Ruthenium-Catalyzed Two-Component Addition To Form 1,3-Dienes: Optimization, Scope, Applications, and Mechanism

Barry M. Trost,* Anthony B. Pinkerton, and Martin Seidel

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305

Received June 11, 2001

Abstract: A two component coupling of an allene and an activated olefin to form 1,3-dienes has been developed. The requisite allenes are synthesized either from terminal alkynes by a one carbon homologation using copper(I) iodide, paraformaldehyde, and diisopropylamine, via an ortho ester-Claisen rearrangement from a propargylic alcohol, or via a Wittig type reaction on a ketene generated in situ from an acid chloride. Mono- through tetrasubstituted allenes could be synthesized by these methods. Either cyclopentadienylruthenium(II) cyclooctadiene chloride or cyclopentadienylruthenium(II) trisacetonitrile hexafluorophosphate catalyze the addition reaction. When the former catalyst is employed, an alkyne activator is added to help generate the active catalyst. Through systematic optimization studies, a range of conditions was examined. The optimal conditions consisted of the use of cerium(III) trichloride heptahydrate as a cocatalyst in dimethylformamide as a solvent at 60 °C. The reaction was found to be chemoselective, and a wide range of functionality was tolerated, including esters, alcohols, nitriles, and amides. When substituted allenes are used, good selectivity can be obtained with proper substitution. A mechanism involving a ruthenacycle is proposed to account for the selectivity or lack thereof in product formation. With disubstituted allenes, selectivity is obtained when β-hydrogen elimination is favored from a specific site. In tri- and tetrasubstituted allenes, steric issues concerning the C−C bond forming event appear to be the dominant factor in determining product formation. This process represents a highly atom-economical synthesis of 1,3-dienes in a controlled fashion. The utility of the 1,3-diene products was demonstrated by their use in Diels−Alder reactions to form a variety of cyclic systems including polycyclic structures. This sequence represents a convergent atom economic method for ring formation by a series of simple additions.

Introduction

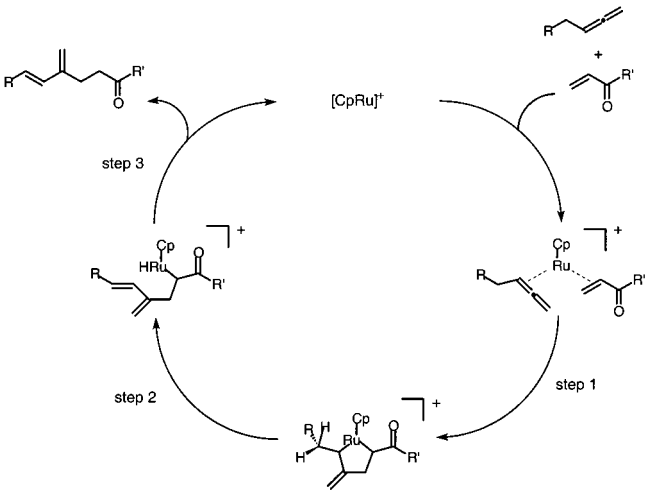
1,3-Dienes represent an important functional group because they are key reactants in a wide range of cycloadditions, especially the Diels−Alder reaction.[1−3] Therefore they represent valuable building blocks to form complex structures through simple addition reactions. Due to their utility, there have been numerous methods developed for their synthesis,[4] including eliminations,[5−8] concerted reactions (for example retro-Diels−Alder reactions, extrusion of sulfur dioxide from sulfolenes,[9] and ring opening of cyclobutenes[10]), Wittig and related reactions,[11−13] cross-couplings,[14,15] cycloisomerizations,[16,17] reductions of enynes,[18] and newer methods[19] such as alkene/alkyne metathesis.[20]

During the course of our development of new ruthenium catalyzed reactions, we envisioned that allenes and alkenes could be reacted to form 1,3-dienes as rationalized in Scheme 1 for the case of enones. Simple alkenes were avoided since they raised issues of selectivity in β-hydrogen elimination in the ruthenacycle intermediate. Due to the success of the ruthenium catalyzed Alder-ene reaction,[21] we imagined that such a catalytic cycle could be viable with formation of a ruthenacycle with initial bonding to the sp allenic carbon[22] followed by a

(1) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990.
(2) Wasserman, A. *Diels−Alder Reactions*; Elsevier: Amsterdam, 1965. Wallweben, H. *Diels−Alder Reaktion*; Thieme: Stuttgart, Germany, 1972.
(3) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 4.1, pp 315−400. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, Chapter 4.4, pp 513−550.
(4) Mehta, G., Rao, S. P. In *The Chemistry of Dienes and Polyenes*; Rappoport, Z., Ed.; Wiley: Chicester, U.K., 1997; Chapter 9, pp 361−467.
(5) Kitahara, T.; Matsuoka, T.; Kiyota, H.; Warita, Y.; Kurata, H.; Horiguchi, A.; Mori, K. *Synthesis* **1994**, 692.
(6) Trost, B. M.; Fortunak, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 2841.
(7) Block, E.; Aslam, M.; Eswarakrishnan, V.; Wall, A. *J. Am. Chem. Soc.* **1983**, *105*, 6165.
(8) Mandai, T.; Yanagi, T.; Araki, K.; Morisaki, Y.; Kawada, M.; Otera, J. *J. Am. Chem. Soc.* **1984**, *106*, 3670. Otera, J.; Misawa, H.; Sugimoto, K. *J. Org. Chem.* **1986**, *51*, 3830.
(9) Bloch, R.; Benecou, C.; Guibé-Jampel, E. *Tetrahedron Lett.* **1985**, *26*, 1301. Mock, W. L. *J. Am. Chem. Soc.* **1966**, *88*, 2856.
(10) Trost, B. M.; Bridges, A. J. *J. Am. Chem. Soc.* **1976**, *98*, 5017.
(11) Naruse, M.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1994**, *59*, 1358.
(12) Trost, B. M.; Brandi, A. *J. Org. Chem.* **1984**, *49*, 4811.
(13) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 781.
(14) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 2271.
(15) Schinzer, D.; Ringe, K.; Jones, P. G.; Döring, D. *Tetrahedron Lett.* **1995**, *36*, 4051.
(16) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781.
(17) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988**, *110*, 7255.
(18) Sonagashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 5. Trost, B. M.; Sorum, M. T.; Chan, C.; Harms, A. E.; Rühter, G. *J. Am. Chem. Soc.* **1997**, *119*, 698. Rodin, J. O.; Leaffer, M. A.; Silverstein, R. M. *J. Org. Chem.* **1970**, *35*, 3152.
(19) For example, see: Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310. Murakami, M.; Ubukata, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 7361.
(20) Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388.
(21) Trost, B. M.; Indolese, A.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. Trost, B. M.; Müller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888.

10.1021/ja011428g CCC: $20.00
Published on Web 11/17/2001

Scheme 1. Formation of 1,3-Dienes

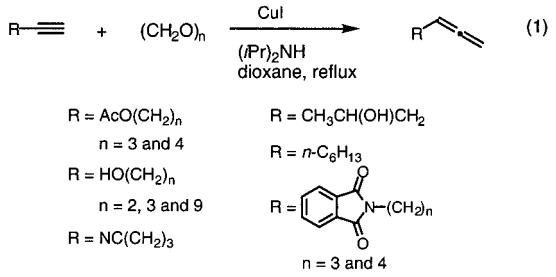


β-hydrogen elimination (step 3) and a reductive elimination (step 4). Further impetus for this study derives from the ease of availability of allenes. This paper details the development of this reaction[23] as well as explores issues of regioselectivity when multiply substituted allenes are used.

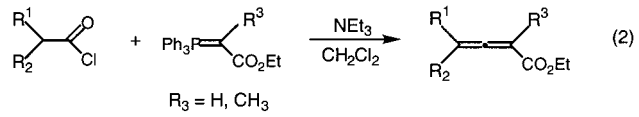
Synthesis of Allenes

There are numerous methods for the synthesis of allenes.[24] The allenes used in this study were synthesized by (1) homologation from the acetylene, (2) Wittig type reactions, and (3) ortho ester-Claisen rearrangements.

Monosubstituted allenes were synthesized from the corresponding terminal acetylene by the method of Crabbé as depicted in eq 1.[25] While this reaction was found to be somewhat capricious, yields up to 83% could be obtained. More details can be found in the Supporting Information.

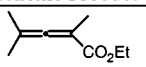
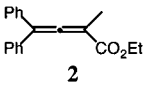
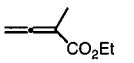
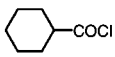
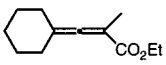
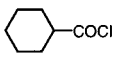
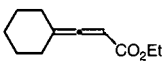


The acylation of Wittig reagents[26] is a convenient means for the preparation of allenes substituted with various electron-withdrawing substituents (eq 2). The ready availability of acid

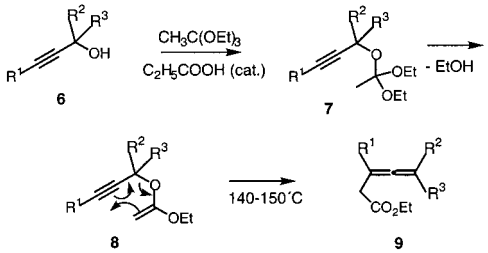


chlorides allows for a wide range of allenes to be accessed. The reaction presumably involves in situ formation of a ketene and its capture by the stabilized ylide. As shown in Table 1, a number of α-allenic esters have been synthesized by this method. The relatively mild conditions (i.e. room temperature for a couple of hours) of this reaction avoid base-catalyzed isomerization of the conjugated allenes to acetylenes and lead to reasonable yields of the desired products.

Table 1. Allene Formation via a Wittig Reaction

Entry	Acid Chloride	Allenic Product	Yield (%)
1		 **1**	58
2		 **2**	59
3	CH_3COCl	 **3**	67
4		 **4**	87
5		 **5**	21

Scheme 2. Formation of Allenes from Claisen Rearrangements



The most versatile and atom economic method involves use of Claisen rearrangements for the preparation of β-allenic ester derivatives with full range of substitution at any position of the molecule.[27] This method has the advantage that the starting propargyl alcohols also are accessed by atom economic addition reactions of terminal acetylenes to aldehydes or ketones (Scheme 2 and Table 2). The reaction of entry 6 was not run to completion due to the desire to have both substrates. Clearly, this reaction could be optimized to form either one product or the other. The lower yields of entries 4 and 7 are most likely a reflection of the volatility of the products.

(22) For some examples of Pd catalyzed bond formation to the central carbon of allenes, see: Trost, B. M.; Kottirsch, G. *J. Am. Chem. Soc.* **1990**, *112*, 2816. See also: References 24−31. Shimizu, I.; Tsuji, J. *Chem. Lett.* **1984**, 233. Larock, R. C.; Veraprath, S.; Lau, H. H.; Fellows, C. A. *J. Am. Chem. Soc.* **1984**, *106*, 5274. Alper, H.; Hartstock, F. W.; Despeyroux, B. *Chem. Commun.* **1984**, 905. Gamez, P.; Ariente, C.; Cazes, B.; Gore, J. *Tetrahedron* **1998**, *54*, 14835. Ahmar, M.; Barieux, J. J.; Cazes, B.; Goré, J.. *Tetrahedron* **1987**, *43*, 513. Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88. Davies, I. W.; Scopes, D. I. C.; Gallagher, T. *Synlett* **1993**, 85. For a Ru catalyzed example: Yamaguchi, M.; Kido, Y.; Omata, K.; Hirama, M. *Synlett* **1995**, 1181. For examples of carbapalladation of allenes, see: Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811. For a proposed hydropalladation mechanism, see: Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156. Trost, B. M.; Michellys, P.-Y.; Gerusz, V. J. *J. Am. Chem. Soc.* **1997**, *36*, 111750. Yamamoto, Y.; Al-Masum, M.; Takeda, A. *Chem. Commun.* **1996**, 831. Meguro, M.; Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1996**, *37*, 7453.

(23) For a preliminary communication, see: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 4068.

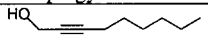
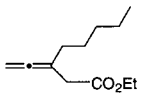
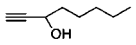
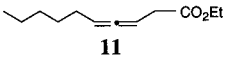
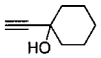
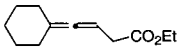
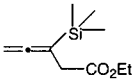
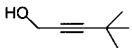
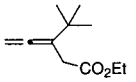
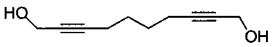
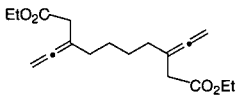
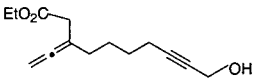
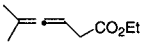
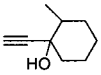
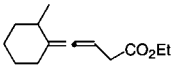
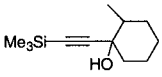
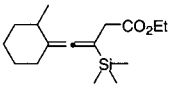
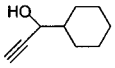
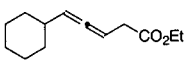
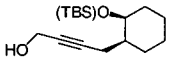
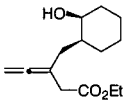
(24) Schuster, H. F. *Allenes in Organic Synthesis*; Wiley: New York, 1984. *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic: New York, 1982. *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: New York, Chichester, U.K., 1980.

(25) Crabbé, P.; Fillion, H.; André, D.; Luche, J.-L. *J. Chem. Soc., Chem. Commun.* **1979**, 859.

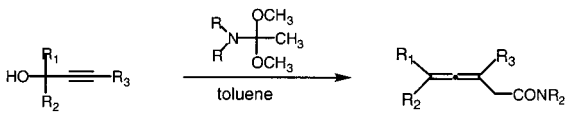
(26) Lang, R. W.; Hansen, H.-J. *Org. Synth.* **1984**, 202.

(27) Crandall, J. K.; Tindell, G. L. *J. Chem. Soc., Chem. Commun.* **1970**, 1411.

Table 2. Formation of Allenes from Claisen Rearrangements

Entry	Propargylic Alcohol	Allenic Product	Yield (%)
1		 **10**	85
2		 **11**	95
3		 **12**	60
4		 **13**	23
5		 **14**	45
6		 **15** and  **16**	16 39
7		 **17**	33
8		 **18**	35
9		 **19**	83
10		 **20**	63
11		 **21**	90

As with the corresponding esters, tertiary allenic amides[28] can also be prepared by the reaction of propargyl alcohols with amide acetals in refluxing hydrocarbon solvents (eq 3). When

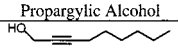
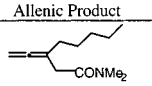
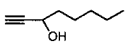
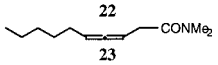
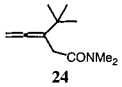
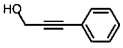
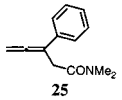


(3)

dimethylacetamide acetals are employed, allenyl acetamides are produced in good yields (Table 3).

The reduction of β-allenic esters[29] (prepared from the ortho ester-Claisen rearrangement) with LAH provides ready access to β-allenic alcohols (eq 4). Under these conditions, neither isomerization nor reduction of the allene is observed and in general the yields are very good (Table 4).

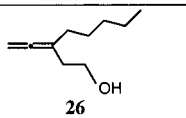
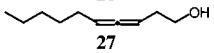
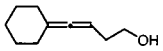
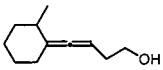
Table 3. Formation of Allenyl Acetamides

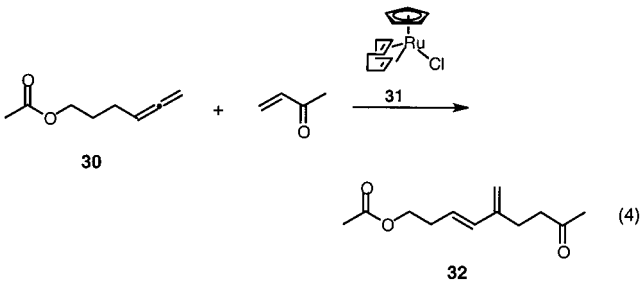
Entry	Propargylic Alcohol	Allenic Product	Yield (%)
1		 **22**	95
2		 **23**	90
3		 **24**	71
4		 **25**	43

(28) Parker, K. A.; Petraitis, J. J.; Kosley, R. W.; Buchwald, S. L. *J. Org. Chem.* **1982**, *47*, 389.

(29) Evans, R. J. D.; Landor, S. R.; Regan, J. P. *J. Chem. Soc., Chem. Commun.* **1965**, 397. Evans, R. J. D.; Landor, S. R.; Regan, J. P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 552.

Table 4. Reduction of Allenyl Esters

Entry	Starting Material	Product	Yield (%)
1	**10**	 **26**	97
2	**11**	 **27**	92
3	**12**	 **28**	85
4	**18**	 **29**	89

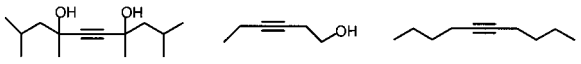


(4)

Reaction Optimization

The reaction of eq 4 using allene **30** and methyl vinyl ketone (MVK) was chosen for the optimization of the reaction conditions. Initially, the reaction was run with catalyst **31**,[30] 2 equiv of the enone partner to the allene, and at a concentration of 0.25 M of the allene. These values were chosen in analogy to the ruthenium catalyzed vinyl halide formation.[31] A range of Lewis acids, additives, and solvents was examined. Tables summarizing the optimization experiments appear in Supporting Information.

Hydrated tin(IV) chloride, a cocatalyst successful in a Ru catalyzed three component coupling, was initially used as a cocatalyst. It was found that switching from conditions used to form vinyl chlorides[31] to more chloride free conditions by removing the ammonium chloride more than doubled the yield (from 14 to 35%). Since the cationic coordinatively unsaturated ruthenium complex is the likely active form of the catalyst and high chloride ion concentration would decrease its concentration, chloride ion was expected to inhibit the reaction and it did. Acetone proved to be a poorer solvent than dimethylformamide (DMF), and no product whatsoever was formed using methanol. It was also found that using more water relative to DMF was detrimental and that, in fact, using DMF alone gave the best results initially. Using DMF as the solvent, a range of cocatalysts was examined. Aluminum trichloride was less effective, and, surprisingly, indium triflate gave no product, which is in contrast to other ruthenium catalyzed reactions of this type. Tin dichloride was inferior, but hydrated cerium trichloride appeared to be marginally better than tin (48% yield), and thus was chosen over tin because of the known toxicity of tin compounds. Triphenylphosphine or ammonium hexafluorophosphate are also detrimental. Using hydrated cerium trichloride as the cocatalyst, some other solvents were examined. Dimethyl sulfoxide, dimethylacetamide, acetone and *N*-methylpyrrolidinone were all less effective. Interestingly, anhydrous cerium chloride gave lower yields, possibly due to the fact that the extra water attenuates the Lewis acidity that could lead to either catalyst deactivation or product decomposition. Finally, indium trichloride, silver triflate (in an attempt to generate a completely coordinatively unsaturated ruthenim by precipitation of the chloride), or camphorsulfonic acid all gave poor results. Thus, we settled on the use of hydrated cerium trichloride as cocatalyst in DMF as solvent.



33 **34** **35**

Figure 1. Alkyne additives.

The effects of concentration and equivalents of MVK were examined. We wished to examine the concentration for several reasons. First, it has been found that in some ruthenium catalyzed reactions a higher concentration has been beneficial in terms of turnover. Obviously, it was also a goal to lower the amount of enone necessary. The amount of MVK can be lowered from 2 to 1.5 equiv with a slight increase in yield to 53% but further lowering was detrimental. This is not fully unexpected, as the enone is not completely stable under the reaction conditions, so at least some excess is necessary. In terms of concentration, 0.25 M in allene proved to be optimal, as both lowering the concentration to 0.125 M and raising it to 0.5 M were detrimental.

Using these newly optimized conditions, the effects of catalyst and cocatalyst loading and temperature were examined. Lowering the amount of catalyst to 5% reduced the yield dramatically. Likewise, raising the catalyst loading to 15% did not increase the yield. Raising or lowering the cocatalyst to 5 or 30% did not have a large effect, and 10% appeared to be optimal. Stability of the product, a sensitive 1,3-diene, to the reaction conditions was a concern. In fact, when the 1,3-diene product was resubmitted to the reaction conditions, the recovery was only about 70%. Thus, it was not surprising that major effects were observed when the temperature was lowered from 100 to 60 °C, wherein the yield increased from 53 to 66%. A further increase in yield to 70% was realized when the reaction time was increased to 6 h. At lower temperatures, the reaction was sluggish, and starting material was recovered—a problem that was not rectified by longer reaction time.

The proposed reaction pathway requires coordinatively unsaturated ruthenium. In the case of CpRu(COD)Cl, both ionization of chloride and removal of the COD is envisioned to be needed. Earlier studies showed that alkynes, but not allenes were capable of removing COD from the coordination sphere of the ruthenium by a [2 + 2 + 2] cycloaddition.[32] The use of alkyne additives was examined in an attempt to activate the catalyst by reacting off the cyclooctadiene (COD) ligand to generate the catalytically active species. Presumably, adding a stoichiometric amount (relative to catalyst) of an alkyne such as **33** or **34** (Figure 1) with a propargylic or homopropargylic coordinating group could effectively generate the coordinatively unsaturated ruthenium.

From the results in Table 5, it is clear that additives with coordinating groups have a noticeable positive effect on yield. The bis-alcohol **33** and monoalcohol **34** appeared to be equally effective (entries 2 and 3), but **34** was adopted as the additive of choice because it was easier to handle. An alkyne without pendant alcohol(s) (**35**) was not effective (entry 6). Whether

(30) Albers, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.

(31) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988.

(32) Trost, B. M.; Imi, K.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 8831.

Table 5. Effect of Additives[a]

entry	additive, amount (mol %)	catalyst (mol %)	allene (M)	**32** (%)
1	none	10	0.25	70
2	**33**, 10	10	0.25	80
3	**34**, 10	10	0.25	81
4	**34**, 5	5	0.25	50
5	**34**, 5	5	0.5	46
6	**35**, 10	10	0.25	68

[a] Run as in eq 5 with **31** and 15% $CeCl_3 \cdot 7H_2O$ with 1.5 equiv of MVK and 0.25 M allene in DMF at 60 °C for 6 h.

Table 6. Use of Other Catalysts[a]

entry	catalyst	**32** (%)
1[b]	CpRu(COD)Cl (**31**)	70
2	$CpRu(PPh_3)_2Cl$ (**36**)	62
3	(Ind)Ru(COD)Cl (**37**)	15
4[b]	$[CpRu(CH_3CN)_3]PF_6$ (**38**)	74
5	$[CpRu(CH_3CN)_3]PF_6$ **(38)**	76
6[c]	$[CpRu(CH_3CN)_3]PF_6$ (**38**)	70

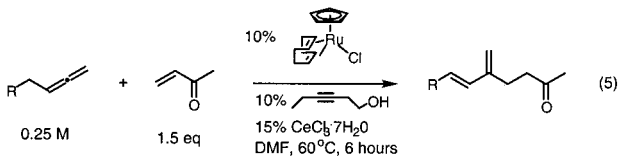
[a] Run as in eq 5 with 10% catalyst and 15% $CeCl_3 \cdot 7H_2O$ with 1.5 equiv of MVK and 0.25 M allene in DMF at 60 °C for 6 h. [b] Run with 10% **35**. [c] Run at room temperature for 4 h.

the increased yield is a result of preactivation or simply stabilization of the catalyst, with the alkynol acting as a ligand, is not clear. It should be noted that no 2 + 2 + 2 products were observed, although the reactions were done on relatively small scale. Unfortunately, even with the use of **34**, the catalyst loading could not be dropped (entry 4) even with an increase in concentration (entry 5).

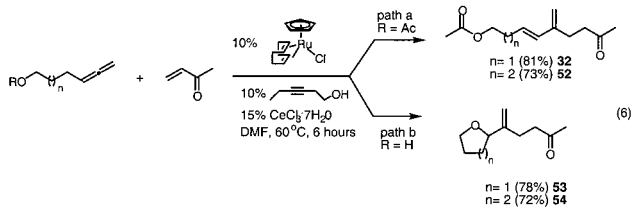
Other Ru complexes were examined as catalysts in the absence of the alkyne additive, as shown in Table 6. Surprisingly, $CpRu(PPh_3)_2Cl$ (**36**)[33] was nearly as effective (entry 2). Given that both chloride and one triphenylphosphine can dissociate from this complex, this observation suggests that only two open coordination sites on the ruthenium may be required. Significantly, the complex **38**[34] was as effective as CpRu(COD)Cl with (entry 4) or without (entry 5) added alkyne. Furthermore, with this complex, the reaction proceeded facilely even at room temperature (entry 6).

Scope

Monosubstituted allenes were the initial substrates to avoid issues of regioselectivity. The reactions were run according to eq 5, and the results are summarized in Table 7.

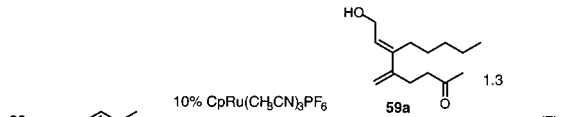


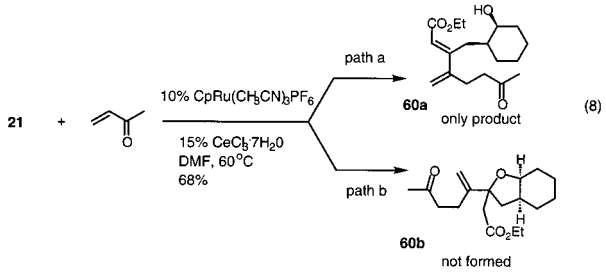
From the range of substrates examined, excellent chemoselectivity is observed—primary and secondary alcohols, esters, nitriles, and amides are all compatible with the reactions conditions. When allenes bearing a free alcohol 5 or 6 carbons from the allenic center are used, cyclic ethers[35] are formed (path b, eq 6). The mechanistic implications of this will be discussed further (vide infra). However, when the alcohols are protected as the acetates, 1,3-dienes are formed in good yield (path a, eq 6). Cyclohexylvinyl ketone (entries 8−10) and phenylvinyl ketone (entries 11−13) also act as coupling partners in this reaction, although with the latter somewhat lower yields were obtained. This may be due to the lack of stability of the products, as decomposition was seen after purification.



With disubstituted allenes, the issue of regioselectivity arises in the coordination and the β-hydrogen elimination. The first class of substrates that was examined were 1,1-disubstituted allenes. For these cases the catalyst precursor used was the trisacetonitrile catalyst **38** instead of the CpRu(COD)Cl/alkyne additive **34** mixture.

As we see from Table 8, entries 1−4, the reaction gives only one regioisomer when one of the β-hydrogens is acidified by being α to an ester or amide (**55**−**58**). Allenes that are too sterically hindered (**13**, **14**, **24**, **25**) do not react in the desired fashion, but give only recovered starting material or decompostion. Bis allenes are also reactive, giving the bis 1,3-diene as the only product, albeit in only 42% yield (entry 3). Entry 4 illustrates the excellent chemoselectivity of the reaction; internal alkynes, including those with propargylic alcohols, are less reactive than allenes under the reaction conditions, giving the 1,3-diene as the only isolated product. When 1,1-disubstituted allenes with no biasing functionality is used, approximately a 1:1 mixture of products **59a** and **59b** is seen (eq 7). This will be discussed subsequently. Interestingly, an allene with a free hydroxyl group that could potentially cyclize to **60b** (i.e. as in path b, eq 6), instead gives only the 1,3-diene products **60a** (eq 8) when the β-hydrogen elimination is activated by the ester

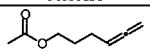
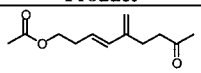
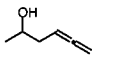
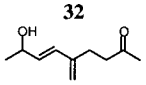
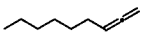
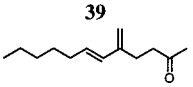
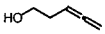
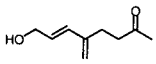
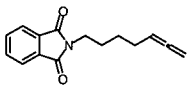
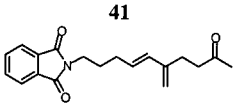
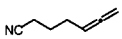
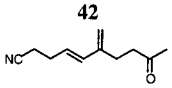
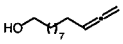
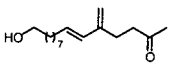
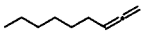
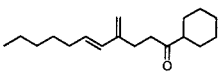
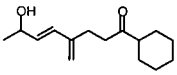
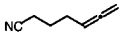
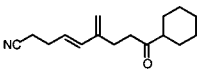
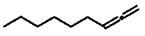
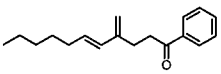
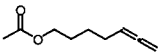
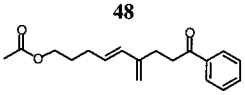
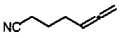
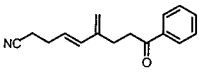




With 1,3-disubstituted allenes, in general a 1:1 mixture of regioisomers is obtained (Table 8, entries 5−9). In the case of entry 5, the other potential product is an aldehyde, which is presumably unstable under the reaction conditions. Interestingly, however, in the case of entry 9, a single regiosiomer is obtained, presumably due to the difficulty of β-hydrogen elimination into

(33) Joslin, F. L.; Mague, J. T.; Roundhill, D. M. *Organometallics* **1991**, *10*, 521.
(34) Gill, T. B.; Mann, K. R. *Organometallics* **1982**, *1*, 485.
(35) This reaction has been developed into a general process. See: Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 10842.

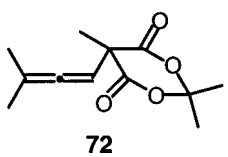
Table 7. Monosubstituted Allenes[a]

Entry	Allene	R'	Product	Isolated Yield (%)
1		-CH_3	 **32**	81
2		-CH_3	 **39**	75
3		-CH_3	 **40**	55
4		-CH_3	 **41**	65
5		-CH_3	 **42**	67
6		-CH_3	 **43**	74
7		-CH_3	 **44**	67
8			 **45**	53
9			 **46**	79
10			 **47**	68
11			 **48**	42
12			 **49**	58
13			 **50**	62

[a] Run as in eq 5 with 10% catalyst, 10% additive, and 15% $CeCl_3 \cdot 7H_2O$ with 1.5 equiv of MVK and 0.25 M allene in DMF at 60 °C for 6 h.

a tertiary center. The mechanistic implications of this result will be discussed subsequently.

With trisubstituted allenes, selective product formation can be observed. As we can see from Table 9 (entries 1−6), good yields can be obtained in most cases, and a range of functionality is tolerated. Yields do suffer somewhat when more hindered substrates are used (for example entries 5 and 6). When the substrate becomes too sterically congested (for example **72**),



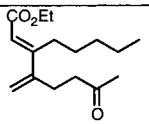
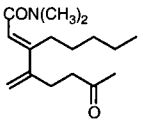
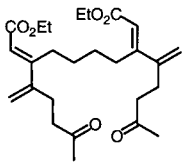
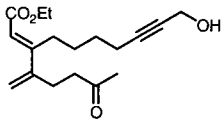
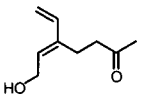
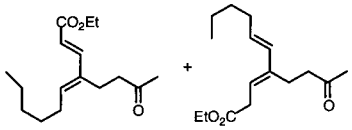
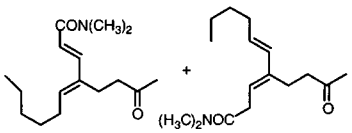
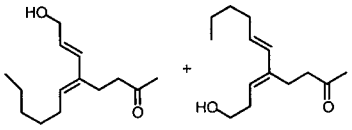
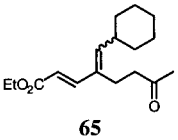
72

no product is formed. Surprisingly, in entries 3 and 4, only one product, **68** and **69**, respectively, is seen (as opposed to the mixtures seen in the case of entries 1 and 2). In entry 4, however, this is probably because the other possible regioisomer would be an aldehyde, which may not be stable under the reaction conditions. Entry 5 illustrates that when a more sterically congested allene is used, a more even distribution of products is seen. Similarly, allene **18** gives a complex mixture of products when subjected to the reaction conditions.

Finally, tetrasubstituted allenes were examined (Table 9, entries 7, 8). The reactions proceed with good regioselectivity with the predominant products **73a** and **74a**, resulting from elimination from the allene double bond that is not conjugated to the ester. Thus, it appears that the ruthenium coordinates to the more electron rich double bond. As expected, the rate is slower and modest yields of the desired adducts were obtained. The low yield of entry 8 may also be attributable to the volatility of the product. Substrates that were even more sterically congested (**2**, **19**, **21**) gave only recovered starting material.

Although initially only enones were examined as the alkene partner, we wished to explore the use of other alkenes. Using

Table 8. Disubstituted Allenes[a]

Entry	Allene	Product	a:b Ratio	Yield (%)
1	**10**	 **55**	---	81
2	**22**	 **56**	---	81
3	**15**	 **57**	---	42
4	**16**	 **58**	---	62
5		 **61**	---	26
6	**11**	 **62a + 62b**	1.2/1	74
7	**23**	 **63a + 63b**	1/1	75
8	**27**	 **64a + 64b**	1/1	58
9	**20**	 **65**	---	73[b]

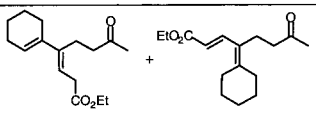
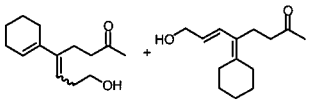
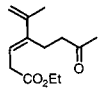
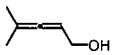
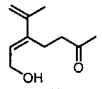
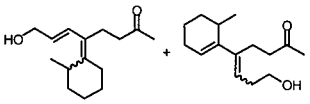
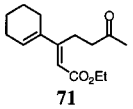
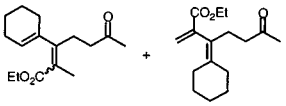
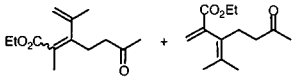
[a] Run as in eq 5 with 10% **38** and 15% $CeCl_3 \cdot 7H_2O$ with 1.5 equiv of MVK and 0.25 M allene in DMF at 60 °C for 4 h. [b] A 1:1 mixture of *E* and *Z* olefins at the indicated position was obtained.

1-octene as a coupling partner gave a complex mixtures of products, with what appeared to be a number of different double bond isomers. One could envisage this coming from competing β-hydrogen eliminations. This result led us to examine partners with no β-hydrogens. Other olefins, such as acrolein, styrene, acrylonitrile, ethyl acrylate, ethyl-2-pentenoate, or crotonal gave no coupling products. The failure of these substrates could mainly be associated with either the instability of these compounds to the reaction conditions or because they are disubstituted olefins (in the case of ethyl-2-pentenoate and crotonal).

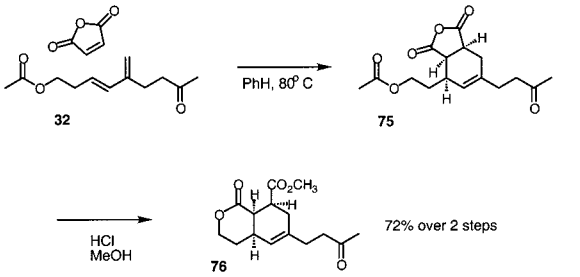
Applications

With the 1,3-dienes in hand, we wished to examine their reactivity in a number of Diels−Alder reactions. We initially chose the reaction of diene **32** with maleic anhydride as the dienophile. As shown in eq 9, the Diels−Alder adduct **75** was not isolated due to the instability of the anhydride. It did however, cyclize smoothly in acidic methanol to give the bicyclic lactone **76** in good yield, which appeared by NMR to be only one diastereomer. The diastereomer shown is the result of the expected endo type transition state.

Table 9. Tri- and Tetrasubstituted Allenes[a]

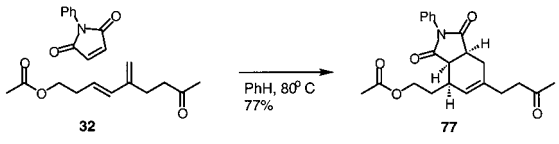
Entry	Allene	Product	a:b Ratio	Yield (%)
1	**12**	 **66a + 66b**	8.3/1	70
2	**28**	 **67a + 67b**	5/1	69
3	**17**	 **68**	---	68
4		 **69**	---	45
5	**29**	 **70a + 70b**	1.8/1	50
6	**5**	 **71**	---	56
7	**4**	 **73a + 73b**	20/1	44
8	**1**	 **74a + 74b**	10/1	14

[a] Run as in eq 5 with 10% **38** and 15% $CeCl_3 \cdot 7H_2O$ with 1.5 equiv of MVK and 0.25 M allene in DMF at 60 °C for 4 h.

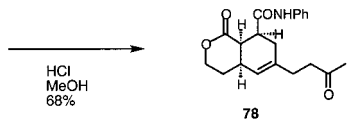


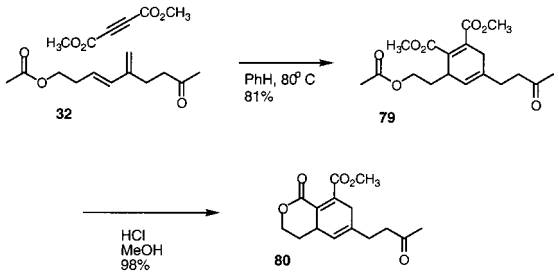
(9)

The reaction of diene **32** was also examined with two other dienophiles. Using maleimide, the Diels−Alder adduct **77** (eq 10) was stable, and also appeared to be one diastereomer by NMR (the diastereomer from the expected endo type transition state is shown). Under similar conditions, it was cyclized to the lactone **78** in 68% yield. A similar sequence was carried out with dimethyl acetylenedicarboxylate, as shown in (eq 11). Diastereoselectivity was not an issue in this case, and the cyclohexadiene adduct **29** was obtained in 81% yield and the corresponding lactone **80** in 98% yield.



(10)

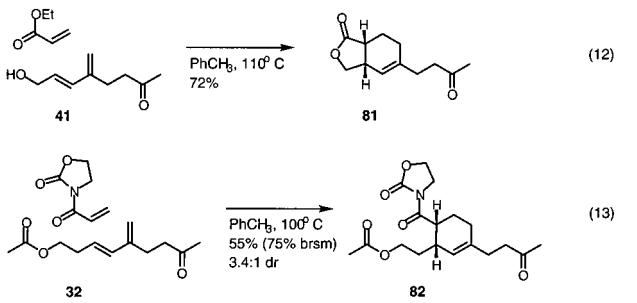




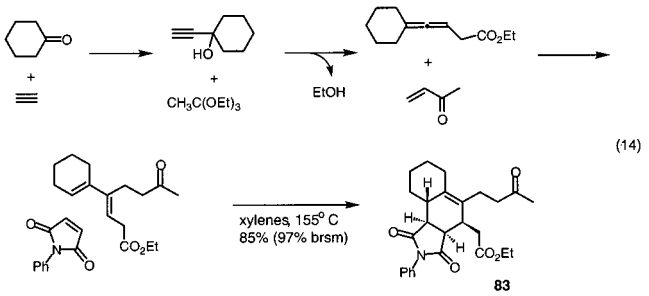
(11)

To explore issues concerning regioselectivity when nonsymmetric dienophiles are used, diene **41** was reacted with ethyl acrylate. In this case, it was hoped that coordination of the alcohol would favor one regioisomer. As shown in eq 12, only one regioisomer, which spontaneously lactonized to form **81**, is observed. Using a diene without such potential coordination with an unsymmetrical dieneophile is shown in eq 13. In this case, a moderate yield of the Diels−Alder adduct **82** is obtained, as a 3.4:1 mixture of diastereomers, with the major diastereomer depicted, expected from an endo type transition state. The products were assigned as diasteromers rather than regioisomers due to the presence of only one peak for each of the carbonyl

signals as well as nearly identical shifts for the olefin signals (δ 136.9 and 123.1 and δ 136.8 and 122.8, respectively) in the ^{13}C NMR spectrum. Also, the ^{1}H NMR showed a multiplet at δ 3.84−3.81 (for the major diasteromer) and a multiplet at δ 3.63−3.59 (for the minor diasteromer) that was not complex enough to be the other regioisomer.



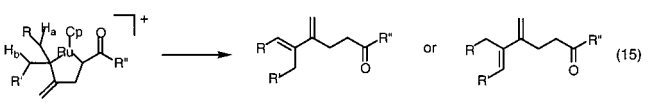
Equation 14 illustrates the highly atom economical manner in which polycyclic systems can be constructed. For example, **83** comes from addition reactions of acetylene, cyclohexanone, triethylorthoacetate, methyl vinyl ketone, and *N*-phenylmaleimide using catalytic reagents with loss only of ethanol. In this case the expected endo product is shown (the product was obtained as a single diastereomer by NMR).



Discussion

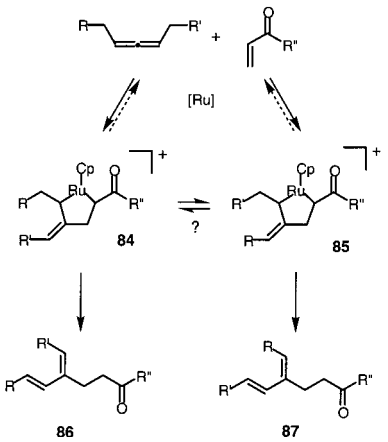
The results with monosubstituted allenes (Table 7) validate the initially postulated mechanism involving a ruthenacycle. Due to the results using tethered alcohols (eq 6, path b), it appears that the ruthenacycle, which contains either a σ- or π-bound metal allyl species, can be trapped with internal nucleophiles. Interestingly, when β-hydrogen elimination is sped up; for example by having an ester, β-hydrogen elimination is favored over this nucleophilic trapping (eq 8). This result opens up the possibility for tuning the reaction conditions to provide either product.

Using 1,1-disubstituted allenes immediately raises the question of chemoselectivity of the β-hydrogen elimination as illustrated in eq 15. In the first case, entry 1, Table 8, R and R′ were chosen such that H_a was "activated" over H_b. Indeed, the reaction gives only one regioisomer when one of the β-hydrogens is acidified by being α to an ester in excellent yield. On the other hand, removal of this "activation" by using a substrate wherein the ester is reduced to the alcohol (eq 7), a nearly equal mixture of products is formed.



1,3-Disubstituted allenes raise the issue of the regioselectivity of the formation of the metallacycle as shown in Scheme 3. If ruthenacycle formation is the rate determining step, then the ratio of **86**:**87** will reflect the ratio of the formation of the initial ruthenacycles **84**:**85**. On the other hand, if ruthenacycle formation is fast and reversible, then the diene ratio will reflect the rate of β-hydrogen elimination from **84** vs **85** (i.e. Curtin−Hammett conditions). This simplified picture can become more complicated because a direct equilibration of **84** and **85** can be envisioned. The fact that the ruthenacycles are σ-allyl complexes[36] raises the prospect of their equilibration by a $\sigma-\pi-\sigma$ mechanism. Thus, the above predictions are valid only in the absence of this possibility. The fact that the σ-C−Ru bond of the ruthenacycle is rather rigidly orthogonal to the π-system might be expected to inhibit this direct equilibration pathway. Looking at the results, not surprisingly, a 1,3-disubstituted allene with no biasing functionality gives a 1:1 mixture of products (entry 8, Table 8). On the other hand, 1,3-diene products could be formed selectively when one β-hydrogen elimination is favored and the other disfavored due to steric considerations (entry 9, Table 8). The results from entries 6 and 7, Table 8, indicate that the two ruthenacycles do not equilibrate rapidly by any mechanism. If there was a rapid equilibration, then elimination to form the conjugated system should have been preferred. To see if one regioisomer could be favored over the other in the reaction of 1,3-disubstituted allenes, we investigated the reaction of entry 6, Table 8. Neither varying the solvent from acetone to DMF nor adding phosphine ligands such as triphenylphosphine or trifurylphosphine had any impact on the regioselectivity. In all cases, good yields could be obtained but the ratios never deviated from 1:1.

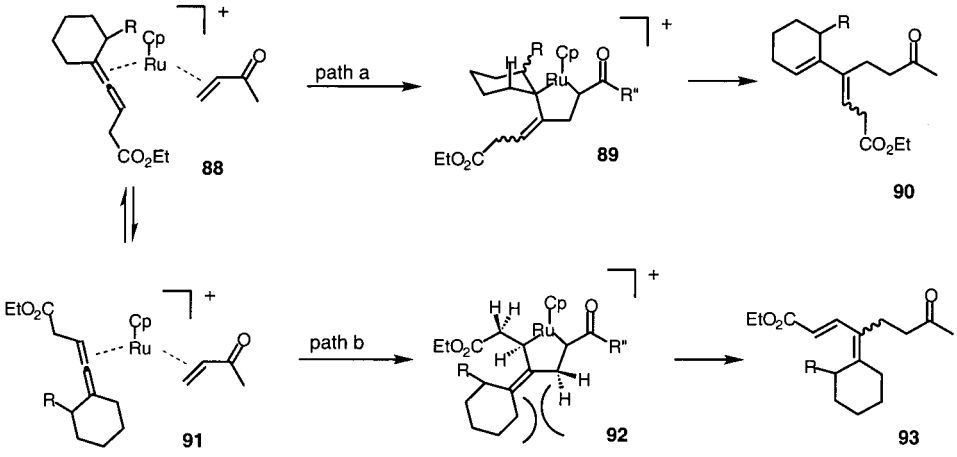
Scheme 3. Mechanistic Possibilities with 1,3-Disubstituted Allenes



With trisubstituted allenes, both factors present in 1,1- and 1,3-disubstituted allenes play a role in which product will be formed. Gratifyingly, good yields and selectivities may be obtained as for example in entries 1−3, Table 9. On the other hand, increasing steric bulk on the cyclohexane ring decreases the selectivity (entry 5, Table 9). Scheme 4 provides a rationale. For the case of R = H, **88**, wherein the sterically less hindered termini form the new C−C bond of the ruthenacycle, is favored. Thus, path a is the dominant one. As we see from the scheme, ruthenacycle **89** is favored over **92**, because, in the latter, you have developing unfavorable $A^{1,3}$ type strain between the allylic substituent in the six-membered ring and the hydrogens on the enone terminus. On the other hand, addition of a methyl group (i.e. R = CH_3) now entails significant steric hindrance with the

(36) For some references of Ru π-allyls, see: Kang, S.-K.; Kim, D.-Y.; Hong, R.-K.; Ho, P. S. Synth. Commun. **1996**, 26, 3225. Zhang, S.-W.; Mitsudo, T.-A.; Kondo, T.; Watanabe, Y. J. Organomet. Chem. **1993**, 450, 197. Minami, I.; Shimizu, I.; Tsuji, J. J. Organomet. Chem. **1985**, 296, 269.

Scheme 4. Reaction with Trisubsituted Allenes



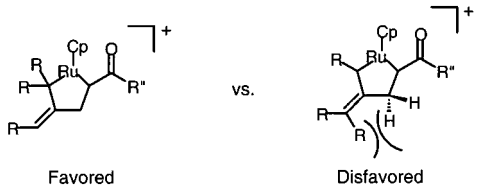


Figure 2. Steric bias in metallacycle formation.

ruthenium that disfavors **88**. Thus, for the example of entry 5, Table 9, both regioisomeric transition states encounter steric resistance and the two paths are more competitive.

In general, from the results seen with trisubstituted allenes, the carbon−carbon bond is formed at the less sterically hindered terminus of the allene as illustrated in Figure 2. This behavior follows that of the ruthenium catalyzed Alder-ene reaction (with alkynes)[37] and also such processes as the Pauson−Khand reaction[38] and the cocatalyzed [2 + 2 + 2] cycloadditions[39] passing through metallacycle intermediates.

Conclusion

In summary, a general procedure for a ruthenium catalyzed two component coupling of an allene and an enone to give 1,3-dienes has been developed. Two ruthenium complexes satisfactorily catalyze this reaction—CpRu(COD)Cl and $CpRu(CH_3CN)_3PF_6$—with the latter generally preferred. The utility of this method stems not only from the generation of these products from unfunctionalized precursors (as opposed to cross-couplings of functionalized alkenes) but also from the use of such products in cycloadditions such as the Diels−Alder reaction. Thus, complex structures can be built up rapidly from simple addition reactions. The ready availability of allenes further enhances the ease with which 1,3-dienes can be formed. When multiply substituted allenes are used, selectivity can be obtained with the proper biasing functionality. Either steric or electronic factors can control the regiochemical outcome of the reaction. The results obtained are consistent with a metallacycle mechanism in which ruthenacycle formation determines the regioselectivity of the reaction.

Experimental Section

Preparation of 3-Cyclohexylidene-2-methylacrylic Acid Ethyl Ester (4). To a stirred solution of (carbethoxyethylidene)triphenylphosphorane (2 g, 5.52 mmol) in dichloromethane (20 mL) is added at 0 °C under nitrogen cyclohexanecarboxylic acid chloride (0.573 mL, 5.52 mmol) and triethylamine (0.77 mL, 5.52 mmol). The reaction mixture is allowed to warm to room temperature and stirred overnight. The solvent was evaporated under reduced pressure and the product extracted from the precipitated triphenylphosphine oxide with pentane. The solution is then cooled to −20 °C, and the rest of the triphenylphosphine oxide is filtered. Removal of the pentane of the filtrate afforded a crude oil, which was purified on silica gel (9:1 petroleum ether:ether) to give 495 mg (58%) of the allene as a colorless oil.

R_f: 0.53 (9:1 petroleum ether/ether). IR (neat): 2981, 2931, 2855, 1962, 1710, 1447, 1367, 1268, 1214, 1120, 1100, 1032, 762 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.14 (q, $J = 7.2$, 2H), 2.20−2.12 (m, 4H), 1.82 (s, 3H), 1.66−1.54 (m, 6H), 1.25 (t, $J = 7.2$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.8, 168.6, 105.0, 92.9, 60.5, 30.6, 27.2, 25.9, 15.6, 14.2. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.32; H, 9.34.

Preparation of Ethyl 5-Cyclohexylpenta-3,4-dienoate (20). A solution of 1-cyclohexyl-prop-2-yn-1-ol (1.0 g, 7.2 mmol) and propionic acid (0.01 mL) in triethylorthoacetate (7.04 g, 8 mL, 43 mmol) was heated to 150 °C for 2.5 h, with removal of the ethanol that was generated by distillation. It was then cooled to room temperature and chromatographed directly on silica gel (20:1 petroleum ether:ether) to give 946 mg (63%) product as a light yellow oil. R_f: 0.37 (20:1 petroleum ether:ether). IR (neat): 2981, 2926, 2853, 1966, 1741, 1448, 1368, 1324, 1298, 1246, 1160, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.25 (qd, $J = 7.1$, 2.7, 1H), 5.19−5.14 (m, 1H), 4.15 (q, $J = 7.1$, 2H), 3.00 (dd, $J = 7.1$, 2.7, 2H), 2.03−1.93 (m, 1H), 1.76−1.60 (m, 5H), 1.27 (t, $J = 7.2$, 3H), 1.21−1.03 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.9, 171.7, 98.2, 84.9, 60.6, 37.0, 35.2, 32.9, 26.2, 25.9, 14.2. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.05; H, 9.49.

Preparation of 3-Pentylpenta-3,4-dien-1-ol (26). To a suspension of LAH (42 mg, 1.11 mmol) in diethyl ether (8 mL) was added a solution of the β-allenic ester (200 mg, 1.02 mmol) in ether (2 mL) at −78 °C under nitrogen. The mixture was allowed to warm to room temperature and stirred for 6 h. Water (3 mL) was added at 0 °C. The white slurry was filtered, and, after addition of ether, the solution was washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo. Purification of the crude oil on silica gel (1:1 petroleum ether:ether) yielded 153 mg (97%) of the allene as a slightly yellow oil.

R_f: 0.54 (1:1 petroleum ether:ether). IR (neat): 3336, 2959, 2928, 2859, 1957, 1700, 1458, 1047, 845 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.73 (m, 2H), 3.74 (m, 2H), 2.23−2.17 (m, 2H), 1.98−1.90 (m, 2H), 1.66 (s, 1H), 1.48−1.27 (m, 6H), 0.88 (t, $J = 6.9$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.4, 100.3, 76.3, 60.7, 35.2, 32.2, 31.4, 27.0, 22.5, 14.0. HRMS. Calcd for $C_{12}H_{20}O_2$ (M^+): 154.1358. Found: 154.1352.

Ruthenium Catalyzed 1,3-Diene Formation. General Procedure A. DMF (1 mL) was added to CpRu(COD)Cl (7.7 mg, 0.025 mmol) and $CeCl_3 \cdot 7H_2O$ (14.0 mg, 0.0375 mmol) in a pressure tube, followed by the allene (0.25 mmol), the vinyl ketone (0.375 mmol), and hex-

(37) Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615.

(38) For a recent review with lead references, see: Ingate, S. T.; MarcoContelles, J. *Org. Prep. Proc. Int.* **1998**, *30*, 121.

(39) For some reviews, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1.

3-yn-1-ol (0.003 mL, 0.025 mmol). The tube was capped and then heated to 60 °C with stirring for 6 h. The reaction was then cooled to room temperature and chromatographed directly.

A typical example is given below.

DMF (1 mL) was added to CpRu(COD)Cl (7.7 mg, 0.025 mmol) and $CeCl_3 \cdot 7H_2O$ (14.0 mg, 0.0375 mmol) in a pressure tube, followed by 1-acetoxy-4,5-hexadiene (35 mg, 0.25 mmol), methyl vinyl ketone (26.5 mg, 0.375 mmol), and hex-3-yn-1-ol (0.003 mL, 0.025 mmol). The tube was capped and then heated to 60 °C with stirring for 6 h. The reaction was then cooled to room temperature and chromatographed (1:1 petroleum ether:ether) directly to give 42.9 mg (81%) of 1,3-diene **32**.

1-Acetoxy-*E*-3-nonen-5-methylene-8-one (32). Light yellow oil. R_f: 0.39 (1:1 petroleum ether:ether). IR (neat): 2958, 1739, 1716, 1650, 1609, 1434, 1386, 1365, 1240, 1162, 1038, 971 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.12 (d, $J = 15.9$, 1H), 5.64 (dt, $J_1 = 15.9$, $J_2 = 7.1$, 1H), 4.93 (s, 1H), 4.87 (s, 1H), 4.10 (t, $J = 6.7$, 2H), 2.62 (t, $J = 7.3$, 2H), 2.48−2.38 (m, 4H), 2.15 (s, 3H), 2.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.2, 171.1, 144.4, 134.1, 125.1, 114.6, 63.6, 42.1, 32.1, 30.0, 25.7, 20.9. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.56; H, 8.55.

General Procedure B. The allene (0.25 mmol) and methyl vinyl ketone (0.375 mmol, 0.032 mL, 1.5 equiv), dissolved in DMF (1 mL), were added to $[CpRu(CH_3CN)_3]PF_6$ (10.9 mg, 0.025 mmol, 0.1 equiv) and $CeCl_3 \cdot 7H_2O$ (14.0 mg, 0.0375 mmol, 0.15 equiv) in a pressure tube. The tube is capped and then heated to 60 °C for 4 h. It is then cooled to room temperature, and after adding 50 mL of ether the reaction mixture is washed three times with saturated sodium bicarbonate solution and dried over $MgSO_4$. Removal of the solvent by rotary evaporation gave a crude oil which was chromatographed on silica gel.

A typical example is given below.

The allene **10** (49 mg, 0.25 mmol) and methyl vinyl ketone (26.5 mg, 0.375 mmol, 0.032 mL, 1.5 equive), dissolved in DMF (1 mL), were added to $[CpRu(CH_3CN)_3]PF_6$ (10.9 mg, 0.025 mmol, 0.1 equiv) and $CeCl_3 \cdot 7H_2O$ (14.0 mg, 0.0375 mmol, 0.15 equiv) in a pressure tube. The tube is capped and then heated to 60 °C for 4 h. It is then cooled to room temperature, and after adding 50 mL of ether the reaction mixture is washed three times with saturated sodium bicarbonate solution and dried over $MgSO_4$. Removal of the solvent by rotary evaporation gave a crude oil which was chromatographed (ether) on silica gel to give 54 mg (81%) of 1,3-diene **55**.

Ethyl 3-*n*-Pentyl-4-methylene-*E*-2-octen-7-one (55). Intense yellow oil. R_f: 0.32 (ether). IR (neat): 3090, 2930, 2860, 1717, 1640, 1494, 1461, 1394, 1361, 1265, 1160, 1128, 1059, 899 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (s, 1H), 5.15 (s, 1H), 5.00 (s, 1H), 2.98 (s, 3H), 2.96 (s, 3H), 2.55 (t, $J = 6.9$, 2H), 2.48 (t, $J = 6.9$, 2H), 2.40 (t, $J = 7.2$, 2H), 2.12 (s, 3H), 1.40−1.18 (m, 6H), 0.86 (t, $J = 6.6$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.9, 168.5, 149.1, 146.5, 119.4, 114.3, 42.3, 37.8, 34.6, 31.8, 30.0, 29.5, 28.5, 27.7, 22.4, 14.0.

Anal. Calcd for $C_{16}H_{27}O_2N$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.60; H, 10.37; N, 4.95.

Synthesis of Bicyclic Lactone 78. The diene **32** (50 mg, 0.24 mmol) and *N*-phenylmaleimide (54.0 mg, 0.33 mmol) were heated in toluene (1 mL) at 80 °C for 2 h. The toluene was evaporated under reduced pressure, and the crude material purified by chromatograpy on silica gel to yield 68 mg of **77** (77%) as a colorless oil. The Diels−Alder adduct **77** (30.0 mg, 0.081 mmol) was redissolved in methanol (4 mL). This solution was cooled to 0 °C and acetyl chloride (15.8 mg, 0.014 mL, 0.202 mmol) was added to generate anhydrous HCl. The reaction was allowed to warm to room temperature and stirred for 16 h. The solvent was then evaporated by rotary evaporation and the crude material chromatographed (1:3 petroleum ether:ether) on silica gel to yield 18.0 mg (68%) of **78** as a colorless oil.

Compound 77. Colorless oil. R_f: 0.11 (1:3 petroleum ether:ethyl ether). IR (neat): 2954, 2852, 1733, 1707, 1598, 1500, 1439, 1386, 1244, 1184, 1039, 952 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (t, $J = 7.7$, 2H), 7.39 (t, $J = 7.4$, 1H), 7.20 (d, $J = 7.3$, 2H), 5.49 (1H), 4.40−4.35 (m, 1H), 4.26−4.21 (m, 1H), 3.49−3.28 (m, 2H), 2.70 (d, $J = 14.9$, 1H), 2.54−2.50 (m, 2H), 2.47−2.46 (m, 1H), 2.41−2.38 (m, 1H), 2.35−2.26 (m, 3H), 2.16−2.10 (m, 1H), 2.09 (s, 3H), 2.0 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.4, 178.6, 176.7, 171.1, 139.8, 131.7, 129.0, 128.6, 126.4, 125.7, 62.6, 42.5, 40.9, 40.6, 33.3, 30.3, 30.2, 29.8, 28.2, 21.0. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.92; H, 6.52; N, 3.65. Found: C, 68.75; H, 6.28; N, 3.51.

Compound 78. Colorless oil. R_f: 0.13 (1:2 petroleum ether:ethyl acetate). IR (neat): 3342, 2922, 2854, 1711, 1599, 1536, 1497, 1441, 1409, 1359, 1320, 1161 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.75 (brs, 1H), 7.57 (d, $J = 7.6$, 2H), 7.35 (t, $J = 8.1$, 1H), 7.13 (t, $J = 7.4$, 2H), 5.36 (s, 1H), 4.37−4.32 (m, 1H), 4.30−4.25 (m, 1H), 3.73 (d, $J = 7.6$, 1H), 3.40 (dd, $J = 6.6$, 2.9, 1H), 3.03 (m, 1H), 2.87−2.83 (m, 1H), 2.61 (t, $J = 7.2$, 2H), 2.39−2.31 (m, 2H), 2.28−2.33 (m, 1H), 2.18 (s, 3H), 1.80−1.74 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 210.6, 184.7, 137.9, 137.5, 128.9, 124.3, 123.9, 120.3, 119.9, 66.5, 45.2, 41.5, 40.7, 33.6, 30.9, 30.1, 28.7, 28.0. HRMS: calcd for $C_{20}H_{34}NO_4$ 341.1627, found 341.1620.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Regional Center of the University of California—San Francisco, supported by the NIH Division of Research Resources. A.B.P. thanks Abbott Laboratories, Glaxo-Wellcome, the ACS Division of Organic Chemistry (sponsored by Bristol-Myers Squibb) and Eli Lilly for fellowship support. M.S. was supported by the Deutscher Akademischer Austauschdienst (DAAD).

Supporting Information Available: Text giving experimental details and tables listing characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA011428G