Pergamon

Tetrahedron Letters 40 (1999) 3217–3220

TETRAHEDRON LETTERS

Formation of a Functionalized Cyclobutane Ring Through the Reaction of γ,γ-Dialkoxyallylic Zirconium Species with Acrylamide

Hisanaka Ito, Azusa Sato and Takeo Taguchi*

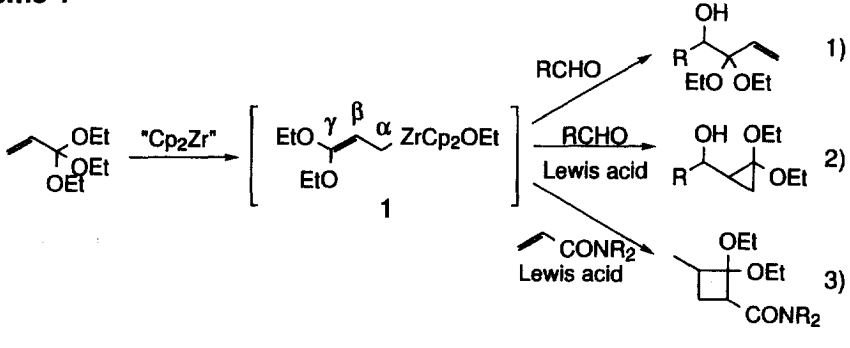
Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 27 January 1999; revised 24 February 1999; accepted 26 February 1999

Abstract: The functionalized cyclobutane derivatives could be obtained by the reaction of γ,γ-dialkoxyallylic zirconium species with acrylamide.

Allylic organometallics play an important role in construction of the carbon-carbon bond in organic synthesis.[1] It is well known that allylic organometallics react with carbonyl compounds at the α or γ position to give the homoallylic alcohol derivatives. Recently, we have been studying the development of novel reactions using γ,γ-dialkoxy allylic zirconium species **1**,[2] which can be easily prepared from acrylic acid ortho ester with zirconocene-butene complex ("Cp_2Zr")[3] through the formation of zirconacyclopropane and the following β-elimination of the alkoxyl group.[4] This species has two reactive sites: one is the allylic zirconium and the other is the ketene dialkyl acetal. For example, in the absence of a Lewis acid, this zirconium species **1** reacted with the carbonyl compound at the γ-position as an α,β-unsaturated acyl anion equivalent (eq. 1, Scheme 1).[2a] On the other hand, under the Lewis acid-promoted conditions, *gem*-dialkoxycyclopropane derivatives were exclusively formed (eq. 2, Scheme 1).[2b] The reaction pathway for the formation of the cyclopropane derivative possibly involves the initial addition of ketene dialkyl acetal (β-position of **1**) to the carbonyl compound followed by cyclization of the resulting alkyl zirconium.[5] Thus, under the reaction conditions, the reactivity of the ketene dialkyl acetal moiety overcomes that of the allylic zirconium character. Following these results, we found an interesting reaction of **1** with α,β-unsaturated carboxylic acid derivatives. We report herein the reaction of γ,γ-dialkoxyallylic zirconium species with α,β-unsaturated amide to form the functionalized cyclobutane derivatives (eq. 3, Scheme 1).

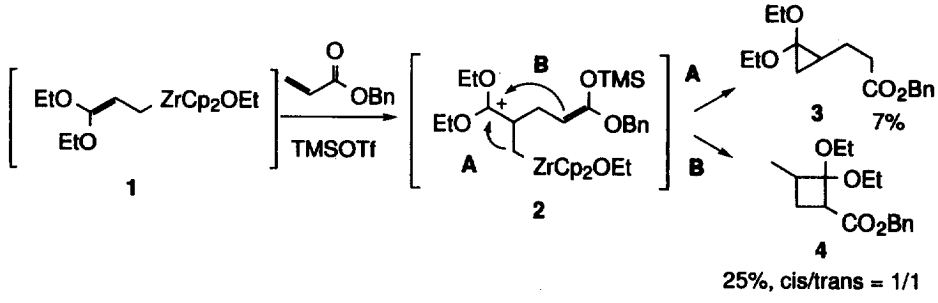
Scheme 1



0040-4039/99/$ - see front matter
PII: S0040-4039(99)00470-0

We investigated the reaction of γ,γ-diethoxyallylic zirconium species **1** with benzyl acrylate in the presence of trimethylsilyl triflate (TMSOTf). Based on our previous report, we expected that this reaction would proceed through 1,4-addition of γ,γ-diethoxyallylic zirconium species **1** to form the cyclopropane derivative **3**. Although the addition reaction did proceed, we obtained a mixture of cyclopropane derivative **3** and cyclobutane derivative **4** (Scheme 2).[6] This result obtained with α,β-unsaturated ester would be explained as follows. In the presence of TMSOTf, γ,γ-diethoxyallylic zirconium species **1** reacts with benzyl acrylate at the β-position and oxonium intermediate **2** should be formed. This intermediate has two nucleophilic sites, one is the alkyl zirconium group[2b] and the other is the ketene silyl acetal group,[7] and each reactive site reacts competitively to the oxonium ion.

Scheme 2



The above-mentioned observation led us to the development of the highly selective formation of the cyclopropane and cyclobutane derivatives, respectively. At first, we surveyed the effective conditions for the formation of cyclobutane derivatives through path **B**.[8] We thought that an increase in the electron density of the ketene acetal moiety in the intermediate **2** by replacing one oxygen atom with a nitrogen atom makes path **B** favorable. Therefore, as the substrate we adopted the acryl amide instead of ester.

The results of the reaction of **1** with acryl amide derivatives in the presence of TMSOTf are shown in Table 1.[9] As expected, the reaction of **1** with *N*,*N*-dimethyl acrylamide smoothly proceeded to give cyclobutane derivative **5** exclusively in moderate yield (entry 1). In this reaction, the cis isomer was predominantly obtained.[10] An improvement in the diastereoselectivity of compound **5** could be achieved by employing a more bulky substituent at the nitrogen atom ($R^1 = R^2$ = Bn or *i*-Pr, entries 2,3). The ratio of cyclobutane **5** and cyclopropane **6** was found to be affected by the electron density on the nitrogen atom. That is, when the electron density of the nitrogen atom was lowered by connecting to an aromatic ring, in the case of *N*,*N*-diphenyl acrylamide, cyclopropane derivative **6** was obtained as a major product (entry 5). These cyclobutane derivatives were unstable under mild acidic conditions such as silica gel column chromatography. The reaction is precluded by the substituent on the acryloyl moiety (crotonamide and methacrylamide) under these conditions.

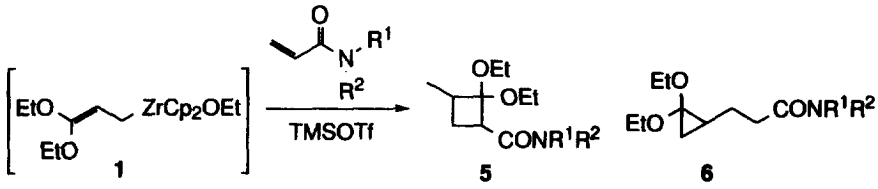


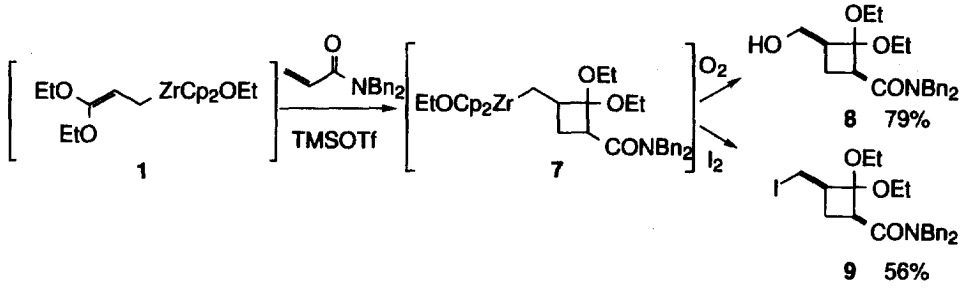
Table 1.

Entry	Amide	Yield (%)[a]	5 / 6[b]	5 : cis / trans[b,c]
1	$R^1 = R^2 = Me$	54	> 95 : 5	82 : 18
2	$R^1 = R^2 = Bn$	83	> 95 : 5	> 95 : 5
3	$R^1 = R^2 = i\text{-}Pr$	56	> 95 : 5	> 95 : 5
4	$R^1 = Me$, $R^2 = Ph$	85	> 95 : 5	83 : 17
5	$R^1 = R^2 = Ph$	61	25 : 75	85 : 15

a) Isolated yield. b) Ratio was determined by 300 MHz ^1H NMR. c) The stereochemistry was determined by NOESY spectra.

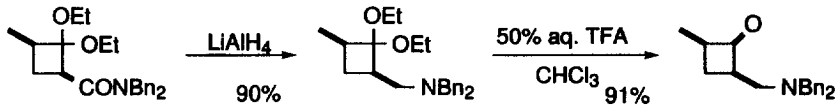
In the cyclobutane-forming reaction, alkylzirconium **7** should be involved as an intermediate, which is clearly supported by trapping with electrophiles. For example, introduction of oxgen gas or iodine to the reaction mixture before aqueous workup gave hydroxyl derivative **8** in 79% yield and iodide derivative **9** in 56% yield, respectively (Scheme 3).

Scheme 3



An example of the functional conversion of cyclobutane carboxamide **5** is shown in Scheme 4. By lithiumaluminum hydride reduction, amide derivative **5** was smoothly converted to amine derivative **10** in good yield (90%). Deprotection of the ketal moiety in compound **10** to ketone **11** could be achieved by treatment with aqueous 50% trifluoroacetic acid in chloroform with high yield (91%).

Scheme 4



5 10 11

We have described here a new preparative method of functionalized cyclobutane derivatives by the reaction of γ,γ-dialkoxyallylic zirconium species with acrylamide. Preparation of biologically active natural compounds through the presented reaction is currently being carried out.

References and Notes

1. For reviews on preparation and reactions of allylic organometallic reagents, see: a) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. c) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. d) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.1. e) Yamamoto, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.2. f) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
2. a) Ito, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 5829. b) Ito, H.; Kuroi, H.; Ding, H.; Taguchi, T. *J. Am. Chem. Soc.* **1998**, *120*, 6623.
3. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
4. a) Ito, H.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1295. b) Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* **1995**, *51*, 4507.
5. Examples for the cyclopropanation reaction of monoalkoxyallylic metals with carbonyl compounds. a) Hoffmann, R. W.; Metternich, R. *Liebigs Ann. Chem.* **1985**, 2390. b) Barrett, A. G. M.; Seefeld, M. A. *Tetrahedron* **1993**, *49*, 7857. c) Marshall, J. A.; Jablonowski, J. A.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 7825.
6. New compounds have been satisfactorily characterized.
7. For reviews on the reaction of ketene dialkylacetal with electron deficient olefins to form the cyclobutane derivatives, see: a) Baldwin, J. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 2.1. b) Scheeren, J. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 71. See also: c) Ahmad, S. *Tetrahedron Lett.* **1991**, *32*, 6997. d) Liu, H.-J.; Chan, W.-H. *Can. J. Chem.* **1979**, *57*, 708.
8. The selective formation of cyclopropane derivatives through path A is discussed in the following paper in this issue.
9. Typical experimental procedure is as follows: A solution of triethyl orthoacrylate (174 mg, 1mmol) in toluene (2 mL) was added to a solution of "Cp_2Zr" (1.2 mmol), adjusted from Cp_2ZrCl_2 with n-BuLi[3,4] at -78 °C. After stirring for 3 h at room temperature, a solution of *N,N*-dibenzylacrylamide (300 mg, 1.2 mmol) in toluene (2 mL) followed by TMSOTf (0.21 mL, 1.1 mmol) was added at -78 °C and stirred at room temperature for 2 h. After neutral workup (NH_4Cl aq.) and purification with neutral silica gel column chromatography, the product **5** was obtained (314 mg, 0.83 mmol, 83%).
10. The stereochemistry was assigned by NOESY spectra.