JOC*Article*

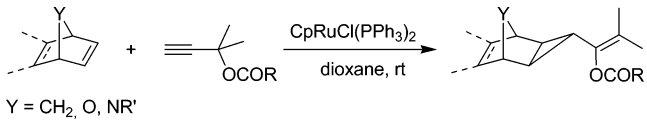
$CpRuCl(PPh_3)_2$-Catalyzed Cyclopropanation of Bicyclic Alkenes with Tertiary Propargylic Acetates

Alphonse Tenaglia* and Sylvain Marc

Laboratoire de Synthèse Asymétrique, UMR CNRS 6180, Université Paul Cézanne, EGIM Sud, Av. Escadrille Normandie Niemen, F-13397 Marseille Cedex 20, France

alphonse.tenaglia@univ.u-3mrs.fr

Received February 9, 2006



The electron-rich cyclopentadienylruthenium complex $CpRuCl(PPh_3)_2$ turns out to be an efficient catalyst for the regio- and stereoselective cyclopropanation of bicyclic alkenes with tertiary propargylic carboxylates. The reaction provides 1,2,3-trisubstituted cyclopropanes in high yields as a single stereoisomer instead of the expected cyclobutenes via [2 + 2] cycloaddition. Functional groups such as ethers, esters, alcohols, phenols, ketones, esters, carboxylic anhydrides, nitriles, halides, sulfones, imides, carbamates, and azines are tolerated with the catalyzed reaction. An efficient cyclopropanation of cyclobutenes was also demonstrated, providing the strained bicyclo[2.1.$0^{1,3}$]pentane framework.

Introduction

The transition-metal-catalyzed decomposition of diazo compounds in the presence of alkenes is a powerful method for the construction of cyclopropane rings.[1] Among the various metals able to catalyze the extrusion of dinitrogen in these reactions, the most widely used are copper or dinuclear rhodium complexes. So far, these metal catalysts proved efficient for the cyclopropanation of electron-rich alkenes; in contrast, palladium catalysts are preferred for the reactions involving electron-deficient as well as strained alkenes.[2] Ruthenium catalysts were recognized in the early 1990s[3] as a cheaper alternative to the more expensive rhodium catalysts with promising results in the area of enantioselective cyclopropanation.[3c,d,4] The ruthenium-catalyzed cyclopropanation of strained bicyclic alkenes such as norbornene **1** pose problems. Usually, in the presence of ruthenium carbene species generated from diazo compounds, norbornene leads to the ROMP (ring-opening metathesis polymerization) via the formation of ruthenacyclobutanes as intermediates.[5] The first ruthenium-catalyzed cyclopropanation of norbornene with nondiazo compounds[6] was reported by Takahashi using propargyl alcohol affording an acetylcyclopropane branched on the norbornane framework (Scheme 1).[7]

The active species are cationic half-sandwich cyclopentadienylruthenium ($CpRu^+$) complexes, and the reaction is believed

(1) (a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919−939. (b) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75−253. (c) Tomilov, Y. V.; Dokichev, V. A.; Dzhemilev, U. M.; Nefodof, O. M. *Russ. Chem. Rev.* **1993**, *62*, 799−838. (d) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091−1160. (e) Ye, T.; McKervey, A. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester, 1995; Vol. 2, Chapter 11. (f) Doyle, M. P. In *Comprehensive Organometallic Chemistry II*; Hedegeus, L. S., Ed.; Pergamon Press: New York, 1995; Vol. 12, Chapters 5.1 and 5.2. (g) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley-Interscience: New York, 1998. (h) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (i) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: New York, 1998. (j) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459−2469.

(2) (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695−702. (b) Nakamura, A.; Koyama, T.; Otsuka, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 593−595. (c) Majchrzak, M. W.; Kotelko, A.; Lambert, J. B. *Synthesis* **1983**, 469−470. (d) Denmark, S. E.; Stavenger, R. A.; Faucher, A.-M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375−3389.

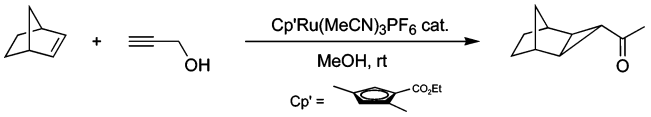
(3) (a) Noels, A. F.; Demonceau, A. *J. Phys. Org. Chem.* **1998**, *11*, 602−609. (b) Maas, G. *Chem. Soc. Rev.* **2004**, *33*, 183−190. (c) Nishiyama, H. In *Ruthenium in Organic Synthesis*; Murahashi, S.-I., Ed.; Wiley-VCH: Weinheim, 2004; pp 179−187. (d) Nishiyama, H. *Topics in Organometallic Chemistry*; Bruneau, C., Dixneuf, P. H., Eds.; Springer-Verlag GmbH: Berlin, 2004; Vol. 11, pp 81−92.

(4) (a) Nishiyama, H.; Itoh, Y.; Matsumoto, H.; Park, S.-B.; Itoh, K. *J. Am. Chem. Soc.* **1994**, *116*, 2223−2224. (b) Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1247−1262. For recent reports, see: (c) Charette, A. B.; Bouchard, J. E. *Can. J. Chem.* **2005**, *83*, 533−542. (d) Marcin, L. R.; Denhart, D. J.; Mattson, R. J. *Org. Lett.* **2005**, *7*, 2651−2654.

(5) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039−2041. (b) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110. (c) Hafner, A.; van der Schaaf, P. A.; Mühlebach, A. *Chimia* **1996**, *50*, 131−134. (d) Simal, F.; Demonceau, A.; Noels, A. F.; Knowles, D. R. T.; O'Leary, S.; Maitlis, P. M.; Gusev, O. *J. Organomet. Chem.* **1998**, *558*, 163−170. (e) Simal, F.; Jan, D.; Demonceau, A.; Noels, A. F. *Tetrahedron Lett.* **1999**, *40*, 1653−1656. (f) Tutusaus, A.; Delfosse, S.; Demonceau, A.; Noels, A. F.; Nunez, R.; Vinas, C.; Teixidor, F. *Tetrahedron Lett.* **2002**, *43*, 983−987.

10.1021/jo060276a CCC: $33.50
Published on Web 04/06/2006

SCHEME 1. Takahashi's Ruthenium-Catalyzed Cyclopropanation of Norbornene with Propargyl Alcohol



to proceed via a ruthenacylopentene formed by coupling the alkene and alkyne moieties. The fine-tuning of electronic properties of the Cp ligands turns out to be the key to promote the cyclopropanation instead of the expected [2 + 2] cycloaddition.[8] For instance, complexes containing both an electron-withdrawing group (CO_2Et) and electron-donating groups (Me) on the Cp ligand exhibited the highest activity. Recently, Uemura reported the vinylcylopropanation of electron-rich alkenes using $[RuCl_2(CO)_3]_2$ as catalyst and propargylic carboxylates as precursors of vinylcarbenoids species affording 1,2-disubstituted cyclopropanes as a mixture of cis/trans stereoisomers (Scheme 2).[9]

In contrast with the results of Takahashi,[7a,b] the cyclopropanation of norbornene was not observed with this catalyst. Our recent investigations in cycloaddition reactions involving alkynes and norbornenes or norbornadienes in the presence of ruthenium catalysts[8m,10] led us to develop a general and safe method of cyclopropanation of bicyclic alkenes with nondiazo compounds.

SCHEME 2. Uemura's Ruthenium-Catalyzed Cyclopropanation of Alkenes with Propargylic Acetates

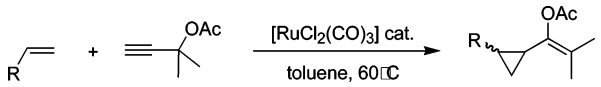
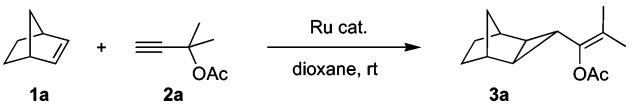


TABLE 1. Ruthenium Catalysts for the Cyclopropanation of Norbornene with Alkyne 2a[a]



1a 2a 3a

entry	catalyst	T (°C)	time (h)	yield[b] (%)
1	$[RuCl_2(CO)_3]_2$	rt	24	
2	$[RuCl_2(CO)_3]_2$	60	24	
3	$HRuCl(CO)(PPh_3)_3$	rt	24	
4	$HRuCl(CO)(PPh_3)_3$	60	48	
5	$TpRuCl(PPh_3)_2$[c]	rt	24	
6	$TpRuCl(PPh_3)_2$[c]	60	24	
7	$(C_9H_7)RuCl(PPh_3)_2$[d]	rt	20	5
8	$(C_9H_7)RuCl(PPh_3)_2$[d]	60	48	8
9	$[(C_6H_6)RuCl_2]_2/PPh_3$ (1/2)	rt	20	
10	$[(C_6H_6)RuCl_2]_2/PPh_3$ (1/2)	60	40	20
11	$[CpRu(MeCN)_3]PF_6$	rt	2.5	86
12	$CpRuCl(PPh_3)_2$	rt	2.5	93
13	CpRuCl(dppe)	60	48	

[a] Reaction conditions: norbornene/**2a**/catalyst (0.75/0.50/0.025 mmol) in dioxane (4 mL). [b] Yields refer to purified products after column chromatography. [c] Tp is for tris(pyrazolyl)borate. [d] C_9H_7 is for indenyl.

In this paper, we report that the electron-rich $CpRuCl(PPh_3)_2$ complex turns out to be an efficient catalyst for the cyclopropanation of a wide range of norbornenes and norbornadienes with propargylic carboxylates. Additionally, the reaction has been applied to cyclobutenes to construct the strained bicyclo-[2.1.0^{1,3}]pentane framework.

Results and Discussion

Catalyst and Optimization of Reaction Conditions. At first, the reaction of norbornene **1a** with 2-methyl-3-butyn-2-yl acetate (**2a**) was examined with several ruthenium complexes in order to find an appropriate catalyst. The reactions were performed in dioxane as the solvent at room temperature or at 60 °C. The results of the screening are given in Table 1.

Actually, as originally reported by Uemura, no cyclopropanation was observed with $[RuCl_2(CO)_3]_2$ as catalyst[9a,b] (entries 1−2). Ruthenium complexes such as $HRuCl(CO)(PPh_3)_3$,[11] $TpRuCl(PPh_3)_2$,[12] or $(\eta^5$-$C_9H_7)RuCl(PPh_3)_2$[13] proved inactive

(6) Cyclopropanations of norbornene with nondiazo reagents in the presence of palladium catalysts have been sporadically reported, but no general applicability was described. See: (a) Catellani, M.; Chiusoli, G. P.; Giroldini, W.; Salerno, G. *J. Organomet. Chem.* **1980**, *199*, C21−C23. (b) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1982**, *233*, C21−C24. (c) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1983**, *250*, 509−515. (d) Catellani, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1983**, *24*, 4493−4496. (e) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem.* **1984**, *275*, 257−262. (f) Chiusoli, G. P. *J. Organomet. Chem.* **1986**, *300*, 57−80. (g) Trost, B. M.; Schneider, S. *J. Am. Chem. Soc.* **1989**, *111*, 4430−4433. (h) Trost, B. M.; Urabe, H. *Tetrahedron Lett.* **1990**, *31*, 615−618. (i) Ohe, K.; Ishihara, T.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1990**, *112*, 9646−9647. (j) Ogoshi, S.; Morimoto, T.; Nishio, K.; Ohe, K.; Murai, S. *J. Org. Chem.* **1993**, *58*, 9−10. (k) Ohe, K.; Matsuda, H.; Ishihara, T.; Ogoshi, S.; Chatani, N.; Murai, S. *J. Org. Chem.* **1993**, *58*, 1173−1177. (l) Liu, C. H.; Cheng, C. H.; Cheng, M. C.; Peng, S. M. *Organometallics* **1994**, *13*, 1832−1839. (m) Ikeda, I.; Ohsuka, A.; Tani, K.; Hirao, T.; Kurosawa, H. *J. Org. Chem.* **1996**, *61*, 4971−4974. (n) Brown, D.; Grigg, R.; Sridharan, V.; Tambyrajah, V.; Thornton-Pett, M. *Tetrahedron* **1998**, *54*, 2595−2606. For a notable recent exception, see: Bigeault, J.; Giordano, L.; Buono, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4753−4757.

(7) (a) Kikuchi, H.; Uno, M.; Takahashi, S. *Chem. Lett.* **1997**, 1273−1274. (b) Matsushima, Y.; Kikuchi, H.; Uno, M.; Takahashi, S. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2475−2482. For recent related studies, see: (c) Villeneuve, K.; Tam, W. *Organometallics* **2006**, *25*, 843−848.

(8) (a) Mitsudo, T.; Kokuryo, K.; Takegami, Y. *J. Chem. Soc., Chem. Commun.* **1976**, 722−723. (b) Mitsudo, T.; Kokuryo, K.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem.* **1979**, *44*, 4492−4496. (c) Mitsudo, T.; Hori Y.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *334*, 157−167. (d) Russell, R. A.; Longmore, R. W.; Weerasuria, K. D. V.; Warrener, R. N. *Aust. J. Chem.* **1991**, *44*, 1341−1345. (e) Warrener, R. N.; Groundwater, P.; Pitt, I. G.; Butler, D. N.; Russell, R. A. *Tetrahedron Lett.* **1991**, *32*, 1885−1888. (f) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580−581. (g) Winling, A.; Russell, R. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3921−3924. (h) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031−3034. (i) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367−2370. (j) Alvarez, P.; Gimeno, J.; Lastra, E.; Garcia-granda, S.; Van der Maelen, J. F.; Bassetti, M. *Organometallics* **2001**, *20*, 3762−3771. (k) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051−6054. (l) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123−2128. (m) Tenaglia, A.; Giordano, L. *Synlett* **2003**, 2333−2336. (n) Villeneuve, K.; Jordan, R. W.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610−613. (o) Villeneuve, K.; Riddell, N.; Jordan, R. W.; Tsui, G. C.; Tam, W. *Org. Lett.* **2004**, *6*, 4543−4546. (p) Jordan, R. W.; Khoury, P. R.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467−8474. (q) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *6*, 3681−3684.

(9) (a) Miki, K.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **2003**, *44*, 2019−2022. (b) Miki, K.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2003**, *68*, 8505−8513. For recent gold-catalyzed versions, see: (c) Fürstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546−2547. (d) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (e) Mézailles, N.; Ricard, L.; Gagosz, F. *Org Lett.* **2005**, *7*, 4133−4136. (f) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002−18003. For platinum-catalyzed intramolecular versions, see: (g) Mainetti, E.; Mouriès, V.; Fensterback, L.; Malacria, M.; Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2132−2135. (h) Blaszykowski, C.; Harrak, Y.; Gonçalves, M.-H.; Cloarec, J.-M.; Dhimane, A.-L.; Fensterback, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 3771−3774. (i) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterback, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656−8657. (j) Anjum, S.; Marco-Contelles, J. *Tetrahedron* **2005**, *61*, 4793−4803.

(10) Tenaglia, A.; Giordano, L. *Tetrahedron Lett.* **2004**, *45*, 171−174.

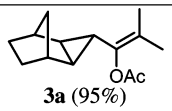
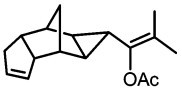
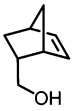
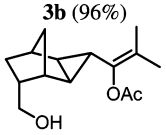
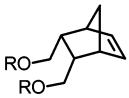
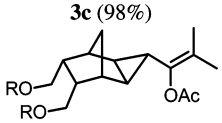
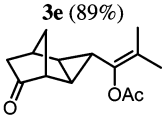
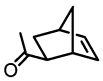
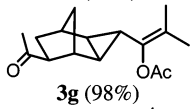
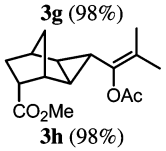
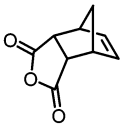
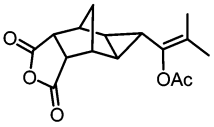
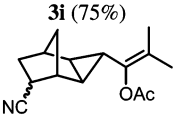
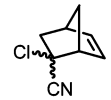
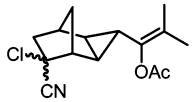
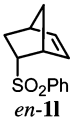
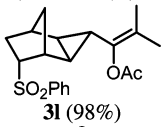
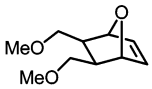
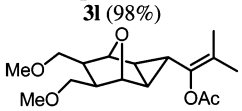
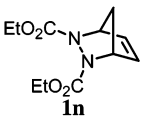
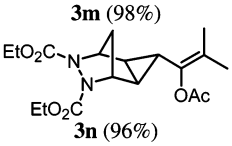
(11) Komiya, S. *Synthesis of Organometallic Compounds. A Practical Guide*; Wiley: Chichester, 1997; pp 196−197.

(entries 3−6) or nearly unefficient (entries 7−8). In situ generated (C_6H_6)Ru(PPh_3)Cl_2 proved moderately efficient at 60 °C giving the cyclopropane **3a** as a single stereoisomer in 20% yield (entry 10). The observation of cyclopropanic protons as a 1H triplet at δ 1.62 (J = 2.9 Hz) and a 2H doublet at δ 0.88 (J = 2.9 Hz) in the NMR spectra supports the stereochemistry assigned for **3a**.[14] The best results that emerged from these studies were observed with the cyclopentadienylruthenium complexes [CpRu(MeCN)$_3$]PF_6[15] and CpRuCl(PPh$_3$)$_2$[16] giving **3a** in 86% and 93% yield, respectively (entries 11−12). This is surprising since these complexes are poorly active ([CpRu(MeCN)$_3$]PF_6) or inactive (CpRuCl(PPh$_3$)$_2$) for the cyclopropanation of norbornene with propargyl alcohol.[7a,b] Moreover, in the presence of a catalytic amount of CpRuCl(PPh$_3$)$_2$, ROMP only takes place when norbornene was treated with ethyl diazoacetate.[5f,17] The fact that no reaction occurred by employing the bidentate dppe as the ligand (entry 13) suggested that the coordination sites required to promote the reaction are best released with the more labile monodentate PPh_3. The catalyst loading can be lowered at the expense of the reaction time and yields. In the presence of 2.5 mol % of CpRuCl(PPh$_3$)$_2$, **3a** was obtained in 90% yield after 18 h (compare with Table 1, entry 12), whereas the yield of **3a** decreased to 70% after 42 h with 1 mol % of catalyst. It turns out that the reactions can be carried out with a wide range of solvents without significant difference of yields. For instance, **3a** was obtained in 92−98% yield in dioxane, toluene, DCE, THF, EtOH, MeOH, $MeNO_2$, acetone, or DMF. Primary or secondary propargylic acetates are not suitable for the cyclopropanation; only mixture of products are observed in these cases.

Cyclopropanation of Norbornenes. With the optimized conditions in hand (2.5 mol % of CpRuCl(PPh$_3$)$_2$, dioxane, rt), the cyclopropanation of various functionalized norbornenes was examined to expand the scope of the reaction and to test the tolerance of the catalyzed reaction toward functional groups. The results are summarized in Table 2.

The cyclopropanation of a wide range of 5-substituted or 5,6-disubstituted norbornenes occurred smoothly at room temperature to afford the expected acetoxyvinylcyclopropanes as single stereoisomer with high yields (75−98%). In contrast with the cyclopropanation of electron-rich alkenes[9a,b] which were performed in moderate polar or apolar solvents (toluene, DCE, or cyclohexane) at 60 °C with a 5-fold molar excess of alkene with respect to **2a**, the reactions were carried out at room temperature in a polar solvent, and more importantly, a 1:1 ratio alkene/**2a** was satisfactory to achieve high yields. The reaction proved totally diastereoselective affording *r*-1,*t*-2,*t*-3-trisubstituted cyplopropanes[18] branched in the configuration *exo* to the

TABLE 2. Ruthenium-Catalyzed Cyclopropanation of Norbornenes[a]

entry	alkene	t (h)	adduct (yield)[b]
1[c]	 **1a**	6.5	 **3a** (95%)
2	 **1b**	21	 **3b** (96%)
3	 *en*-**1c**	21	 **3c** (98%)
4	 **1d** R = H	21	 **3d** (98%)
5[a]	**1e** R = Ac	96	**3e** (89%)
6	 **1f**	24	 **3f** (98%)
7	 *ex*-**1g**	17	 **3g** (98%)
8	 *en*-**1h**	22	 **3h** (98%)
9	 *en*-**1i**	42	 **3i** (75%)
10	 **1j** (*en*:*ex* 59:41)	20	 **3j/3j'** (*en*:*ex* 59:41) (98%)
11	 **1k** (10:2.3 md)	46	 **3k** (10:2.3 md) (94%)
12	 *en*-**1l**	45	 **3l** (98%)
13[d]	 **1m**	20	 **3m** (98%)
14	 **1n**	40	 **3n** (96%)

[a] Reaction conditions: alkene (0.5 mmol), **2a** (0.5 mmol), CpRuCl(PPh$_3$)$_2$ (0.0125 mmol), dioxane (4 mL), room temperature. [b] Yield refer to isolated compounds after column chromatography. [c] Norbornene (0.75 mmol). [d] Aerobic conditions.

(12) Alcock, N. W.; Burns, I. D.; Claire, K. S.; Hill, A. F. *Inorg. Synth.* **1992**, *31*, 2906−2908.

(13) Oro, L. A.; Ciriano, M. A.; Campo, M.; Foces-Foces, C.; Cano, F. H. *J. Organomet. Chem.* **1985**, *289*, 117−131.

(14) The masked keto group of **3a** was revealed by treatment with K_2CO_3 in methanol at room temperature affording quantitatively the known 3-methyl-1-tricyclo[3.2.1.0^{2,4}]oct-3-ylpropan-1-one. See ref 6k.

(15) (a) Trost, B. M.; Older, C. *Organometallics* **2002**, *21*, 2544−2546. (b) Kündig, P. E.; Monnier, F. R. *Adv. Synth. Catal.* **2004**, *346*, 901−904.

(16) Bruce, M. I.; Windsor, N. J. *Aust. J. Chem.* **1977**, *30*, 1601−1604.

(17) (a) Even in the absence of ethyl diazoacetate, the ROMP of norbornene or norbornadiene was observed at room temperature with a catalytic amount of Ru(η^5-C_9H_7)Cl(cod). See: Alvarez, P.; Gimeno, J.; Lastra, A. *Organometallics* **2002**, *21*, 5678−5680.

(18) The rules of nomenclature for trisubstituted cyclopropanes recommended by Cross and Klyne were applied. See: Cross, L. C.; Klyne, W. *Pure Appl. Chem.* **1976**, *45*, 11−30.

bicyclic unit. The compatibility of the catalyst with functional groups such as alcohols, ethers, ketones, esters, carboxylic anhydrides, nitriles, α-chloronitriles, azines, and sulfones was established. The regioselectivity of the reaction is illustrated by the conversion of dicyclopentadiene **1b** to cyclopropane **3b** (entry 2). In the presence of an excess of **2a**, **1b** afforded exclusively **3b**, even carrying out the reactions at elevated temperature (90 °C). The mild and neutral conditions allowed the reaction to proceed without epimerization (entries 7, 8, 10, and 12). Diastereomeric adducts **3j** and **3j′** were easily separated by column chromatography and fully characterized independently (entry 10). The presence of heteroatom(s) in the bicyclic framework such as for alkenes **1m** and **1n** is not detrimental to the reaction affording the expected cyclopropanes **3m** and **3n**, respectively (entries 13 and 14). Next, the reactions with bicyclo-[2.2.1]hepta-2,5-dienes were examined in order to expand the scope of the cyclopropanation.

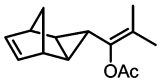
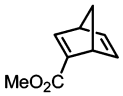
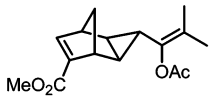
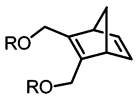
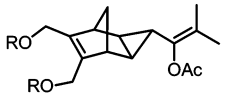
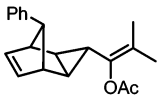
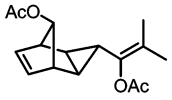
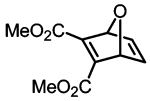
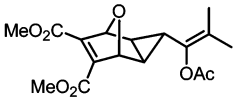
Cyclopropanation of Norbornadienes. In contrast to the results observed with norbornene, norbornadiene (NBD) **4a** did not undergo the cyclopropanation with propargyl alcohol in the presence of [Cp′Ru(MeCN)$_3$]PF$_6$ (Cp′ = η^5-ethoxycarbonyl-2,4-dimethylcyclopentadienyl) (see Scheme 1).[7] Additionally, the cyclopropanation of norbornene was inhibited by the presence of a catalytic amount of NBD in the reaction media due to the formation of the stable [Cp′Ru(η^4-NBD)(MeCN)]-PF$_6$ complex. We anticipated that under our optimized conditions with a noncationic complex, the cyclopropanation of norbornadienes is expected to proceed due to a better coordination ability of an alkyne compared with a 1,4-diene.

Under our optimized conditions (2.5 mol % of CpRuCl-(PPh$_3$)$_2$, dioxane, room temperature), norbornadiene **4a** was recovered unchanged. Gratifyingly, when the reaction was carried out at 60 °C the expected adduct **5a** (49%) and the bis-cyclopropane **6** (18%) were formed quite easily (Table 3, entry 1). The reaction was also performed under air without significant changes in terms of reaction time or yield. Accordingly, except where stated, the reactions were now conducted under these new conditions at 60 °C. In the presence of 2.5 molar equiv of acetate **2a**, the bis-cyclopropane **6** was obtained as the sole product (single diastereomer) in 98% yield (Table 3, entry 2). The assigned *exo*,*exo* stereochemistry for **6** rests upon the observation of only seven types of protons in a 2/6/2/6/6/4/2 ratio in its ^{1}H NMR spectrum and of 10 lines in the ^{13}C NMR spectrum in agreement with a highly symmetrical structure (i.e., C_{2v} symmetry). The reaction was extended to various functionalized norbornadienes bearing substituents at C-5, C-6, or C-7 affording the expected cycloadducts in good to excellent yields (Table 3).

A notable feature is the site selectivity. The cyclopropanation takes place exclusively at the more electron-rich (entries 3 and 8), unsubstituted (entries 4 and 5), and more *exo*-facial available double bond (entries 6 and 7). Unlike norbornadiene **4a**, which undergoes Ru-catalyzed double cyclopropanation (entry 1), bis-adducts were not observed for alkenes **4b**−**g**.

Cyclopropanation of Benzonorbornadienes. A series of substituted benzonorbornadienes including heteroatom analogues at the bridgehead position or featuring heteroatom substituents at the phenyl ring were examined to evaluate substituents effects on the course of the cyclopropanation. As shown in Table 4, benzonorbornadienes **7a**−**k** and alkyne **2a** afforded the cyclopropane adducts **8a**−**k** in excellent yields. With the exception of **7f** and **7k**, the transformation takes place at room temperature,

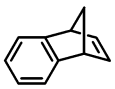
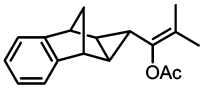
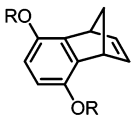
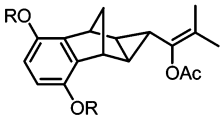
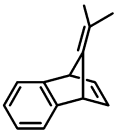
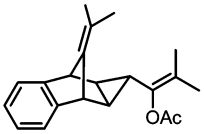
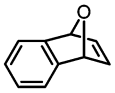
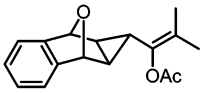
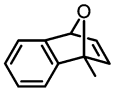
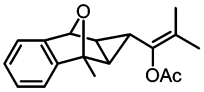
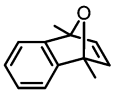
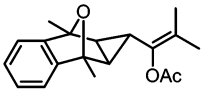
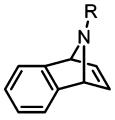
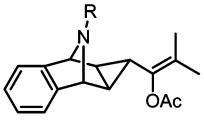
TABLE 3. Ruthenium-Catalyzed Cyclopropanation of Norbornadienes[a]

entry	alkene	t (h)	adduct (yield)[b]
1			
	4a	48	**5a** (49%)
			
			6 (18%)
2[c]	**4a**	18	**6** (98%)
3		21	
	4b		**5b** (73%)
			
4	**4c** R = CO_2Me	1	**5c** (98%)
5	**4d** R = Ac	3	**5d** (95%)
6[d]		44	
	4e		**5e** (88%)
7		24	
	4f		**5f** (96%)
8		4	
	4g		**5g** (73%)

[a] Reaction conditions: alkene (0.5 mmol), **2a** (0.5 mmol), CpRuCl(PPh$_3$)$_2$ (0.0125 mmol), dioxane (4 mL), 60 °C, aerobic conditions. [b] Yield refer to isolated compounds after column chromatography. [c] **2a** (1.25 mmol). [d] Reaction carried out at 90 °C.

as already observed in the case of norbornenes (Table 2). 1,4-Di-*O*-substitution on the phenyl ring of benzonorbornadienes **7b**−**d** was not detrimental to the cyclopropanation (entries 2−4). As expected, the cyclopropanation of diene **7e** featuring a double bond at the bridgehead position afforded selectively monocyclopropane **8e** (entry 5). The course of the cyclopropanation of heteroatom bridgehead benzonorbornadienes **7f**−**k** was not affected by the nature of the heteroatom involved or by the presence of methyl group(s) at one or both bridgehead position(s) (**7g**−**h**). The cyclopropanation of substituted 7-oxabenzonorbornadiene **7h** bearing two methyl groups at the bridgehead carbons required a longer reaction time compared with the reaction of **7g** with a single methyl substituent (entries 7−8). In contrast, 7-oxabenzonorbornadiene **7f** did not react at room

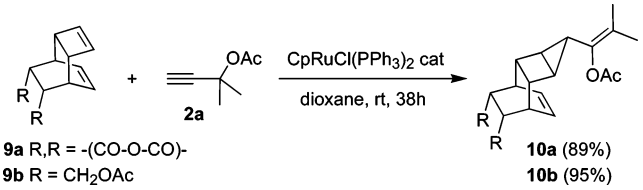
TABLE 4. Ruthenium-Catalyzed Cyclopropanation of Benzonorbornadienes[a]

entry	alkene	t (h)	adduct (yield)[b]
1		19	
	7a		**8a** (98%)
			
2	**7b** R = OH	48	**8b** (98%)
3	**7c** R = OMe	41	**8c** (98%)
4	**7d** R = OAc	23	**8d** (98%)
5		24	
	7e		**8e** (98%)
6[d]		1	
	7f		**8f** (98%)
7		23	
	7g		**8g** (76%, 100%[c])
8		45	
	7h		**8h** (77%)
			
9	**7i** R = Boc	8.5	**8i** (97%)
10	**7j** R = CO_2Me	70	**8j** (98%)
11[d]	**7k** R = Ts	3.5	**8k** (98%)

[a] Reaction conditions: alkene (0.5 mmol), **2a** (0.5 mmol), CpRuCl(PPh$_3$)$_2$ (0.0125 mmol), dioxane (4 mL), room temperature, aerobic conditions. [b] Yield refer to isolated compounds after column chromatography. [c] Yield based upon recovery of the starting material. [d] Reaction carried out at 60 °C.

temperature (not in Table 4) but was readily converted at 60 °C to cyclopropane **8f** in 98% yield (entry 6). The cyclopropanation of *N*-protected 7-azabenzonorbornadienes **7i**−**k** provided adducts **8i**−**k** in nearly quantitative yields (entries 9−11). The structure of adduct **8i** was confirmed from single-crystal X-ray analysis.[19] A methoxycarbonyl group on the nitrogen atom

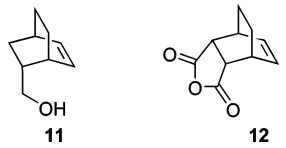
SCHEME 3. Ruthenium-Catalyzed Cyclopropanation of Cyclobutenes



retards the cyclopropanation compared with a *tert*-butyloxycarbonyl group (entries 9 and 10), whereas **7k** with a *p*-toluenesulfonyl group was recovered unchanged at room temperature (not in Table 4) but reacted satisfactorily at 60 °C to afford **8k** (entry 11).

Cyclopropanation of Other Cycloalkenes. Although the purpose of this work was to develop the cyclopropanation of norbornenes and to expand its applicability to congeners, we briefly examined the reactions of bicyclic [2.2.2]alkenes and cyclobutenes. Subjected to the cyclopropanation conditions with alkyne **2a**, tricyclo[4.2.2.0^{2,5}]deca-3,7-dienes **9a**,**b**, featuring both bicyclic [2.2.2]alkene and cyclobutene subunits, were smoothly converted to afford exclusively cyclopropanes **10a** (89%) and **10b** (95%), respectively (Scheme 3).

The cyclopropanation was observed at the more strained double bond to form single stereoisomeric adducts. The assigned stereochemistry for **10a** was established by NOESY experiments (see the Supporting Information). To make sure that the less strained double bond of the bicyclo[2.2.2]octenes **9**, compared with the norbornenes, was resistant to the cyclopropanation, alkenes **11** and **12** were subjected to the reaction. As anticipated, these compounds remained unchanged even at 90 °C.



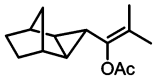
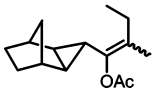
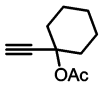
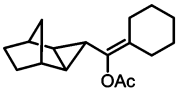
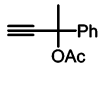
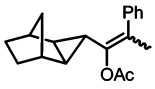
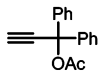
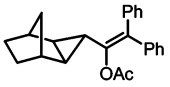
Finally, contrary to the results of Uemura[9a,b] with [RuCl$_2$(CO)$_3$]$_2$, cyclopentene or cyclopentadiene were unreactive toward the cyclopropanation in the presence of CpRuCl(PPh$_3$)$_2$.[20]

Cyclopropanation of Norbornene with Tertiary Propargyl Carboxylates. In a first set of experiments, the cyclopropanation of norbornene **1a** with tertiary propargylic acetates was examined in the presence of CpRuCl(PPh$_3$)$_2$ (2.5 mol %) at room temperature for 6.5 h (see Table 2, entry 1) in order to evaluate the influence of the substitution patterns on the course of the reaction. In a second set of experiments, the same reactions were carried out with prolonged reaction time to ensure the best conditions for the conversion. The results are summarized in Table 5.

The relative rate conversion decreased steadily from alkyl- to cycloalkyl-substituted terminal propargyl acetates (entries 1−3). Acetates **2d** and **2e** with one or two phenyl groups, respectively, reacted slugglishly, and no appreciable product was formed with the latter (entries 4 and 5). Under prolonged reaction time, the cyclopropanation yield increased satisfactorily (entries 1−4) except for alkyne **2e**, which afforded at best 41%

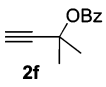
(19) See the Supporting Information for details.
(20) Even styrene, a substrate of choice in metal-catalyzed cyclopropanations, did not undergo the cyclopropanation under our conditions.

TABLE 5. Ruthenium-Catalyzed Cyclopropanation of Norbornene 1 with Various Propargylic Acetates[a]

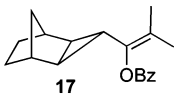
entry	alkyne	product (yield)[b]	t(h), optimized yield[b]
1			-
	2a	**3a** (95%)	
2			20h, 98%
	2b	**13** (87%) (*Z*:*E* 1:1)	
3			20h, 98%
	2c	**14** (50%)	
4			96h, 80%
	2d	**15** (5%) (*Z*:*E* 1:1)	
5			48h, 41%
	2e	**16** (-)	

[a] Reaction conditions: norbornene (0.75 mmol), alkyne (0.5 mmol), $CpRuCl(PPh_3)_2$ (0.0125 mol), dioxane (4 mL), room temperature, 6.5 h. [b] Yield refer to isolated compounds after column chromatography.

yield of **16** after 48 h at 90 °C (entry 5). Compared with acetate **2a** (Table 5, entry 1), the propargylic benzoate **2f** reacted sluggishly with norbornene **1a** to give **17** in 83% yield after 96 h at room temperature.



2f

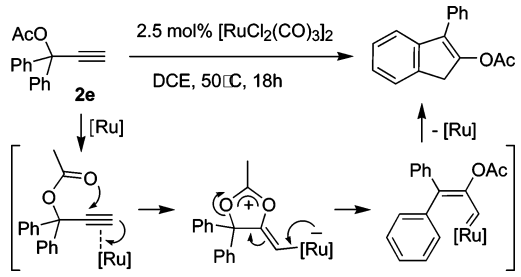


17

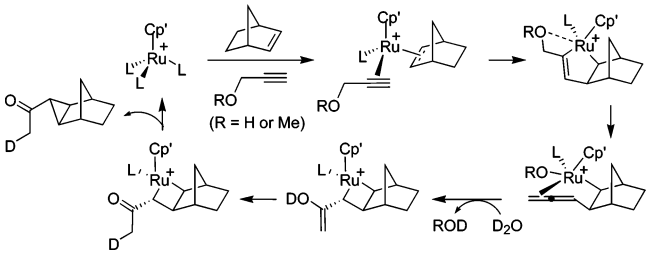
Mechanism Considerations. The first question addressed by the present cyclopropanation of bicyclic alkenes concerns the occurrence of ruthenium vinylcarbenoid intermediates. Indeed, these species generated from various propargylic carboxylates have been involved in transition-metal-catalyzed cyclopropanations.[9] Uemura reported the ruthenium-catalyzed cyclopropanation of electron-rich alkenes using propargylic carboxylates that involve ruthenium vinylcarbenoid species.[9a,b] However, in these cases, norbornene did not undergo the cyclopropanation. Among others, the formation of an indene derivative from alkyne **2e** strongly supports the formation of **2e**-derived vinyl ruthenacarbene which underwent an intramolecular insertion to the C−H bond at the ortho position of the phenyl ring (Scheme 4).

In contrast with the above observations, in the presence of $CpRuCl(PPh_3)_2$ instead of $[RuCl_2(CO)_3]_2$ alkyne **2e** reacted slugglishly (90 °C, 48 h) with norbornene **1a** to form the expected adduct **16** in 41% yield as the sole product (Table 5, entry 5). The same reaction performed in the absence of **1a** left **2e** unchanged. Moreover, the ROMP of these bicyclic alkenes which is expected in the presence of ruthenacarbenes[5] was never

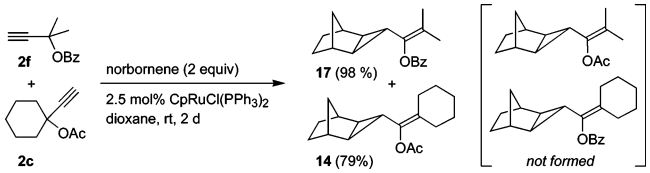
SCHEME 4. Proposed Mechanism by Uemura for the Formation of an Indene Derivative from Alkyne 2e



SCHEME 5. Proposed Mechanism by Takahashi for the Acetylcyclopropanation of Norbornene 1a



SCHEME 6. Attempted Crossover Reaction of Norbornene 1a with Propargylic Carboxylates 2c and 2f



observed under our conditions. The strikingly different pattern of reactivity makes such intermediates unlikely in the present work.

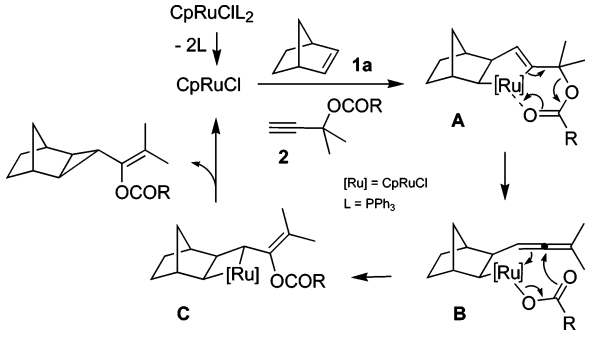
The mechanism rationale for the actual cyclopropanation is closely related to the mechanism of Takahashi using propargylic alcohols, although differences in reactivity profile (nature of the catalyst and of alkynes) and reaction conditions are notable. For instance, cationic ruthenium species with specific cyclopentadienyl ligand (see Scheme 1) and methanol as the solvent are crucial to promote the cyclopropanation and the hydroxyl group migration is likely to occur by intermolecular fashion since labeling experiments using MeOD + D_2O have shown that deuterium incorporation occurred at propargyglic carbon atom of the starting alkynol (Scheme 5).

To probe such an intermolecular transfer of acetate group when using propargylic acetates, the cyclopropanation of norbornene **1a** was performed at room temperature with an equimolar mixture of propargylic carboxylates **2c** and **2f** as competitive reactants. This experiment afforded selectively the cyclopropanes **14** and **17** in high yields without any crossover adducts (Scheme 6).

This result supports that the 1,2-carboxylate transfer occurs in an intramolecular fashion. The mechanism rationale proposed for the actual cyclopropanation involves a double intramolecular carboxylate transfer as depicted in Scheme 7.

The catalytic cycle starts with the formation of the coordinatively unsaturated CpRuCl which leads to the ruthenacyclopentene **A**. An intramolecular carboxylate group transfer generates the η^2-allene−ruthenium intermediate **B**. The second intramolecular transfer of the carboxylate at the central carbon

SCHEME 7. Mechanism Proposal for the Ruthenium-Catalyzed Cyclopropanation of Bicyclic Alkenes with Propargylic Carboxylates



of the η^2-allene forms the ruthenacyclobutane **C**. Reductive elimination releasing the cyclopropane adduct and the coordinatively unsaturated CpRuCl species completes the catalytic cycle.

Conclusion

An effective operationnally simple catalytic procedure based on CpRuCl(PPh$_3$)$_2$ as a mediator has been developed for the cyclopropanation of bridgehead bicyclic alkenes such as norbornenes or norbornadienes with propargylic carboxylates affording 1,2,3-trisubstituted vinylcyclopropanes as a single stereomer. The catalyst is tolerant of a variety of functional groups, including alcohols, ethers, ketones, esters, anhydrides, nitriles, halides, and sulfones, and the presence of air is not detrimental for the reaction. The catalyzed reaction proved also effective for the cyclopropanation of cyclobutenes affording bicyclo[2.1.0^{1,3}]pentanes. The conditions for this transformation have been optimized to provide a complementary method to the Uemura cyclopropanation which is not applicable to strained cyclic alkenes.

Experimental Section

Only a representative procedure and characterization of the product is described here. Full details can be found in the Supporting Information.

General Procedure for the Preparation of Vinylcyclopropane Products. Vinylcyclopropane 3a. CpRuCl(PPh$_3$)$_2$ (9.1 mg, 0.0125 mmol) and dioxane (2 mL) were placed in a flame-dried Schlenk flask. A solution of norbornene **1a** (70.5 mg, 0.75 mmol) and 2-methylbut-3-yn-2-yl acetate **2a** (63.1 mg, 0.5 mmol) in dioxane (2 mL) was added at once, and the mixture was stirred at room temperature for 6.5 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography over silica gel (AcOEt/hexanes 3/97) to afford 105 mg (0.475 mmol, 95%) of **3a** as a colorless oil: R_f (AcOEt/hexanes 1/19) 0.38; IR (neat) ν 2951, 2870, 1749, 1690, 1213 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.30 (br s, 2H), 2.11 (s, 3H), 1.77 (s, 3H), 1.62 (br t, J = 2.9 Hz, 1H), 1.50 (s, 3H), 1.42 (m, 2H), 1.21 (m, 2H), 0.99 (br d, J = 10.8 Hz, 1H), 0.88 (d, J = 2.9 Hz, 2H), 0.66 (d, J = 10.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1 (s), 141.0 (s), 119.3 (s), 35.6 (2 × d), 29.2 (2 × t), 28.1 (t), 22.3 (2 × d), 20.3 (q), 18.5 (q), 17.8 (q), 13.6 (d). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.17; H, 9.08.

Acknowledgment. This work was supported by the CNRS. Dr. Innocenzo De Riggi in our department is thanked for help with the NMR.

Supporting Information Available: Detailed procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060276A