Titanium-Templated [4 + 2] Oxidative Cycloadditions: A Facile Route to 7-Hydroxynorbornenes

Craig A. Merlic* and Holly D. Bendorf

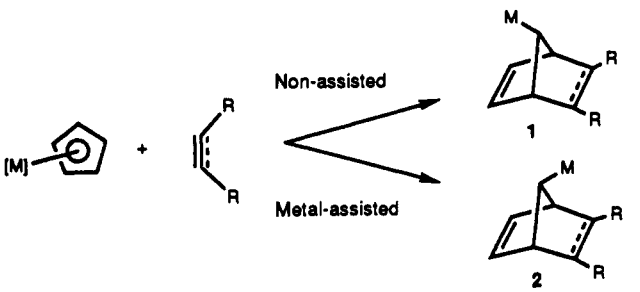
Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California 90024-1569

Received November 16, 1992

Substituted 7-hydroxynorbornenes were prepared in a single step by the reaction of titanocene dichloride with electron-deficient alkenes. The reaction is diastereoselective and also exhibits mild regioselectivity. The effects of solvents, added reagents and alkene structure upon the reaction were studied. The reaction is proposed to occur via a metal-assisted oxidative cycloaddition. Zirconocene dichloride also reacts with electron-deficient alkenes, but yields unoxidized cycloaddition products.

Introduction

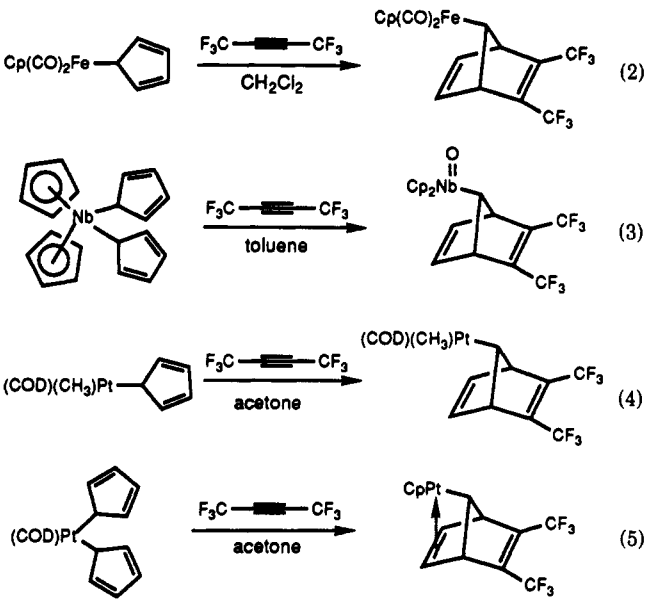
Transition metals have shown great utility as templates for the control of regio- and stereochemistry as well as for activating otherwise inert substrates in cycloaddition reactions.[1] The mechanism by which a reaction occurs varies depending on the transition-metal complex involved. This is illustrated by the formal [4 + 2] cycloaddition reactions of alkenes and alkynes with cyclopentadienyl ligands to yield 7-metallanorbornenes and 7-metallanorbornadienes. The pathway followed depends upon the nature of the initial transition metal complex and may occur via a metal-assisted or non-assisted mechanism. The non-assisted reaction is a formal [4 + 2] which occurs on the face of the cyclopentadienyl ligand opposite the sterically demanding metal moiety to produce a compound of the general structure 1 and does not involve precoordination of the alkene or alkyne to the metal (eq 1). The



(1)

metal-assisted pathway requires initial precoordination of the alkene or alkyne to the metal center followed by reaction with a cyclopentadienyl ligand to yield a compound of the general structure 2 (eq 1). On comparison of compounds 1 and 2, it can be noted that the stereochemical relationship of the metal and the added alkene or alkyne is indicative of the mechanistic pathway followed.

η^1-Coordinated cyclopentadienyl ligands typically react via the nonassisted mechanism. For example, bis(cyclopentadienyl)iron dicarbonyl,[2] tetrakis(cyclopentadienyl)-niobium,[3] cyclopentadienylmethylplatinum cyclooctadiene, and bis(cyclopentadienyl)platinum cyclooctadiene[4,5] react with electron-deficient alkynes to yield *syn*-7-metallanorbornadienes (eqs 2–5) where the syn stereo-



chemistry of these products is indicative of a nonassisted cycloaddition pathway. Bis(cyclopentadienyl)iron dicarbonyl also reacts with electron-deficient alkenes to yield *syn*-7-hydroxynorbornenes. The stereochemistry of the alkene is maintained except in the case of *cis*-2,3-dicyanohexafluoro-2-butene in which the trans-substituted product is obtained exclusively.[2a] Mechanisms invoking a concerted [4 + 2] cycloaddition were proposed to account

(1) For examples see: (a) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (b) Lautens, M.; Edwards, L. G. *J. Org. Chem.* **1991**, *56*, 3761. (c) Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 5627. (d) Lautens, M.; Edwards, L. G. *Tetrahedron Lett.* **1989**, *30*, 6813. (e) Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1. (f) Vollhardt, K. P. C. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*,539. (g) tom Dieck, H.; Diercks, R. *Angew. Chem.* **1983**, *95*, 801. (h) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904. (i) Wender, P. A.; Jenkins, J. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (j) Noyori, R. *Acc. Chem. Res.* **1979**, *12*, 61. (k) Matsuda, I.; Shibata, M.; Sato, S.; Izumi, Y. *Tetrahedron Lett.* **1987**, *28*, 3361.

(2) (a) Williams, J. P.; Wojcicki, A. *Inorg. Chem.* **1977**, *16*, 3116. (b) Davidson, J. L.; Green, M.; Stone, F. G. H.; Welch, A. J. *J. Chem. Soc., Dalton Trans.* **1976**, 2044. (c) Davidson, J. L.; Green, M.; Stone, F. G. H.; Welch, A. J. *J. Chem. Soc., Chem. Commun.* **1975**, 286.

(3) Mercier, R.; Douglade, J.; Amaudrut, J.; Sala-Pala, J.; Guerchais, J. *J. Organomet. Chem.* **1983**, *244*, 145.

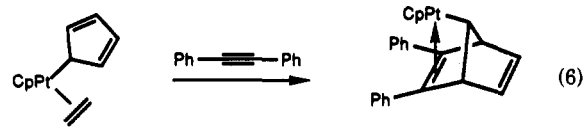
(4) (a) Clark, H. C.; Ibbott, D. C.; Payne N. C.; Shaver, A. *J. Am. Chem. Soc.* **1975**, *97*, 3555. (b) Clark, H. C.; Shaver, A. *Can. J. Chem.* **1976**, *54*, 2068.

(5) (a) Day, C. S.; Day, V. W.; Shaver, A.; Clark, H., C. *Inorg. Chem.* **1981**, *20*, 2188. (b) Ibbott, D. G.; Payne, N. C.; Shaver, A. *Inorg. Chem.* **1981**, *20*, 2193.

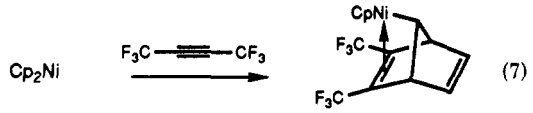
0276-7333/93/2312-0559$04.00/0

for these products with the potential of alkene isomerization before cycloaddition reaction also being proposed.[2a,6,7] The iron moiety is easily displaced to yield 7-carbomethoxy-[8] and 7-aminonorbornenes.[9]

Bis(cyclopentadienyl)platinum ethylene[10] and nickelocene[11-13] react with alkynes to yield metal-assisted cycloaddition products. Stone and co-workers found that bis(cyclopentadienyl)platinum ethylene reacts under mild conditions with diphenylacetylene to yield a cycloaddition product (eq 6).[10] Stone proposed a mechanism involving



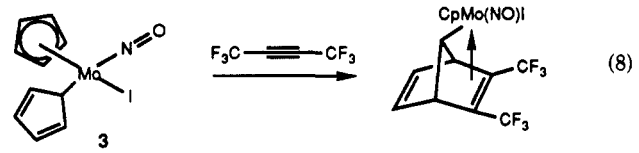
(6)



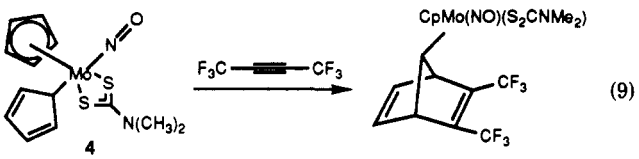
(7)

loss of ethylene and precoordination of the alkyne to activate it toward addition to the cyclopentadienyl ligand in a stepwise reaction. Nickelocene reacts with electron-deficient alkynes to yield norbornadiene products as shown in eq 7.[11-13] The stereochemistry of thes adducts has been verified by X-ray crystallography[14] and is indicative of a metal-assisted mechanism. The nickel–carbon bond of this type of product can be cleaved by a variety of methods to yield 7-halo- and 7-hydroxynorbornadienes.[15]

McCleverty and Hunt have reported that the addition of electron-deficient alkynes to $(C_5H_5)_2Mo(NO)I$ (3) and $(C_5H_5)_2Mo(NO)[(CH_3)_2NCS_2]$ (4) most likely proceeds via a metal-assisted process (eqs 8 and 9).[16] The products of



(8)



(9)

the reaction of 3 and 4 with TCNE are assigned the opposite stereochemistry, implying that precoordination of the alkene does not occur and that an alternate mechanism is in effect. However, their structural characterization is not conclusive and it is possible that the TCNE adducts are structurally analogous to the alkyne adducts and that the two reactions occur via the same metal-assisted mechanism.

While transition-metal chemistry offers efficient routes into 7-substituted norbornenes of defined stereochemistry, traditional synthetic organic methods have also been used to approach these systems, in particular 7-hydroxynorbornenes. Early routes to *syn*- and *anti*-7-hydroxynorbornene were developed by both Winstein[17,18] and Baird.[19] Gassman has approached the anti isomer by the reduction of norbornenone with lithium aluminum hydride.[20] 7-Acetoxynorbornadiene can also be reduced with lithium aluminum hydride to yield *anti*-7-hydroxynorbornene, while treatment with Grignard reagent yields the unstable 7-hydroxynorbornadiene.[21] Baird and co-workers have extensively studied routes to 7-hydroxynorbornenes via diimide reductions,[22] metal-catalyzed hydrogenations,[23] and oxymercuration–demercuration[24] of 7-alkoxy- and 7-acetoxynorbornadienes.[25] Danheiser and co-workers prepared *anti*-7-hydroxynorbornene in modest yield via the rearrangement of an allylcyclopropane.[26] Substituted *syn*- and *anti*-7-hydroxynorbornenes can also be prepared via a silicon-controlled carbocation rearrangement developed by Fleming.[27]

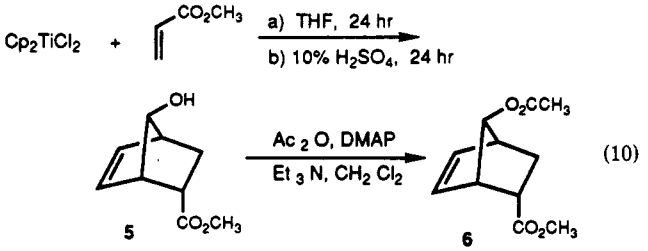
These methods provide routes to 7-hydroxynorbornene systems, but all have the drawbacks of being multistep procedures or are not compatible with the introduction of substituents. In contrast, the metal-mediated preparation of substituted 7-hydroxynorbornenes holds promise as a facile method, yet has remained unexplored. We report here a titanium-templated [4 + 2] oxidative cycloaddition which allows facile access to substituted 7-hydroxynorbornenes in a single step from commercially available starting materials. The reaction is believed to proceed via a metal-assisted mechanism as *anti*-7-hydroxynorbornenes are formed exclusively.

Results

The reaction of Cp_2TiCl with epoxides in the presence of excess methyl acrylate provides products of radical addition as well as titanium(IV) species.[28] While using this methodology in conjunction with our research,[29] we noted the formation of a small amount of an unexpected product, 5. Further experiments revealed the compound

(6) Glass, R. S.; McConnell, W. M. *Organometallics* **1984**, *3*, 1630.
(7) Williams, J. P.; Wojcicki, A. *Inorg. Chem.* **1977**, *16*, 2506.
(8) (a) Wright, M. E. *Organometallics* **1983**, *2*, 558. (b) Wright, M. E.; Hoover, J. F.; Nelson, G. O.; Scott, C. P.; Glass, R. S. *J. Org. Chem.* **1984**, *49*, 3059.
(9) Glass, R. S.; McConnell, W. M.; Andruski, S. W. *J. Org. Chem.* **1986**, *51*, 5123.
(10) Boag, N. M.; Goodfellow, R. J.; Green, M.; Hessner, B.; Howard, J. A. K.; Stone, F. G. A. *J. Chem. Soc. Dalton Trans.* **1983**, 2585.
(11) McBride, D. W.; Dudek, E.; Stone, F. G. A. *J. Chem. Soc.* **1964**, 1752.
(12) Dubeck, M. *J. Am. Chem. Soc.* **1960**, *82*, 6193.
(13) Roe, D. M.; Massey, A. G. *J. Organomet. Chem.* **1969**, *20*, P1.
(14) Dahl, L. F.; Wei, C. H. *Inorg. Chem.* **1963**, *2*, 713.
(15) (a) Luh, T. Y.; Lung, C. L. *J. Chem. Soc., Chem. Commun.* **1982**, 57. (b) Bleasdale, C.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1983**, 214. (c) Bleasdale, C.; Jones, D. W. *J. Chem. Soc., Perkin Trans. 1* **1986**, 157.
(16) Hunt, M. M.; McCleverty, J. A. *J. Am. Chem. Soc., Dalton Trans.* **1978**, 480.
(17) (a) Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183. (b) Winstein, S.; Shatavsky, *J. Am. Chem. Soc.* **1956**, *78*, 592.
(18) Winstein, S.; Stafford, E. T. *J. Am. Chem. Soc.* **1957**, *79*, 505.
(19) Baird, W. C. Jr. *J. Org. Chem.* **1966**, *31*, 2411.
(20) Gassman, P. G.; Pape, P. G. *J. Org. Chem.* **1964**, *29*, 160.
(21) Story, P. R. *J. Org. Chem.* **1961**, *26*, 287.
(22) Baird, W. C. Jr.; Franzus, B.; Surridge, J. H. *J. Am. Chem. Soc.* **1967**, *89*, 410.
(23) (a) Franzus, B.; Baird, W. C. Jr.; Snyder, E. I.; Surridge, J. H. *J. Org. Chem.* **1967**, *32*, 2845. (b) Baird, W. C. Jr.; Franzus, B.; Surridge, J. H. *J. Org. Chem.* **1969**, *34*, 2944.
(24) Baird, W. C. Jr.; Buza, M. *J. Org. Chem.* **1968**, *33*, 4105.
(25) For the preparation of 7-oxygenated norbornadienes see: (a) Story, P. R.; Fahrenholtz, S. R. In *Organic Syntheses*; Parham, W. E., Ed.; John Wiley and Sons: New York, 1964; Vol. 44, p 12. (b) Tanida, H.; Tsuji, T. *Chem. Ind.* **1963**, 211.
(26) (a) Danheiser, R. L.; Martinez-Davila, C.; Morin, S. M. Jr. *J. Org. Chem.* **1980**, *45*, 1340. (b) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443.
(27) (a) Fleming, I.; Michael, J. P. *J. Chem. Soc. Chem. Commun.* **1978**, 245. (b) Fleming, I.; Michael, J. P. *J. Chem. Soc. Perkin Trans. 1* **1981**, 1549.
(28) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1989**, *111*, 4525.
(29) Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855.

to be a product of the reaction of titanium(IV) species present with methyl acrylate. In fact, reaction of titanocene dichloride with methyl acrylate in the presence of air, followed by an aqueous 10% sulfuric acid quench, yields the cycloaddition product **5** as a single diastereomer in 38% yield (eq 10). Despite the complexity of the initial

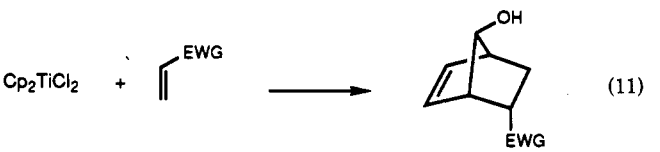


(10)

product mixture, none of the other possible isomers of **5** were detected. The structure and stereochemistry of the product was established by the ^1H NMR spectrum, which exhibits resonances at 6.09 and 5.84 ppm for the vinyl protons, at 2.88 and 2.57 ppm for the bridgehead protons, at 2.09 and 1.46 ppm for the methylene protons, at 3.64 ppm for the C-7 proton, and at 3.17 ppm for the ester methine proton. The endo stereochemistry of the carbomethoxy group was established by the ^3J coupling of 4.0 Hz between the ester methine proton and the neighboring bridgehead proton. A coupling constant of this magnitude is indicative of an exo proton since the coupling between an endo proton and the bridgehead proton is generally very small.[30] The broad singlet at 3.64 ppm narrows upon irradiation of the resonance at 1.46 ppm, indicating the presence of W-coupling between the proton at C-7 and the endo-methylene proton. The acetate **6**, prepared by treatment of the crude reaction mixture with acetic anhydride and (dimethylamino)pyridine, shows a significant W-coupling of 1.3 Hz, confirming the stereochemical assignment.

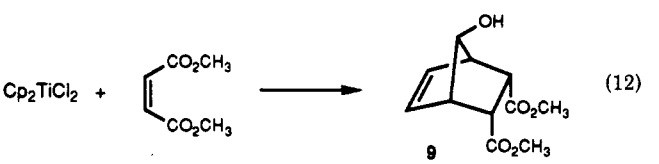
This reaction of titanocene dichloride with methyl acrylate is sensitive to changes in the reaction conditions. Heating (THF reflux) or cooling (−20 °C) the reaction did not result in product formation. Irradiation of the reaction with a sunlamp results in a decreased isolated yield (17%). Use of THF as the reaction solvent gives the highest yields (38%). While dioxane solvent gives yields comparable to THF, less polar solvents such as benzene and dichloromethane result in dramatically decreased yields. Strongly coordinating solvents such as DMF or acetonitrile inhibit the formation of the desired product. Addition of reagents which can potentially abstract a chloride ligand from titanium ($AgBF_4$) or exchange with a chloride ligand to help promote cyclopentadienyl ring slippage (acetylacetone + K_2CO_3) results in reduced yields. Although the reaction requires exposure to air, bubbling oxygen through the solution or adding silver oxide results in vast mixtures of products with little or no formation of **5**. Reaction under an atmosphere of carbon monoxide fails to yield **5** or possible CO insertion products. Product yield is also affected by the length and type of quench, with longer acid quenches resulting in significantly higher yields. Quenching with 10% aqueous sulfuric acid for 24 h proved to be the optimal condition. Most surprisingly, adding aqueous sulfuric acid at the start of reaction provides a comparable isolated yield of **5**. A simple water quench provides substantially lower (8%) isolated yields of **5** and an additional product identified as the unoxidized cycloadduct 5-carbomethoxybicyclo[2.2.1]hept-2-ene. A water quench with oxygen bubbled through the solution gives a complex mixture with no **5** present. Quenching with methanol to obtain the 7-methyl ether or with phenyl disulfide to obtain the 7-phenyl sulfide are not successful.

The novelty of the reaction and the complexity[31] of the product obtained from such a simple reaction warranted further exploration despite the modest yield of **5**. In particular, the scope of the alkene reactants was examined and the reaction was found to be sensitive to steric and electronic factors. Electron-deficient, sterically unencumbered alkenes besides methyl acrylate such as acrolein, methyl vinyl ketone, and dimethyl maleate all reacted with titanocene dichloride to yield substituted 7-hydroxynorbornenes **7**, **8**, and **9** in 23%, 19%, and 16% yield, respectively (eqs 11 and 12). Structural and stereochemical



(11)

7 EWG = CHO
8 EWG = $COCH_3$



(12)

characterizations were analogous to those for compound **5**. In every case, only the product with an anti hydroxyl group and an endo activating substituent were isolated. Again the isolated yields were modest, but the ease of obtaining products of such substitution is intriguing.

More sterically demanding substituted alkenes such as diethyl fumarate, methyl crotonate and cyclohexenone and electronically unactivated alkenes such as norbornene failed to yield cycloaddition products. Acrylamide also failed to yield a cycloaddition product, possibly due to competing coordination of the carbonyl group, rather than the alkene unit, to the titanium center. 7-Hydroxynorbornadienes could not be isolated from the reaction of titanocene dichloride with diphenylacetylene or dimethyl acetylenedicarboxylate. It should be noted that 7-hydroxynorbornadienes are unstable compounds and their successful isolation is difficult;[15b,c] thus, sensitivity to the reaction conditions may have precluded isolation of cycloadduct.

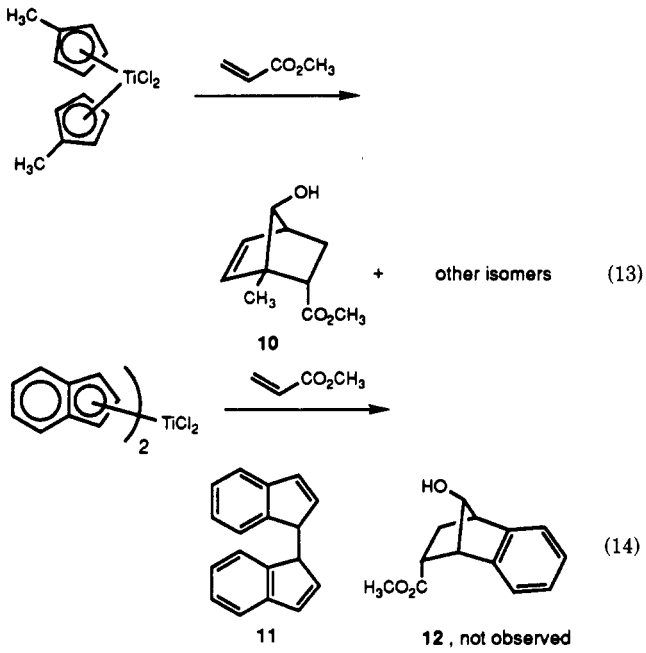
The reactions of bis(methylcyclopentadienyl)titanium dichloride[32] and bis(indenyl)titanium dichloride[33] were investigated to expand the methodology to the synthesis of highly substituted norbornenes. Reaction of bis(methylcyclopentadienyl)titanium dichloride with methyl acrylate provided cycloadducts and exhibited mild regioselectivity (eq 13). The major isomer **10** (18%) was easily separated from the mixture of other regioisomers (8%) and is characterized by the absence of coupling between

(30) No coupling is observed between the *endo* methylene proton and the neighboring bridgehead proton in compound **5**.

(31) Bertz, S. H. *J. Am. Chem. Soc.* **1982**, *104*, 5801.

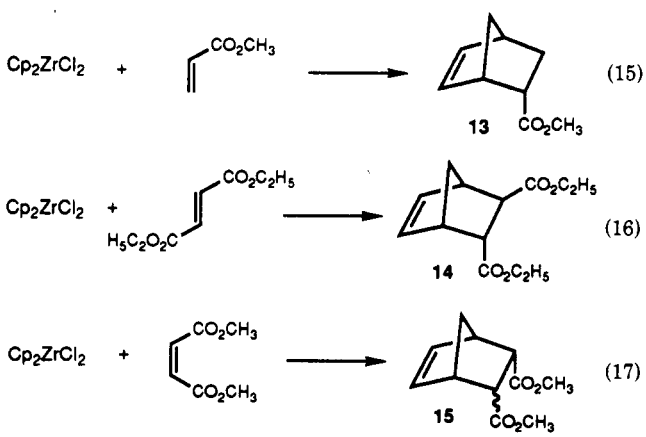
(32) (a) *Organometallic Syntheses*; Eisch, J. J.; King R. B., Eds., Academic Press: New York, 1965; Vol 1, p 75. (b) Petersen, J. L.; Dahl, L. F. *J. Am. Chem. Soc.* **1975**, *97*, 6422.

(33) Samuel, E.; Setton, R. *J. Organomet. Chem.* **1965**, *4*, 156.



a bridgehead proton and the ester methine proton in the ^{1}H NMR spectrum. Due to the air sensitivity of bis(indenyl)titanium dichloride, reaction with methyl acrylate was under nitrogen and was only opened to air upon quenching with aqueous 10% sulfuric acid. The desired cycloaddition product **12** was not formed, and instead bis(indene) **11**,[34] a product of net reductive coupling of the indenyl ligands, was obtained in 35% yield as a one-to-one mixture of diastereomers (eq 14).

In order to test reaction selectivity based on the metal, reactions of zirconocene dichloride with electron-deficient alkenes such as methyl acrylate and diethyl fumarate were examined. Products from a formal [4 + 2] cycloaddition were obtained, but in contrast to the reactions of titanocene dichloride, alcohol products were not found; only the 7-methylene compounds **13** and **14** were isolated in 73% and 18% yields, respectively (eqs 15 and 16). These are

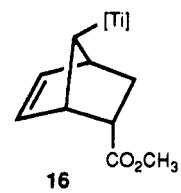


the products of net cycloaddition followed by protonation, and all of the spectroscopic properties were in accord with literature data.[35,36] Reaction with dimethyl maleate also provided cycloaddition products, but the double-bond stereochemistry was partially lost and **15** was obtained (17%) as a mixture of isomers (eq 17).

Discussion

anti-7-Hydroxynorbornenes with endo substituents are obtained in a single step from the reaction of commercially available titanocene dichloride and an appropriate alkene. A number of products are formed in the reaction, possibly due to catalysis of olefin metathesis by titanocene alkyl species;[37] however, the 7-hydroxynorbornene products predominate and are isolated as single diasteromers. Although the yields are low to modest, the simple procedure offers significant advantages over the traditional multistep syntheses for this class of compounds.

A detailed mechanistic picture is not available, but some general predictions are supported by the experimental observations. Precoordination of the activated alkene to a titanium center is proposed, followed by insertion into the cyclopentadienyl–titanium bonds in a manner analogous to that proposed by Stone and co-workers for the reaction of diphenylacetylene with bis(cyclopentadienyl)platinum ethylene (eq 6).[10] An intermediate such as **16**



16

is proposed to result from this net cycloaddition, but attempts to detect or trap this intermediate have been unsuccessful. The exact nature of the titanium center both before and after the alkene insertion is not known, but some change of the ligand sphere is expected. The observed endo,anti stereochemistry of the product is the principle evidence for a metal-assisted process and is consistent with the precedents discussed (vide supra). Ring slippage to an η^1-cyclopentadienyl ligand with subsequent [4 + 2] cycloaddition is unlikely since this should lead to the syn product which is not observed. The hydroxyl group of the product is likely formed by insertion of oxygen into the titanium-carbon bond of **16** to yield a peroxide which can be reduced by other metal species in solution, or possibly via disproportionation with another molecule of **16**. Precedent for this step is found in hydrozirconation chemistry.[38]

The observed sensitivity of the reaction to the effects of solvents, added reagents and the nature of the alkene substrate supports the proposed metal-assisted cycloaddition pathway. Polar solvents which do not coordinate strongly to titanium, such as THF and dioxane, are a requirement for the reaction and may stabilize coordinatively unsaturated intermediates. However, strongly coordinating solvents (acetonitrile, DMF) appear to inhibit alkene coordination to the metal center and prevent product formation. Addition of reagents which can act as effective ligands for titanium also result in diminished yields or stop the reaction completely. Alkene reactivity

(34) Heimer, N. E.; Hojjatie, M.; Panetta, C. A. *J. Org. Chem.* **1982**, *47*, 2593.
(35) Chenier, P. J.; Stevens, B. J.; Adams, B. R. *Synth. Commun.* **1988**, *18*, 1947.
(36) Marchand, A. P.; Reddy, G. M. *Synthesis* **1991**, 198.
(37) (a) Lee, J. B.; Gajda, G. J.; Schaefer, W. P.; Howard, T. R.; Ikariya, T.; Straus, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 7358. (b) Lee, J. B.; Ott, K. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1982**, *104*, 7491.
(38) (a) Blackburn, T. F.; Labiner, J. A.; Schwartz, J. *Tetrahedron Lett.* **1975**, *35*, 3041. (b) Schwartz, J.; Labinger, J. A. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333.

depends on both steric and electronic factors; only sterically unemcumbered electron-deficient alkenes yielded 7-hydroxynorbornene products. The steric effects support the requirement of alkene precoordination to the titanium since cycloaddition to the cyclopentadienyl ligand from the side opposite the metal would not be greatly influenced by the steric environment of the alkene. The requirement of an electron withdrawing substituent is presumably necessary to promote coordination to titanium or insertion into the carbon titanium bonds.

Unlike the reactions involving titanocene dichloride, zirconocene dichloride reacts with electron deficient alkenes to yield formal [4 + 2] cycloaddition products without the additional hydroxyl substituent at the 7-position. Most likely, the alkene adds to the cyclopentadienyl ligand to yield an intermediate analogous to **16**, but hydrolysis occurs faster than oxygen insertion. Without a hydroxyl group acting as a sterochemical probe to differeniate pathways, the net cycloaddition to the cyclopentadienyl ligand may occur by either a metal-assisted or nonassisted mechanism. It is unlikely, however, that the alkene undergoes a concerted cycloaddition with an η^1-cyclopentadienyl ligand or with free cyclopentadiene resulting from decomposition of zirconocene dichloride in view of the loss of the double bond stereochemistry in the case of dimethyl maleate. In contrast with the products obtained from the titanium-based reactions, the products from the zirconium-based reactions are more readily prepared by direct Diels–Alder reactions using cyclopentadiene.

Conclusion

The reaction of titanocene dichloride with electron-deficient olefins presented here offers a facile route to diastereomerically pure, substituted 7-hydroxynorbornenes which are otherwise difficult to prepare. The reaction is believed to proceed via a metal-assisted cycloaddition followed by oxidative cleavage of the titanium–carbon bond to yield product. The reaction of bis(methylcyclopentadienyl)titanium dichloride with methyl acrylate exhibits mild regioselectivity and offers a potential route to more highly substituted norbornene derivatives. The reaction of zirconocene dichloride with electron-deficient alkenes provides an interesting contrast by yielding unoxidized norbornene cycloadducts.

Experimental Section

General Considerations. All reactions were carried out under nitrogen by standard reaction techniques, unless noted otherwise. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl under nitrogen. Dichloromethane and hexane were distilled from calcium hydride, and all alkenes were distilled prior to use. All other reagents were used as received. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). Infrared spectra were recorded on a Nicolet 205 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AF 200, AM 360, and AM 500 spectrometers. Chemical shifts are reported in ppm with Me_4Si or $CDCl_3$ as internal standards. Mass spectra were recorded at 70 eV on AEI MS902, VG ZAB-SE, or VG Autospec instruments.

***endo,anti*-2-Carbomethoxybicyclo[2.2.1]hept-5-en-7-ol (5).** Methyl acrylate (1.09 mL, 12.1 mmol) was added to a solution of titanocene dichloride (0.302 g, 1.21 mmol) in tetrahydrofuran (24 mL) open to air. After stirring for 24 h, 10% aqueous sulfuric acid (20 mL) was added and stirring was continued for an additional 24 h. The solution was added to water (100 mL) and extracted with ether (3 × 50 mL). The ether extracts were combined and washed with saturated aqueous sodium bicarbonate (3 × 50 mL), water (3 × 50 mL), and brine (1 × 50 mL). The ether solution was dried ($MgSO_4$) and the solvent removed in vacuo. The orange oil (0.161 g) was purified by flash chromatography on Florisil (8:2 hexane/ethyl acetate) to yield 0.079 g (38%) of **5** as a colorless oil. Reaction using 1.50 g of Cp_2TiCl_2 gave a comparable yield of **5**. IR ($CHCl_3$): 3459, 2959, 1736, 1434, 1342, 1265, 1201, 1075 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.46 (1H, dd, J = 11.8, 4.0 Hz), 2.09 (1H, ddd, J = 11.8, 9.2, 3.9 Hz), 2.57 (1H, m), 2.63 (1H, s, br), 2.88 (1H, m), 3.17 (1H, dt, J = 9.2, 4.0 Hz), 3.60 (3H, s), 3.64 (1H, s), 5.84 (1H, ddd, J = 6.2, 3.4, 0.6 Hz), 6.09, (1H, ddd, J = 6.2, 3.5, 0.6 Hz). ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 176.0, 136.4, 131.4, 83.3, 51.6, 49.6, 46.3, 40.6, 26.0. MS: m/e 168 (M^+, 98), 150 (46), 136 (100), 118 (20), 108 (74). Mass calcd for $C_9H_{12}O_3$: 168.0786; Found: 168.0787.

***endo,anti*-7-Acetoxy-2-carbomethoxybicyclo[2.2.1]hept-5-ene (6).** The crude product (0.166 g) obtained from reaction of methyl acrylate (1.27 mL, 14.1 mmol) and titanocene dichloride (0.352 g, 1.41 mmol) was added to a solution of acetic anhydride (0.168 mL, 1.77 mmol), (dimethylamino)pyridine (0.012 g, 0.099 mmol), and triethylamine (0.343 mL, 2.46 mmol) in methylene chloride (10 mL). The solution was stirred 12 h and then added to ether (75 mL) and washed with water (1 × 25 mL), 3N HCl (3 × 25 mL), and saturated aqueous sodium bicarbonate (3 × 25 mL). The ether solution was dried ($MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography on silica gel (85:15 hexane/ethyl acetate) to yield a colorless oil (0.072 g, 35% from titanocene dichloride). IR ($CHCl_3$): 2995, 2952, 1748, 1440, 1384, 1244, 1046, 765, 715 cm^{-1}. ^{1}H NMR (360 MHz, C_6D_6): δ 1.54 (3H, s), 1.63 (1H, ddd, J = 11.9, 4.2, 1.0 Hz), 1.92 (1H, ddd, J = 11.9, 9.2, 3.9 Hz), 2.56 (1H, m), 3.00 (1H, dt, J = 9.2, 4.2 Hz), 3.09 (1H, m), 3.29 (3H, s), 4.44 (1H, d, br, J = 1.3 Hz), 5.82 (2H, m). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 174.7, 170.2, 135.8, 131.1, 83.3, 51.6, 46.9, 43.9, 40.8, 26.2, 21.1. MS: m/e 210 (M^+, 46), 189 (24), 179 (63), 168 (98), 150 (85), 136 (97), 108 (100). Mass calcd for $C_{11}H_{14}O_4$: 210.0892; Found: 210.0899.

***endo,anti*-7-Hydroxybicyclo[2.2.1]hept-5-ene-2-carbaldehyde (7)**: prepared from acrolein (0.663 mL, 9.93 mmol) and titanocene dichloride (0.495 g, 1.99 mmol) as described for **5**. Purification by flash chromatography on silica gel (8:2 hexane/ethyl acetate) gave 0.063 g (23%) of a colorless oil. IR ($CHCl_3$) 3409, 2960, 1715, 1335, 1215, 1062, 759 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.53 (1H, dd, J = 11.9, 4.0 Hz), 2.10 (1H, ddd, J = 11.9, 9.0, 3.9 Hz), 2.66 (1H, m), 2.98 (1H, m), 3.16 (1H, dtd, J = 9.0, 4.0, 2.1 Hz), 3.69 (1H, s, br), 5.90 (1H, ddd, J = 6.2, 3.1, 0.7 Hz), 6.11 (1H, ddd, J = 6.2, 3.5, 0.8 Hz), 9.58 (1H, d, J = 2.1 Hz). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 204.9, 136.4, 130.9, 83.2, 50.0, 48.5, 46.5, 24.2. MS: m/e 138 (M^+, 30), 137 (100), 109 (41), 107 (50), 91 (99), 84 (68). Mass calcd for $C_8H_{10}O_2$: 138.0681; Found: 138.0675.

***endo,anti*-2-(1-Oxoethyl)bicyclo[2.2.1]hept-5-en-7-ol (8)**: prepared from methyl vinyl ketone (0.747 mL, 8.97 mmol) and titanocene dichloride (0.447 g, 1.79 mmol) as described for **5**. Purification by flash chromatography on silica gel (9:1 hexane/ethyl acetate) yielded 0.049 g (18%) of a colorless oil. IR ($CHCl_3$): 3438, 2973, 2931, 1714, 1356, 1194, 1089, 908, 786, 737 cm^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.55 (1H, dd, J = 11.8, 4.3 Hz), 1.95 (1H, ddd, J = 11.8, 8.9, 3.9 Hz), 2.01 (1H, s), 2.12 (3H, s), 2.58 (1H, m), 2.93 (1H, m), 3.24 (1H, dt, J = 8.9, 4.3 Hz), 3.69 (1H, s, br), 5.79 (1H, dd, J = 6.0, 3.1 Hz), 6.07 (1H, dd, J = 6.0, 3.4 Hz). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 210.4, 137.1, 131.2, 84.4, 50.5, 50.4, 47.2, 30.1, 24.9. MS: m/e 152 (M^+, 10), 134 (42), 109 (61), 92 (74), 91 (75), 82 (51), 81 (55), 79 (100), 77 (54). Mass calcd for $C_9H_{12}O_2$: 152.0837; Found: 152.0837.

***endo,endo,anti*-2,3-Bis(carbomethoxy)bicyclo[2.2.1]-hept-5-en-7-ol (9)**: prepared from dimethyl maleate (1.71 mL, 13.6 mmol) and titanocene dichloride (0.340 g, 1.36 mmol) as decribed for **5**. Purification by flash chromatography on silica gel (75:25 hexane/ethyl acetate) yielded 0.050 g (16%) of a colorless oil. IR ($CHCl_3$): 3494, 2952, 1743, 1434, 1201, 1166, 1075 cm^{-1}. ^{1}H NMR

(360 MHz, $CDCl_3$): δ 2.91 (2H, m), 3.55 (2H, t, J = 1.6 Hz), 3.62 (6H, s), 3.68 (1H, t, J = 2.0 Hz), 3.80 (1H, s), 6.15 (2H, t, J = 2.2 Hz). ^{13}C NMR (90.6 MHz, $CDCl_3$): δ 173.3, 133.3, 82.2, 51.6, 50.1, 45.4. MS: m/e 226 (M^+, 20), 195 (100), 194 (78), 166 (20), 143 (38), 113 (39), 107 (62). Mass calcd for $C_{11}H_{14}O_5$: 226.0841; Found: 226.0845.

***endo,anti*-2-Carbomethoxy-1-methylbicyclo[2.2.1]hept-5-en-7-ol (10)**: prepared from methyl acrylate (0.242 mL, 2.69 mmol) and bis(methylcyclopentadienyl)titanium dichloride (0.149 g, 0.539 mmol) in tetrahydrofuran (11 mL) as described for **5**. The crude product was purified by flash chromatography on silica (8:2 hexane/ethyl acetate) to yield *endo,anti*-2-carbomethoxy-1-methylbicyclo[2.2.1]hept-5-en-7-ol as a colorless oil (0.0183 g, 19%) plus a mixture of isomers as a colorless oil (0.0081 g, 8%). IR (pure isomer, $CHCl_3$): 3445, 3022, 1722, 1644, 1223, 757 cm^{-1}. ^1H NMR (pure isomer, 360 MHz, $CDCl_3$): δ 1.32 (3H, s), 1.60 (1H, dd, J = 11.9, 4.3 Hz), 1.91 (1H, s, br), 2.26 (1H, ddd, J = 11.9, 9.3, 3.9 Hz), 2.56 (1H, s, br), 2.82 (1H, dd, J = 9.3, 4.2 Hz), 3.31 (1H, s, br), 3.63 (3H, s), 5.77 (1H, d, J = 6.1 Hz), 6.10 (1H, dd, J = 6.1, 3.6 Hz). ^{13}C NMR (pure isomer, 90.6 MHz, $CDCl_3$): δ 175.5, 136.5, 134.2, 87.1, 55.0, 51.4, 46.1, 45.3, 29.6, 14.2. MS (pure isomer): m/e 182 (M^+, 3), 164 (11), 151 (11), 122 (20), 105 (85), 93 (100), 79 (74). Mass calcd for $C_{11}H_{14}O_5$: 182.0943; Found: 182.0950. ^1H NMR (mixture, olefinic region, 360 MHz, $CDCl_3$): δ 5.41 (1H, m), 5.70 (1H, m), 5.77 (1H, d, J = 6.1 Hz), 5.87 (1H, dd, J = 6.1, 3.1 Hz), 5.91 (1H, dd, J = 6.2, 3.1), 6.11 (1H, m), 6.16 (1H, dd, J = 6.2, 3.4 Hz). MS (mixture): m/e 182 (M^+, 39), 164 (19), 151 (45), 122 (75), 105 (72), 93 (100), 79 (43), 71 (41). Mass calcd for $C_{10}H_{14}O_3$: 182.0943; Found: 182.0948.

1,1′-Bi-1*H*-indene (11). Methyl acrylate (0.215 mL, 2.38 mmol) was added to a solution of bis(indenyl)titanium dichloride (0.0832 g, 0.238 mmol) in tetrahydrofuran (5 mL) under an atmosphere of nitrogen. The solution was stirred 24 h and then opened to the air to add 10% aqueous sulfuric acid (20 mL). The reaction was stirred an additional 24 h and then added to water (100 mL) and extracted with ether (3 × 50 mL). The ether extracts were combined and washed with saturated aqueous sodium bicarbonate (3 × 50 mL), water (3 × 50 mL), and brine (1 × 50 mL). The ether solution was dried ($MgSO_4$) and the solvent removed in vacuo to yield 0.0363 g of a brown oil. The crude product was purified by preparative thin-layer chromatography (silica, 1000 μm, 9:1 hexane/ethyl acetate). No bicyclo[2.2.1]-heptene products were detected. The indene dimer, a yellow oil, was obtained as a one to one mixture of diastereomers (0.0177 g, 32%) with spectral data consistent with the literature values reported for 1,1′-bi-1*H*-indene.[34]

***endo*-2-Carbomethoxybicyclo[2.2.1]hept-5-ene (13)**: prepared from methyl acrylate (1.45 mL, 16.1 mmol) and zirconocene dichloride (0.470 g, 1.61 mmol) in tetrahydrofuran (32 mL) as described for **5**. The crude product (0.179 g) was purified by flash chromatography on silica gel (9:1 hexane/ethyl acetate) to yield 0.161 g (73%) of a colorless oil. The spectral data obtained for the product are consistent with literature values.[35]

***endo,exo*-2,3-Bis(carboethoxy)bicyclo[2.2.1]hept-5-ene (14)**: prepared from diethyl fumarate (1.67 mL, 10.2 mmol) and zirconocene dichloride (0.595 g, 2.03 mmol) in tetrahydrofuran (41 mL) as described for **5**. Purification by flash chromatography on silica gel (9:1 hexane/ethyl acetate) provided an inseparable mixture of *endo,exo*-2,3-bis(carboethoxy)bicyclo[2.2.1]hept-5-ene and diethyl fumarate, and the yield was estimated by NMR to be 18%. The spectral data of the product are consistent with literature values.[36]

***endo,exo*- and *endo,endo*-2,3-Bis(carbomethoxy)bicyclo-[2.2.1]hept-5-ene (15)**: prepared from dimethyl maleate (1.16 mL, 8.91 mmol) and zirconocene dichloride (0.521 g, 1.78 mmol) in tetrahydrofuran (36 mL) as described for **5**. Purification by flash chromatography on silica gel (8:2 hexane/ethyl acetate) yielded *endo,exo*-2,3-bis(carbomethoxy)bicyclo[2.2.1]hept-5-ene (0.0271 g, 7%) and a mixture of *endo,endo*-2,3-bis(carbomethoxy)-bicyclo[2.2.1]hept-5-ene and dimethyl maleate (0.656 g). The dimethyl maleate was removed by vacuum transfer distillation to yield 0.039 g (10%) of *endo,endo*-2,3-bis(carbomethoxy)-bicyclo[2.2.1]hept-5-ene. The spectral data obtained for the products are consistent with literature values.[36]

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

OM920563M