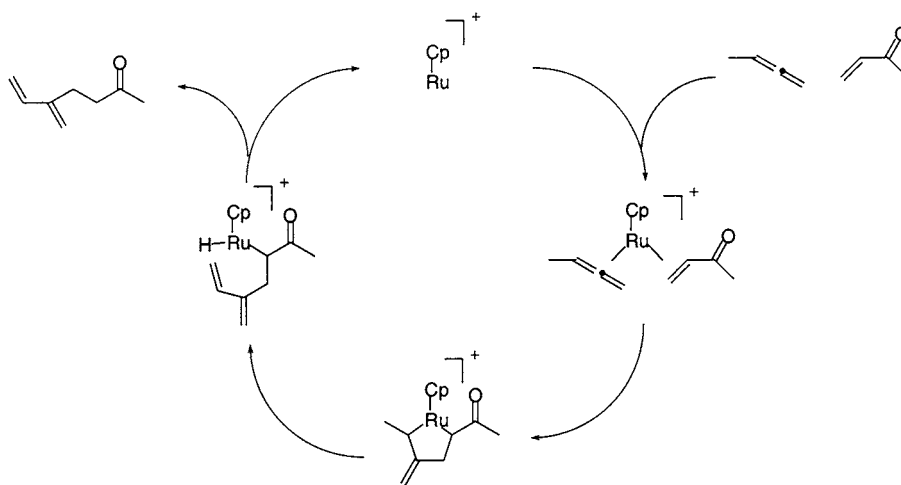
A Ru-Catalyzed [5 + 2] Cycloaddition

The metallacycle mechanism becomes a basis to propose new processes. For example, a [2 + 2 + 2] cycloaddition, as illustrated in eq 32 for a ruthenacyclopentadiene, is

$$\text{(32)}$$

analogous to such processes for many other metals such as cobalt[48] and rhodium.[49] Equation 33 illustrates this process for both an alkene (path a)[50] and an alkyne (path b).[51]

$$\text{(33)}$$
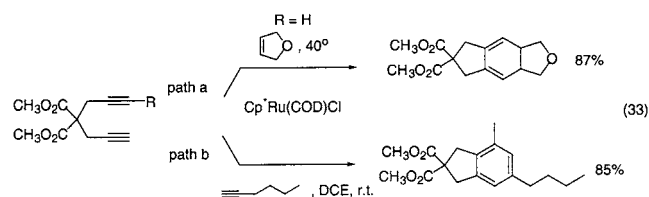
Scheme 7 raises the question of the effect of a small strained ring proximal to the alkene. Formation of the

ruthenacyclopentene creates a cyclopropylcarbinyl-ruthenium system which sets the stage for release of strain energy by invoking a cyclopropylcarbinyl to homoallyl rearrangement. Reductive elimination then completes a [5 + 2] cycloaddition to form a cyclohepta-diene.[52]

Equation 34 demonstrates the great facility of this cycloaddition to form perhydroazulenes—the reactions frequently being completed within 30 min at ambient temperature.[53] Furthermore, it illustrates the ability to

$$\text{(34)}$$
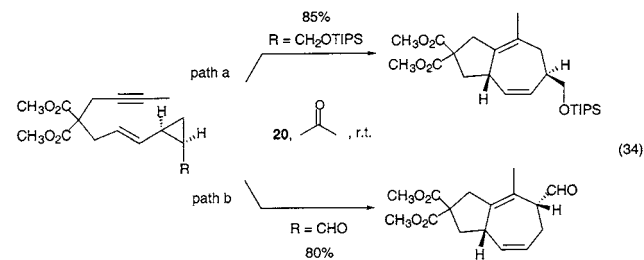
control the regioselectivity by simple choice of the nature of the substituent. Complex polycyclic systems can be

Scheme 7. A [5+2] Cycloaddition
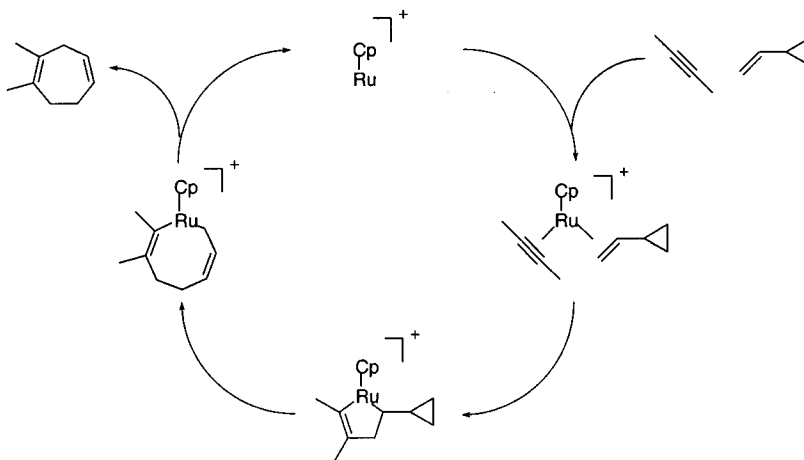
formed equally well, as illustrated in eq 35, which sets the stage for the application of this methodology for the synthesis of complex natural products.[54]
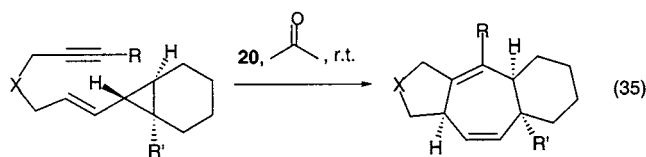
X = TsN, R = TMS, R' = H	71%
X = (CH₃O₂C)₂C, R = CH₃, R' = H	93%
X = (CH₃O₂C)₂C, R = CH₃, R' = CH₂OTBDMS	85%

Conclusion

There are many issues that must be addressed to make organic synthesis more environmentally benign by design. One fundamental consideration is the stoichiometry of the process. Until the present, virtually all attention focused on solving problems of selectivity regardless of the price that might be paid in terms of atom economy—olefination protocols being a prime example. There is no reason to believe that selectivity and atom economy are mutually exclusive goals. The fact that we have barely begun to probe the possibilities offered by catalysis broadly speaking and transition metal catalysis in particular emphasizes that extraordinary opportunities exist to improve our toolbox of methodologies that are more atom economical. Our work to date in the organic chemistry of ruthenium highlights this point. Using just one type of ruthenium complex, over 20 new reactions have evolved. Considering how many ruthenium catalysts can be imagined, the number of reactions yet to be discovered must be staggering. As illustrated herein, a semirational process provides valuable guidance—semirational since the proposed hypothesis leading to the discovery does not always turn out to be the actual mechanism. This issue must be the first step in helping to make chemical synthesis more environmentally friendly.

References

(1) Trost, B. M. The Atom Economy—A Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471–1477. Trost, B. M. Atom Economy. A Challenge for Organic Synthesis—Homogeneous Catalysis Leads the Way. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. Sheldon, R. A. Organic Synthesis—Past, Present, and Future. *Chem. Ind. (London)* **1992**, 903–906. Sheldon, R. A. Catalysis and Pollution Prevention. *Chem. Ind. (London)* **1997**, 12–15.

(2) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.1, pp 315–400. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.4, pp 513–550.

(3) Breit, B.; Seiche, W. Recent Advances on Chemo-, Regio- and Stereoselective Hydroformylation. *Synthesis* **2001**, 1–36.

(4) Solaza, B.; Huguet, J.; Karpf, M.; Dreiding, A. S. The Synthesis of (±)-Isoptychanolide by Application of the α-Alkynone Cyclisation. *Tetrahedron* **1987**, *43*, 4875–4886. Ackroyd, J.; Karpf, M.; Dreiding, A. S. The Total Synthesis of (±)-Clovene. On the Stereoelectronic Requirements on the α-Alkynone Cyclisation. *Helv. Chim. Acta* **1984**, *67*, 1963–1971.

(5) Bruce, M. I.; Swincer, A. G. Vinylidene and Propadienylidene (Allenylidene) Metal Complexes. *Adv. Organomet. Chem.* **1983**, *22*, 59–128. Nugent, W. A.; Mayer, J. M. *Metal—Ligand Multiple Bonds*; Wiley: New York, 1988. Bruce, M. I. Organometallic Chemistry of Vinylidene and Related Unsaturated Carbenes. *Chem. Rev.* **1991**, *91*, 197–257.

(6) Bruneau, C.; Dixneuf, P. H. Metal Vinylidenes in Catalysis. *Acc. Chem. Res.* **1999**, *32*, 311–323. Davies, S. G.; McNally, J. P.; Smallridge, A. J. Chemistry of the Cyclopentadienyl Bisphosphine Ruthenium Auxilliary. *Adv. Organomet. Chem.* **1990**, *30*, 1–76. Bruce, M. I.; Wong, F. J.; Skeleton, B. W.; White, A. H. Cyclopentadienyl-Ruthenium and -Osmium Chemistry. Part 20. Synthesis and X-Ray Structure of a Cationic Ruthenium-Vinylidene Complex, [Ru=C=C(H)Me(PMe₃)₂(η-C₅H₅)]PF₆. *J. Chem. Soc., Dalton Trans.* **1982**, 2203–2207.

(7) Trost, B. M.; Dyker, G.; Kulawiec, R. J. A Ruthenium-Catalyzed Reconstitutive Condensation of Acetylenes and Allyl Alcohols. *J. Am. Chem. Soc.* **1990**, *112*, 7809–7811. Trost, B. M.; Kulawiec, R. J. On the Mechanism of the Ruthenium-Catalyzed Reconstitutive Condensation of Allylic Alcohols and Terminal Alkynes. *J. Am. Chem. Soc.* **1992**, *114*, 5579–5584. Nishibayashi, Y.; Takei, I.; Hidai, M. Synthesis, Structures, and Reactivities of Rhodium and Ruthenium Complexes with a Novel Chiral Cyclopentadienyl-Ferrocenyldiphenylphosphine Bidentate Ligand. *Organometallics* **1997**, *16*, 3091–3093.

(8) Trost, B. M.; Flygare, J. A. A Practical Synthesis of Rosefuran. Furans From Acetylenes and Allyl Alcohols. *J. Org. Chem.* **1994**, *59*, 1078–1082.

(9) Trost, B. M.; Thommen, M., unpublished results. For steroid side chain elaboration, see: Trost, B. M.; Flygare, J. A.; Hammes, A. Ruthenium Catalyzed Reconstitutive Condensation. Application to Functionalized Steroid Side Chains. *Tetrahedron Lett.* **1993**, *34*, 587–590.

(10) Selegue, J. P.; Young, B. A.; Logan, S. L. Reactions of [RuCl-(PMe₃)₂(Cp)] with Aliphatic Alkynols Leading to Cationic Vinyl-vinylidene and Neutral Enynyl Complexes and Reactions of the Enynyls with Heteroallenes. *Organometallics* **1991**, *10*, 1972–1980. Le Bozec, H.; Touchard, D.; Dixneuf, P. H. Organometallic Chemistry of Arene Ruthenium and Osmium Complexes. *Adv. Organomet. Chem.* **1989**, *29*, 163–247. Berke, H.; Grossmann, J.; Huttner, G.; Zsolnai, L. Di-*tert*-butylallenyliden-Komplexe des Eisens. *Chem. Ber.* **1984**, *117*, 3432–3442.

(11) Trost, B. M.; Flygare, J. A. A Novel Ru Catalyzed Tandem Cyclization-Reconstitutive Addition of Propargyl Alcohols with Allyl Alcohols. *Tetrahedron Lett.* **1992**, *114*, 5476–5477.

(12) Trost, B. M.; Flygare, J. A. A Synthesis of the Spiroketal Subunit of (−)-Calyculin A. *Tetrahedron Lett.* **1994**, *35*, 4059–4062.

(13) Trost, B. M.; Kulawiec, R. J. Chemoselectivity in the Ruthenium Catalyzed Redox Isomerization of Allyl Alcohols. *J. Am. Chem. Soc.* **1993**, *115*, 2027–2036. Slugovc, C.; Rúba, E.; Schmid, R.; Kirchner, K. Improved Efficiency of the Ruthenium-Catalyzed Redox Isomerization of Allyl Alcohols. *Organometallics* **1999**, *18*, 4230–4233. Markó, I. E.; Gautier, A.; Tsukazaki, M.; Llobet, A.; Plantalech-Mir, E.; Urch, C.; Brown, S. M. Novel and Efficient Isomerization of Allylic Alcohols Promoted by a Tetrapropyl-ammonium Perruthenate Catalyst. *Angew. Chem., Int. Ed.* **1999**, *38*, 1960–1962.

(14) Trost, B. M.; Livingston, R. C. A Two Metal Catalyst System for Redox Isomerization of Propargyl Alcohols to Enals and Enones. *J. Am. Chem. Soc.* **1995**, *117*, 9586–9587.

(15) (a) Trost, B. M.; Livingston, R. C., unpublished work. (b) Quimpère, M.; Ruest, L.; Deslongchamps, P. Synthesis and Transannular Diels−Alder Reaction of a 13-Membered Macrocyclic Triene. A New Synthetic Approach Towards the Tricyclic Part A.B.C.[6.6.6] of the Veratrum Alkaloids. *Synthesis* **1992**, 132–140.

(16) Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. F. Ru Catalyzed Addition of Allyl Alcohols and Acetylenes. A Simple Synthesis of γ,δ-Unsaturated Ketones. *J. Am. Chem. Soc.* **1993**, *115*, 10402–10403.

(17) Trost, B. M.; Toste, F. D. A New Ru Catalyst for Alkene-Alkyne Coupling. *Tetrahedron Lett.* **1999**, *40*, 7739–7743.

(18) Also see: Dérien, S.; Dixneuf, P. H. Ruthenium Catalysed Synthesis of Unsaturated Acetals and Aldehydes *via* C−C Bond Coupling of Alkynes with Allyl Alcohol. *Chem. Commun.* **1994**, 2551–2552. Dérien, S.; Jan, D.; Dixneuf, P. H. Ruthenium-Catalysed Coupling of Allyl Alcohol With Alkynes: A New Route to γ-δ-Unsaturated Acetals and Aldehydes. *Tetrahedron* **1996**, *52*, 5511–5524. Dérien, S.; Gomez Vincente, B.; Dixneuf, P. H. Ruthenium catalysed formation of 2-alkoxy-5-methylenetetra-hydropyrans. *Chem. Commun.* **1997**, 1405–1406. Dérien, S.; Ropartz, L.; Le Paih, J.; Dixneuf, P. H. Synthesis of 2-Alkoxy-5-methylenetetrahydropyrans: A Regioselective Ruthenium-Cata-lyzed C−C Coupling Reaction of Prop-2-yn-1-ols with Allyl Alcohol. *J. Org. Chem.* **1999**, *64*, 3524–3531.

(19) Trost, B. M.; Imi, K.; Indolese, A. F. 1,5-Cyclooctadiene as a bis-Homodiene Partner in a Metal Catalyzed [2+2+2] Cycloaddition. *J. Am. Chem. Soc.* **1993**, *115*, 8831–8832. For a related stoichio-metric coupling of cycloheptatriene and an alkyne, see: Itoh, K.; Mukai, K.; Nagashima, H.; Nishiyama, H. Selective [π6s + π2s] Cycloaddition of a Coordinated Cyclic Triene with Alkynes. Formation of Bicyclo[4.2.2]Decatriene Skeleton of a Ru(0) Tem-plate. *Chem. Lett.* **1983**, 499–502.

(20) Trost, B. M.; Indolese, A. A Ruthenium Catalyzed Addition of Alkenes to Acetylenes. *J. Am. Chem. Soc.* **1993**, *115*, 4361–4362. Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. A Ru Catalyzed Addition of Alkenes to Alkynes. *J. Am. Chem. Soc.* **1995**, *117*, 615–623.

(21) Trost, B. M.; Probst, G. D.; Schoop, A. Ru Catalyzed Alder Ene Type Reactions. A Formal Synthesis of Alternaric Acid. *J. Am. Chem. Soc.* **1998**, *120*, 9228–9236.

(22) Trost, B. M.; Sperrle, M., unpublished work.

(23) Trost, B. M.; Pinkerton, A. B.; Toste, F. D.; Sperrle, M. A Synthesis of 1, 1-Disubstituted Alkenes via a Ru Catalyzed Addition. *J. Am. Chem. Soc.* **2001**, *123*, 12504–12509.

(24) Gill, T. P.; Mann, K. R. Photochemical Properties of the Cyclo-pentadienyl (η⁶-benzene) Ruthenium(II) Cation: The Synthesis and Reactions of a Synthetically Useful Intermediate: The Cyclopenta-dienyltris(acetonitrile) Ruthenium(II) Cation. *Organometallics* **1982**, *1*, 485–488.

(25) Trost, B. M.; Machacek, M.; Schnaderbeck, M. J. A Regioselective Ru Catalyzed Alkene-Alkyne Coupling. *Org. Lett.* **2000**, *2*, 1761–1764. Trost, B. M.; Surivet, J.-P.; Toste, F. D. An Atom Economical Three Carbon Chain Extension of Alkynes to Form E-Enol Silanes. *J. Am. Chem. Soc.* **2001**, *123*, 2897–2898.

(26) Trost, B. M.; Müller, T. J. J. A Butenolide Synthesis Based Upon a Contra-Electronic Addition in a Ru Catalyzed Alder Ene Reaction. Synthesis and Absolute Configuration of (+)-Ancepsenolide. *J. Am. Chem. Soc.* **1994**, *116*, 4985–4986. Trost, B. M.; Müller, T. J. J.; Martinez, J. A Ru Catalyzed Synthesis of Butenolides and Pentenolides via Contra-Electronic alpha-Alkylation of Hydroxy-alkynoates. *J. Am. Chem. Soc.* **1995**, *117*, 1888–1899. Trost, B. M.; Calkins, T. L. Synthetic Studies to Acetogenins. The Hydroxy-butenolide Terminus. *Tetrahedron Lett.* **1995**, *36*, 6021–6024. Trost, B. M.; Roth, G. J. On the Synthesis of Z-γ-Amino-α,β-Unsaturated Esters Via Ru Catalyzed Coupling. *Org. Lett.* **1999**, *1*, 67–70.

(27) Trost, B. M.; Calkins, T. L.; Bochet, C. G. A Convergent Synthesis of (+)-Parviflorin, (+)-Squamocin K, and (+)-5S-Hydroxyparvi-florin. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632–2635.

(28) Trost, B. M.; Gunzner, J. L. Total Synthesis of Deschlorocallipel-toside A. *J. Am. Chem. Soc.* **2001**, *123*, 9449–9450.

(29) For ruthenacyclopentenes, see: Mitsudo, T.; Kokuryo, K.; Shin-sugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. Ruthenium-Catalyzed [2+2] Cross-Addition of Norbornene Derivaties and Dimethyl Acetylenedicarboxylate. *J. Org. Chem.* **1979**, *44*, 4493–4496. Mitsudo, T.; Zhang, S.-W.; Nago, M.; Watanabe, Y. Ruthe-nium Complex-Catalyzed Highly Selective Codimerisation of Acetylenes and Alkenes. *Chem. Commun.* **1991**, 598–599. Mit-sudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. Ruthenium Complex-Catalyzed [2+2] Cycloaddition of Norbornenes and Derivatives with Ethyne Derivatives. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580–581. Warrener, R. N.; Abbenants, G.; Kennard, C. H. L. A Tandem Cycloaddition Protocol for the Controlled Syn-thesis of [n]Ladderanes: New Rods and Spacers. *J. Am. Chem. Soc.* **1994**, *116*, 3645–3646. Kikuchi, H.; Uno, M.; Takahashi, S. A New Ruthenium-Catalyzed Reaction with Propargyl Alcohol: Cyclopropanation of Norbornene. *Chem. Lett.* **1997**, 1273–1274. Matsushima, Y.; Kikuchi, H.; Uno, M.; Takahashi, S. Ruthenium-Catalyzed Cyclopropanation of Norbornene with Propargyl Alco-hol. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2475–2482.

(30) Trost, B. M.; Sundermann, M., unpublished work.

(31) Trost, B. M.; Toste, F. D. Ruthenium-Catalyzed Cycloisomerizations of 1,6- and 1,7-Enynes. *J. Am. Chem. Soc.* **2000**, *122*, 714–715.

(32) For a review, see: Trost, B. M.; Krische, M. J. Transition Metal Catalyzed Cycloisomerizations. *Synlett* **1998**, 1–16.

(33) Cf.: Mori, M.; Kozawa, Y.; Nishida, M.; Kanamaru, M.; Onozuka, K.; Takimoto, M. Synthesis of Carbapenam Skeletons Using a Ruthenium-Catalyzed Cyclization. *Org. Lett.* **2000**, *2*, 3245–3247. Le Paih, J.; Rodriguez, D. C.; Dérien, S.; Dixneuf, P. H. A New Cycloisomerization Catalyst of Enynes. One-step Syntheses of 3,4-Dialkylidenetetrahydrofurans from Allyl Propargyl Ethers. *Synlett* **2000**, 95–97.

(34) Trost, B. M.; Portnoy, M.; Kurihara, H. A Ru Catalyzed Three Component Addition to Form 1,5-Diketones. *J. Am. Chem. Soc.* **1997**, *119*, 836–837.

(35) For addition of carboxylic acids, see: Le Paih, J.; Dérien, S.; Dixneuf, P. H. Ruthenium-Catalyzed Multiple Component Trans-formations: One-step Stereoselective Synthesis of Functional Dienes From Alkynes and Carboxylic Acids. *Chem. Commun.* **1999**, 1437–1438. For an overview, see: Bruneau, C.; Dixneuf, P. H. Selective Transformations of Alkynes with Ruthenium Cata-lysts. *Chem. Commun.* **1997**, 507–512.

(36) Trost, B. M.; Brown, R. E.; Toste, F. D. A Ruthenium Catalyzed Hydrative Cyclization and [4+2] Cycloaddition of Yne-Enones. *J. Am. Chem. Soc.* **2000**, *122*, 5877–5878.

(37) Trost, B. M.; Krause, L.; Portnoy, M. Propargyl Alcohols as Synthons for Allenols in Conjugate Addition. *J. Am. Chem. Soc.* **1997**, *119*, 11319–11320.

(38) Trost, B. M.; Pinkerton, A. B. A Ruthenium Catalyzed Three Component Coupling to Form E-Vinyl Chlorides. *J. Am. Chem. Soc.* **1999**, *121*, 1988–1989.

(39) Trost, B. M.; Pinkerton, A. B. Stereoselective Formation of Z-Vinyl Bromides Utilizing a Ruthenium Catalyzed Three Component Coupling. *Angew. Chem., Int. Ed.* **2000**, *39*, 360–362.

(40) Trost, B. M.; Pinkerton, A. B. A Three Component Coupling Approach to Cyclopentanoids. *J. Org. Chem.* **2001**, *66*, 7714–7722. Trost, B. M.; Pinkerton, A. B. Enhanced Geometrical Control in a Ru-Catalyzed Three Component Coupling. *Tetrahedron Lett.* **2000**, *41*, 9627–9631.

(41) For capture of a Ru enolate by an aldehyde in a Baylis-Hillman type process, see: Sato, S.; Matsuda, I.; Shibata, M. Rhodium(I)- or Ruthenium(II)-Catalyzed Direct Coupling of Vinyl Ketones with Aldehydes and the Subsequent Reduction to Give Aldol Deriva-

tives Anti-Selectively. *J. Organomet. Chem.* **1989**, *377*, 347−356. Matsuda, I.; Shibata, M.; Sato, S. A Selective Synthesis of α-Methylene-β-Hydroxyalkanones Catalyzed by Tetrakis(triphenyl-phosphine)Ruthenium Dihydride. *J. Organomet. Chem.* **1988**, *340*, C5−C7.

(42) Trost, B. M.; Pinkerton, A. B. A Ru Catalyzed Four-Component Coupling. *J. Am. Chem. Soc.* **2000**, *122*, 8081−8082.

(43) For nonrelated Ru catalyzed reactions involving allenes as substrates, see: Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. Synthesis of Exo-Enynes by Ruthenium-Catalyzed Cross Coupling Reaction of Hydroxy Allenes and 1-Alkynes. *Synlett* **1995**, 1181−1186. Yoneda, E.; Kaneko, T.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. γ- and δ-Lactones. *Org. Lett.* **2000**, *2*, 441−443.

(44) Trost, B. M.; Pinkerton, A. B. A Ruthenium Catalyzed Two Component Addition to Form 1,3-Dienes. *J. Am. Chem. Soc.* **1999**, *121*, 4068−4069. Trost, B. M.; Pinkerton, A. B.; Seidel, M. Ruthenium Catalyzed Two Component Addition to Form 1,3-Dienes: Optimization, Scope Applications and Mechanism. *J. Am. Chem. Soc.* **2001**, *123*, 12466−12476.

(45) Morusaki, Y.; Kondo, T.; Mitsudo, T. Ruthenium-Catalyzed Allylic Substitution of Cyclic Allyl Carbonates with Nucleophiles. Stereoselectivity and Scope of the Reaction. *Organometallics* **1999**, *18*, 4742−4746. Kang, S.-K.; Kim, D.-Y.; Hong, R.-K.; Ho, P.-S. Palladium-Catalyzed Carbonyl Allylation of Aldehydes with Allylic Phosphates: Synthesis of Homoallylic Alcohols. *Synth. Commun.* **1996**, *26*, 1493−1498. Zhang, S. W.; Mitsudo, T.; Kondo, T.; Watanabe, Y. Ruthenium Complex-Catalyzed Allylic Alkylation of Carbonucleophiles with Allylic Carbonates. *J. Organomet. Chem.* **1993**, *450*, 197−207. Minami, I.; Shimizu, I.; Tsuji, J. Reactions of Allylic Carbonates Catalyzed by Palladium, Rhodium, Ruthenium, Molybdenum, and Nickel Complexes; Allylation of Carbonucleophiles and Decarboxylation-Dehydrogenation. *J. Organomet. Chem.* **1985**, *296*, 269−280.

(46) Trost, B. M.; Pinkerton, A. B. A Ruthenium Catalyzed Alkylative Cycloetherification. *J. Am. Chem. Soc.* **1999**, *121*, 10842−10843.

(47) Trost, B. M.; Pinkerton, A. B.; Kremzow, D. A Ruthenium Catalyzed Pyrrolidine and Piperidine Synthesis. *J. Am. Chem. Soc.* **2000**, *122*, 12007−12008.

(48) Vollhardt, K. P. C. Cobalt-Mediated [2+2+2]: A Maturing Synthetic Strategy. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539−556.

(49) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 741.

(50) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. Cp*Ru(cod)Cl-Catalyzed [2+2+2] Cycloaddition of 1,6-Heptadiynes with Allylic Ether. A Decisive Role of Coordination to the Ether Oxygen Atom. *J. Org. Chem.* **1998**, *63*, 9610−9611. Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Kawaguchi, H.; Tatsumi, K.; Itoh, K. Ru(II)-Catalyzed Cycloadditions of 1,6-heptadiynes with Alkenes: New Synthetic Potential of Ruthenacyclopentatrienes as Biscarbenoids in Tandem Cyclopropanation of Bicycloalkenes and Heteroatom-Assisted Cyclocotrimerization of 1,6-Heptadiynes with Heterocyclic Alkenes. *J. Am. Chem. Soc.* **2000**, *122*, 4310−4319. Yamamoto, Y.; Kitahara, H.; Hattori, R.; Itoh, K. Ruthenium-Catalyzed Tandem[2+2+2]/[4+2] Cycloaddition of 1,6-heptadiyne with Norbornene. *Organometallics* **1998**, *17*, 1910−1912.

(51) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. Highly Chemo- and Regio-selective [2+2+2] Cycloaddition of Unsymmetrical 1,6-diynes with Terminal Alkynes Catalyzed by Cp*Ru(cod)Cl Under Mild Conditions. *Chem. Commun.* **2000**, 549−550. Lindener, E.; Janson, R.-M.; Mayer, H. A.; Hiller, W.; Fawzi, R. Preparation, Properties, and Reactions of Metal-Containing Heterocycles. 65. The Behavior of Tetracarbonyl(Eta-2-Ethene)Ruthenium Toward Activated Alkenes and Alkynes. *Organometallics* **1989**, *8*, 2355−2360. Ernst, C.; Walter, O.; Dinjus, E.; Arzberger, S.; Görl, H. Structural Characterization of Cp*Ru-intermediates of Phenylacetylene Cyclotrimerization. *J. Prakt. Chem.* **1999**, *341*, 801−804.

(52) For a Rh-catalyzed version, see: Wender, P. A.; Love, J. A. The Synthesis of Seven-Membered Rings: General Strategies and the Design and Development of a New Class of Cycloaddition Reactions. *Adv. Cycloaddition* **1999**, *5*, 1−45. Also see: Wang, B.; Cao, P.; Zhang, X. An Efficient Rh-Catalyst System for the Intramolecular [4+2] and [5+2] Cycloaddition Reactions. *Tetrahedron Lett.* **2000**, *41*, 8041−8044.

(53) Trost, B. M.; Toste, F. D.; Shen, H. Ruthenium Catalyzed Intramolecular {5+2} Cycloadditions. *J. Am. Chem. Soc.* **2000**, *122*, 2379−2380. Trost, B. M.; Shen, H. On the Regioselectivity of the Ru Catalyzed Intramolecular [5+2] Cycloaddition. *Org. Lett.* **2000**, *2*, 2523−2525.

(54) Trost, B. M.; Shen, H. Constructing Tricyclic Compounds Containing a 7-Membered Ring by Ruthenium Catalyzed Intramolecular [5+2] Cycloaddition. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313−2316.