The Journal of
Organic
Chemistry

VOLUME 57, NUMBER 22 OCTOBER 23, 1992

Communications

Reductive Cyclization of Ester-Containing Enynes with a Practical Titanocene Reagent. Synthesis of Bicyclic Cyclopentenones and Iminocyclopentenes

Robert B. Grossman and Stephen L. Buchwald*

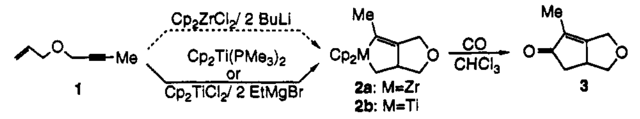
Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received July 17, 1992

Summary: The combination of Cp_2TiCl_2 with 2 equiv of EtMgBr provides an effective reagent for the reductive cyclization of enynes, including ester-containing enynes, to bicyclic titanacyclopentenes. These metallacycles may then be transformed into bicyclic cyclopentenones or iminocyclopentenes in good yields by reaction with CO or an isocyanide, respectively.

The group 4 metallocene-mediated reductive cyclization of enynes[1-3] is a valuable method for the construction of mono- and bicyclic carbocycles by hydrolysis[1] or carbonylation[2,3] of the intermediate metallacycles. The original reaction procedure for intramolecular reductive cyclization, developed by Nugent,[1a] involved the reduction of Cp_2TiCl_2 with Na/Hg and $PhPMe_2$ in the presence of the enyne. Subsequently, Negishi demonstrated that the corresponding zirconium-mediated reaction could be achieved using Cp_2ZrCl_2 that was reduced with Mg and $HgCl_2$,[2a] a reagent combination that was first developed by Farona.[4] This procedure was made much simpler operationally when Negishi introduced the use of 2 equiv of *n*-BuLi as the reducing agent instead of $Mg/HgCl_2$.[2b] However, it still suffered the drawback of lack of tolerance for polar functionalities such as esters. We thought that a method for generating a reduced titanocene reagent that was as simple as the $Cp_2ZrCl_2/2$ *n*-BuLi method for generation of "zirconocene" might have considerable synthetic value, as the substantially reduced oxophilicity of titanium relative to zirconium[5] might allow substrates with more polar functional groups to be used in the cyclization reaction. In this initial report, we demonstrate that the combination of Cp_2TiCl_2 with EtMgBr provides an effective reagent for the reductive cyclization of enynes, including those containing esters, to bicyclic titanacyclopentenes. These metallacycles may then be transformed into cyclopentenones[6] or iminocyclopentenes[7] in good yields by reaction with CO or an isocyanide, respectively.

Scheme I



Our work in this area began when we found that only small amounts of **2a** were obtained upon reaction of enyne **1** with the $Cp_2ZrCl_2/2$ *n*-BuLi reagent.[8] Addition of **1** to

---

[1] (a) Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. (b) RajanBabu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128. (c) Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788. (d) Parshall, G. W.; Nugent, W. A.; Chan, D. M.-T.; Tam, W. *Pure Appl. Chem.* **1985**, *57*, 1809.

[2] (a) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. (b) Negishi, E.-i.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829. (c) Negishi, E.-i.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.

[3] Other zirconacyclopentene carbonylations: (a) Swanson, D. R.; Rousset, C. J.; Negishi, E.-i.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521. (b) Wender, P. A.; McDonald, F. E. *Tetrahedron Lett.* **1990**, *31*, 3691. (c) Agnel, G.; Negishi, E.-i. *J. Am. Chem. Soc.* **1991**, *113*, 7424. (d) Agnel, G.; Owczarczyk, Z.; Negishi, E.-i. *Tetrahedron Lett.* **1992**, *33*, 1543. (e) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Org. Chem.* **1992**, *57*, 3519.

[4] (a) Thanedar, S.; Farona, M. F. *J. Organomet. Chem.* **1982**, *235*, 65. (b) Sabade, M. B.; Farona, M. F. *J. Organomet. Chem.* **1986**, *310*, 311.

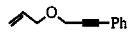
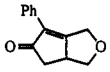
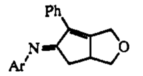
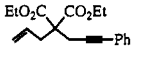
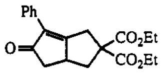
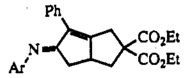
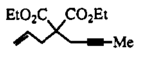
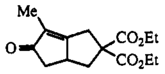
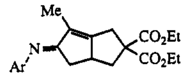
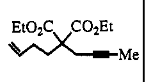
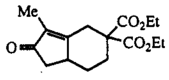
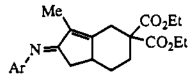
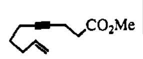
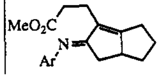
[5] (a) Berk, S. C.; Kreutzer, K. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 5093. (b) Berk, S. C.; Buchwald, S. L. *J. Org. Chem.* **1992**, *57*, 3751.

[6] Other metal-mediated methods for the synthesis of cyclopentenones: (a) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (b) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (c) Schore, N. E. *Org. React.* **1991**, *40*, 1. (d) Pearson, A. J.; Dubbert, R. A. *J. Chem. Soc., Chem. Commun.* **1991**, 202. (e) Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1941. (f) Oppolzer, W.; Xu, J.-Z.; Stone, C. *Helv. Chim. Acta* **1991**, *74*, 465.

[7] Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 1286.

0022-3263/92/1957-5803$03.00/0 © 1992 American Chemical Society

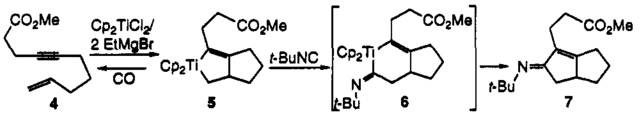
Table I

substrate[a]	cyclopentenone	yield[a]	iminocyclopentene (Ar = 2,6-$Me_2C_6H_3$)	yield[a]
		49%[b]		63%
		58%		65%
		58%		81%
		58%		86%
	no ketone obtained			67%

[a] All compounds were fully characterized by ^1H NMR, ^{13}C NMR, and IR spectroscopy. Satisfactory elemental analyses or high-resolution mass spectra were obtained for new compounds. Yields are isolated yield of >95% pure product. [b] Isolated with an additional 7% of one diastereomer of the saturated ketone, identified spectroscopically.

a solution of $Cp_2Ti(PMe_3)_2$[9] in C_6D_6, however, gave clean formation of **2b** (Scheme I).[10] We desired a more synthetically practical reagent than $Cp_2Ti(PMe_3)_2$, though, so we decided to test the ability of Cp_2TiCl_2/2 EtMgBr to effect the transformation as well. Addition of 2 equiv of EtMgBr to a suspension of Cp_2TiCl_2 in THF at -78 °C, followed by addition of a slight deficiency of **1**, warming to room temperature, and stirring for >3 h, again resulted in clean formation of **2b**, as judged by ^1H NMR.[11] As this titanocene reagent system seemed to be more tolerant of oxygen functionality than the zirconium system, we decided to see if ester-containing enynes could be cyclized.[12] To our delight, esters did not interfere with the reaction, and enynes with ester substituents were cyclized to the corresponding metallacycles in good yields.[13] Some of the enynes which were successfully cyclized are shown in the first column of Table I. Note that both 1,6- and 1,7-enynes could be cyclized, in contrast to what was observed in the $Cp_2Ti(PMe_3)_2$-mediated cyclization of enones and ynones.[14]

Scheme II



4 5 6 7

To introduce a maximum level of functionality, we next decided to transform the titanacycles into cyclopentenones, in analogy to the well-established transformation of zirconacyclopentenes into cyclopentenones.[2,3] To our knowledge, only a single example of the carbonylation of a titanacyclopentene, with no experimental details, had appeared previously in the literature.[1d,15] Carbonylation of **2b** in THF proceeded to give none of the desired cyclopentenone **3**, but in chloroform the reaction proceeded to give **3** (Scheme I) in good yield as determined by ^1H NMR against an internal standard. Other titanacycles, prepared in situ by the Cp_2TiCl_2/2 EtMgBr method, could also be carbonylated to give the corresponding highly functionalized cyclopentenones. These were isolated and purified in good yields (Table I, column 2),[16] although isolation of **3** itself in good yield proved difficult.

Inexplicably, the titanacycle **5** derived from substrate **4** did not give the expected cyclopentenone upon carbonylation; instead, **4** was observed as the only organic product (Scheme II). The titanacycle was relatively stable to chloroform in a control experiment, so oxidative regeneration of enyne was probably induced by CO. Although we were unable to obtain the desired ketone, we felt that we might be able to obtain a highly functionalized product in other ways, for example, by isonitrile insertion to give the iminoacyl compound[17a] **6** followed by iodinolysis to give the iodonitrile.[18] Accordingly, addition of *tert*-butyl isocyanide to **5** in C_6D_6 gave a product whose ^1H NMR spectrum was consistent with **6**, but a minor product, which displayed no resonances attributable to a Cp_2Ti moiety, was also observed. This species, which gradually became more abundant at the expense of **6** until it was the only product in the reaction mixture, was determined to be iminocyclopentene **7**, the product of reductive elimination of "Cp_2Ti" from **6**.[17] Other isocyanides and other titanacycles gave similar results.

A nickel-mediated synthesis of iminocyclopentenes from enynes and isonitriles had been reported by Tamao,[7] but this was the first example of this reaction in an early transition-metal system. Isolation and purification of the iminocyclopentenes were possible when 2,6-dimethylphenyl isocyanide was used as the isocyanide;[7] this reaction proceeded best in chloroform at room temperature.[16] The iminocyclopentenes that have been isolated to date are

---

[8] It has very recently been reported that treatment of allyl alkyl ethers with Cp_2ZrCl_2/2 *n*-BuLi results in formation of an allylzirconium alkoxide via β-alkoxy elimination.[8a] However, enynes with silyloxy groups in the allylic and propargylic positions have been successfully cyclized by others.[1b,8b] Several dipropargyl ethers have also been cyclized successfully with the Cp_2ZrCl_2/2 *n*-BuLi reagent.[1d,8c] (a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295. (b) Lund, E. C.; Livinghouse, T. *J. Org. Chem.* **1989**, *54*, 4487. (c) Mohamadi, F.; Spees, M. M. *Organometallics* **1992**, *11*, 1398.

[9] Binger, P.; Müller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krüger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035.

[10] Titanacyclopentadienes and alkyne complexes of titanocene have been synthesized in a similar manner: (a) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 394. (b) Alt, H. G.; Engelhardt, H. E.; Rausch, M. D.; Kool, L. B. *J. Am. Chem. Soc.* **1985**, *107*, 3717. (c) Shur, V. B.; Burlakov, V. V.; Vol'pin, M. E. *J. Organomet. Chem.* **1988**, *347*, 77. (d) Burlakov, V. V.; Rosenthal, U.; Petrovskii, P. V.; Shur, V. B.; Vol'pin, M. E. *Metalloorg. Khim.* **1988**, *1*, 953.

[11] *n*-Butyllithium may also be used, although the efficiency of cyclization is not as good for some substrates. Also, at least for some substrates, unreacted starting material is observed if the cyclization is not allowed to proceed for at least three hours at room temperature, resulting in lower yields of products. This in contrast to the analogous zirconium-mediated reaction, which is usually complete by the time the reaction mixture warms to room temperature.

[12] (a) Wender has reported the zirconium-mediated cyclization of an enyne containing a *tert*-butyl ester in 25–29% yield.[3b] (b) Treatment of $Cp_2Ti(CO)_2$ with $MeO_2CC{\equiv}CCO_2Me$ has been reported to give the corresponding metallacycle. Demerseman, B.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1981**, 665. (c) For a very recent example of a reaction of an ester-containing diyne with a low-valent titanium complex, see: Wilson, A. M.; Waldman, T. E.; Rheingold, A. L.; Ernst, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 6252.

[13] Reaction of the second substrate in Table I with Cp_2ZrCl_2/2*n*-BuLi gave a complex mixture of unidentified products.

[14] Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1990**, 1684.

[15] The carbonylation of titanacyclopentanes has been reported rarely, and then only in highly substrate-dependent yields. (a) McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6529. (b) Grubbs, R. H.; Miyashita, A. *J. Chem. Soc., Chem. Commun.* **1977**, 864.

[16] Full experimental details are given in the supplementary material.

[17] (a) Durfee, L. D.; Rothwell, I. P. *Chem. Rev.* **1988**, *88*, 1059. (b) Rothwell has seen similar chemistry in the reaction of *t*-BuNC with the isoelectronic dialkyltitanium complex $(RO)_2Ti(CH_2Ph)_2$ to give the η^2-imine complex $(RO)_2Ti[\eta^2\text{-}t\text{-}BuN{=}C(CH_2Ph)_2]$. Durfee, L. D.; Hill, J. E.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1990**, *9*, 75. Also see: (c) Dennehy, R. D.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1992**, 35.

[18] Cuny, G. D.; Gutiérrez, A.; Buchwald, S. L. *Organometallics* **1991**, *10*, 537.

shown in the third column of Table I.[19]

In conclusion, we have developed a simple procedure for the titanocene-mediated reductive cyclization of enynes. In contrast to the analogous procedure using the zirconium reagent, this procedure is tolerant of ester functionality in the substrate. We have also shown that in general the product titanacycles may be converted into highly functionalized cyclopentenones in good yield without isolation of any air-sensitive compounds. We have also discovered the first early transition-metal-mediated synthesis of iminocyclopentenes, which are easily prepared from the corresponding titanacycles (prepared in situ) and an isocyanide. We are continuing to investigate the scope of these reactions, with special regard to the functional group and substrate skeleton compatibility of the reaction. We are also conducting a mechanistic study of the isocyanide insertion and reductive elimination reaction,[20] and we are exploring conditions under which the reductive cyclization and "iminylation" of enynes may be rendered catalytic in titanium.

Acknowledgment. We thank the National Institutes of Health for support of this work. S.L.B. is a fellow of the Alfred P. Sloan foundation and a Camille and Henry Dreyfus Teacher-Scholar. We also thank Professor K. Tamao (Kyoto University) for helpful suggestions.

Supplementary Material Available: Detailed experimental procedures for the preparation of previously unreported substrates and all products in Table I and spectroscopic characterization of these compounds (23 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

[19] Tamao has shown that iminocyclopentenes are easily converted into the corresponding cyclopentenones.[7]

[20] Cámpora, J.; Buchwald, S. L. Unpublished results.

Stereochemistry in Carbenoid Formation by Bromine/Lithium and Bromine/Zinc Exchange Reactions of 1,1-Dibromoalkenes: Higher Reactivity of the Sterically More Hindered Bromine Atom

Toshiro Harada,* Takeshi Katsuhira, and Akira Oku*

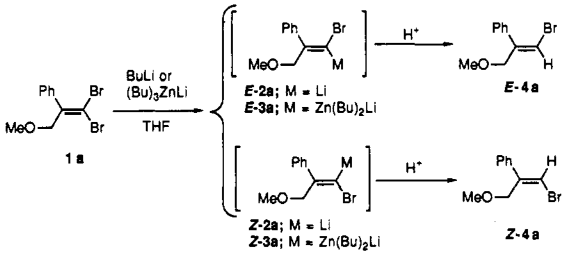
Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606, Japan

Received July 21, 1992

Summary: Both lithium and zincate carbenoids ($R^1(R^2)C{=}C(Br)M$; M = Li and $Zn(Bu)_2Li$) generated by the halogen/metal exchange reaction of 1,1-dibromoalkene **1** with BuLi and $(Bu)_3ZnLi$, respectively, are configurationally stable at low temperatures, but in the presence of excess **1**, the lithium carbenoids undergo facile isomerization at the carbenoid carbons. Under kinetically controlled conditions, both the Br/Li and Br/Zn exchange reactions take place preferentially at the sterically more hindered bromine atom of **1**.

α-Haloorganometallic compounds (metal carbenoids) possessing both nucleophilic and electrophilic reactivities are versatile intermediates in carbon-carbon bond-forming reactions.[1,2] The tetravalent nature of carbenoids, if their stereochemistry is properly controlled, may endow these reactions with a high level of stereoselectivity, which is difficult to attain by using divalent free carbenes. The halogen/metal exchange reaction of *gem*-dihalo compounds is one of the most efficient and frequently employed methods of generating carbenoids. However, factors governing the stereochemistry of the reaction have not been fully elucidated.[3] We report herein an investigation of the stereochemistry in carbenoid formation by the Br/Li and Br/Zn exchange reaction of 1,1-dibromoalkenes. Observation of selective reactions at the sterically more hindered bromine atom under kinetic conditions provides information concerning the mechanism of carbenoid formation by the halogen/metal exchange reactions.

Addition of a THF solution of dibromoalkene **1a** to a THF/hexane solution of BuLi (2 equiv) at −94 °C during a 90-s period followed by immediate treatment of the resulting lithium carbenoid **2a** with AcOH/THF gave a 73:27 mixture of (*E*)- and (*Z*)-**4a** in 84% yield (eq 1).[4] Carbenoid



(1)

2a is configurationally stable under these conditions; the *E*/*Z* ratio did not change when the above reaction mixture

---

[1] (a) Regitz, M. Carbene (Carbenoid). In Houben-Weyl, Methoden der Organische Chemie; Georg Thieme: Verlag 1989; Teil 12a,b. (b) Moss, R. A.; Jones, M., Jr. *Carbenes*; Wiley: New York, 1975; Vols. 1 and 2. (c) Kirmse, W. Carbene Chemistry, 2nd ed.; Academic Press: New York, 1971.

[2] (a) Duraisamy, M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1984**, *106*, 5035. (b) Warner, P. M.; Chang, S. C.; Koszewski, N. J. *Tetrahedron Lett.* **1985**, *26*, 5371. (c) Rachon, J.; Goedken, V.; Walborsky, H. M. *J. Am. Chem. Soc.* **1986**, *108*, 7435. (d) Harada, T.; Hattori, K., Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6035.

[3] For stereochemical aspects of carbenoid generation by halogen/metal exchange reaction, see: (a) Seyferth, D.; Lambert, R. L., Jr.; Massol, M. *J. Organomet. Chem.* **1975**, *88*, 255. (b) Kitatani, K.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2158. (c) Zwiefel, G.; Lewis, W.; On, H. P. *J. Am. Chem. Soc.* **1979**, *101*, 5102. (d) Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2095.

[4] Unless otherwise noted, *E*/*Z* ratios and yields of products were determined by capillary GC. All new compounds showed satisfactory spectral and/or analytical data. Stereochemical determination of products derived from **1a**–**d** is based on NOESY analyses.