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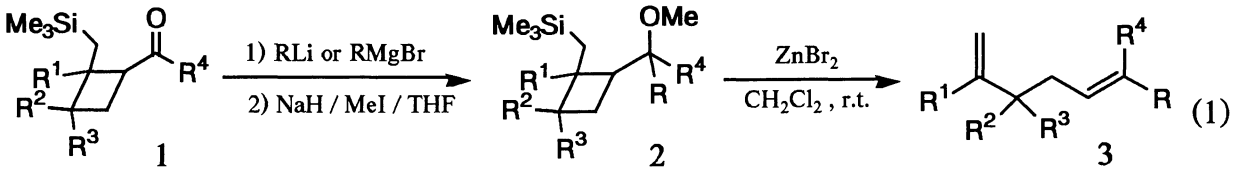
$ZnBr_2$-catalyzed Stereospecific 1,4-Elimination of 1-Methoxymethyl-2-(trimethylsilylmethyl)-cyclobutanes. Stereoselective Preparation of 1,1,5-Trisubstituted (*E*)- and (*Z*)-1,5-Dienes

Tooru FUJIWARA, Atsushi SUDA, and Takeshi TAKEDA*
Department of Applied Chemistry, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184

The stereoselective addition of alkylmetals to 2-(trimethylsilylmethyl)-1-cyclobutyl ketones and the $ZnBr_2$-catalyzed stereospecific ring-opening reaction of resulting 1-methoxymethyl-2-(trimethylsilylmethyl)cyclobutanes gave 1,1,5-trisubstituted 1,5-dienes with high stereoselectivity.

It is well known that the 1,4-elimination is a useful method for the preparation of unsaturated compounds such as 1,3-dienes, and various reactions have been developed.[1] Since the carbon-carbon bond cleavage proceeds stereospecifically and olefinic bonds are introduced regio- and stereoselectively, the 1,4-elimination accompaning ring cleavage is of special interest.[2] Recently we showed that the triethylaluminum-catalyzed ring-opening reaction of 2-(trimethylsilylmethyl)-1-cyclobutyl ketones (**1**) gave (*Z*)-enol trimethylsilyl ethers.[3] These results prompted us to explore new methods for the stereoselective preparation of trisubstituted olefins using the cyclobutyl ketones (**1**). In this communication, we wish to report the stereoselective synthesis of 1,5-hexadienes (**3**) by $ZnBr_2$-catalyzed stereospecific 1,4-elimination of 1-methoxymethyl-2-(trimethylsilyl-methyl)cyclobutanes (**2**), which were easily synthesized by the reaction of **1** with organolithium or -magnesium reagents in THF or ether (PhLi / -20 – 0 °C or RMgBr / 0 °C) followed by methylation (NaH / MeI / THF / 0 °C – room temperature) (Eq. 1).



(1)

First we examined the reaction using 2-phenylcyclobutyl ketones (*trans*- and *cis*-**1g**) (Eq. 2). Starting from *trans*-**1g**, the two diastereoisomers of methyl ethers (*trans*-**2g-1** and *trans*-**2g-1'**) were isolated. Treatment of these methyl ethers with $ZnBr_2$ in CH_2Cl_2 at room temperature gave the (*E*)- and (*Z*)-1,5-dienes (**3g**), respectively. Two methyl ethers were also produced by methylation of the cyclobutylcarbinol prepared from *cis*-**1g**. However, one diastereomer decomposed to give 1,5-diene during work-up or purification procedure. As a result, the methyl ether (*cis*-**2g-1**) and (*E*)-**3g** were isolated. It was also found that the 1,4-elimination of *cis*-**2g-1** gave (*Z*)-**3g** stereoselectively. All these results suggest that the $ZnBr_2$-promoted 1,4-elimination of **2** with the cleavage of cyclobutane ring proceeds stereospecifically. Since it is reasonable to assume that the present ring-opening reaction proceeds via a most stable six-membered cyclic transition state (Eq. 3), each methyl ether (**2g**) would have the stereochemistry shown in the equation.

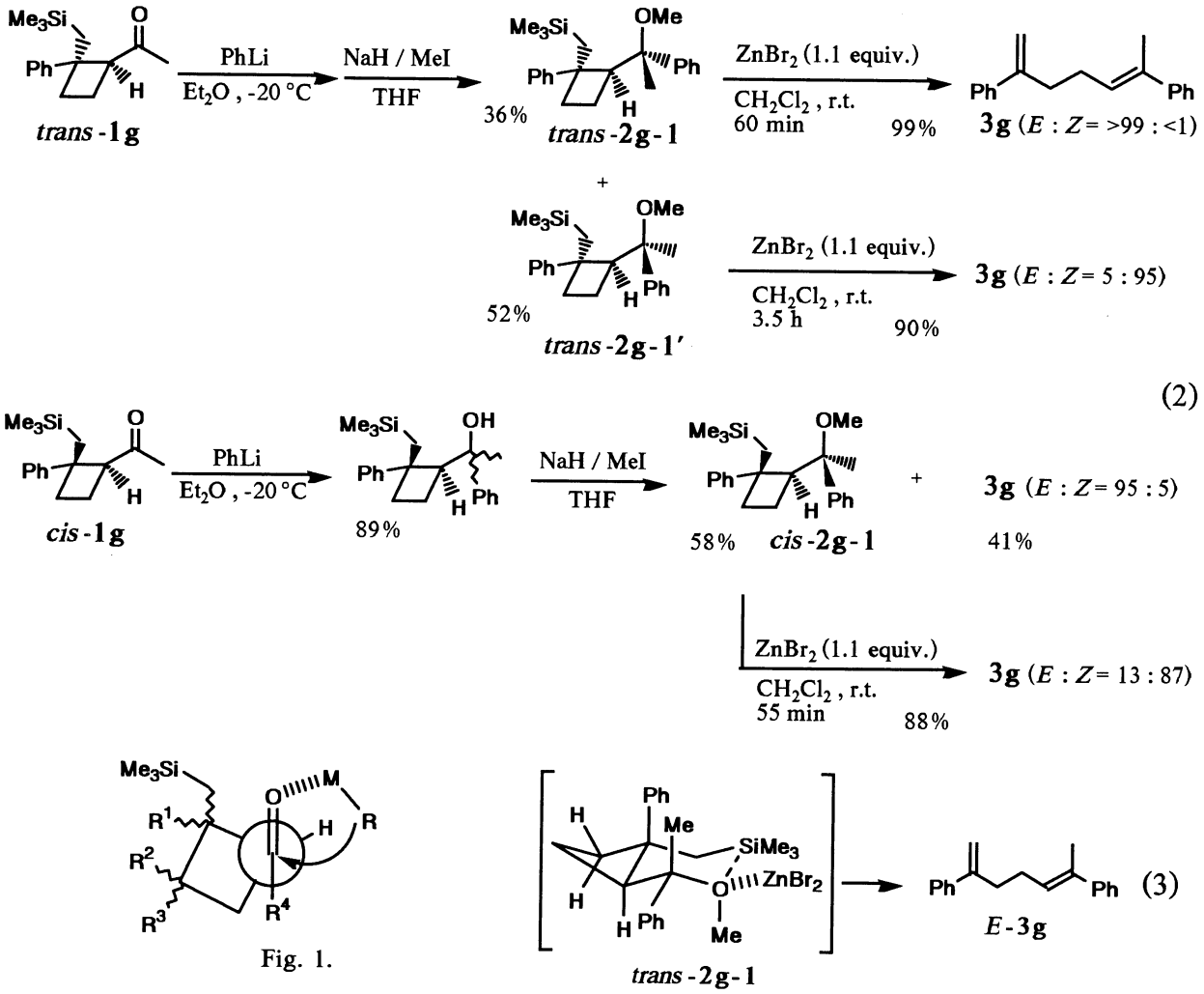
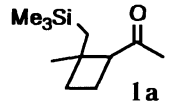
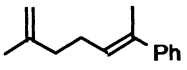
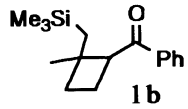
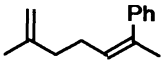
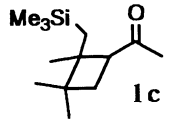
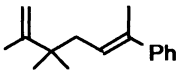
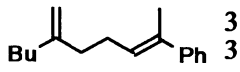
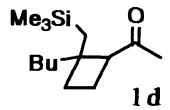
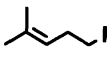
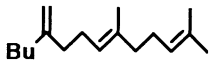
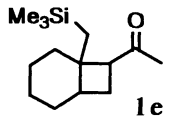
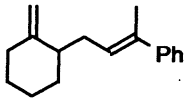
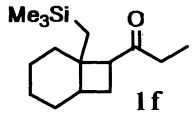
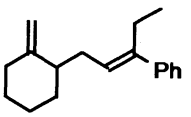


Fig. 1.

Then the various cyclobutanes (**2**) were synthesized from the diastereoisomeric mixtures of 2-alkylcyclobutyl ketones (**1**), and their transformation to the 1,5-dienes (**3**) was examined. As shown in the Table, the 1,4-elimination of **2** proceeded using only a catalytic amount of $ZnBr_2$. The diene (**3e-1**) was also obtained in good yield when the corresponding alcohol was used (Entry 10). What is striking is a fact that all these reactions gave trisubstituted olefins with high stereoselectivity without any procedure for separation of diastereoisomers. It was found that the configuration of the major products were ones in which the substituent originated from the organometallic species occupies a *trans* position.[4] The stereoselectivity of the present reaction is well explained by the stereoselective attack of organometallic species from the less hindered side of the conformer depicted in Fig. 1. In such a conformation, repulsions between the carbonyl group coordinated with organometallic species and the substituents on the cyclobutane ring are minimized. However, the stereochemistry observed in the reaction of the phenyl group substituted cyclobutanes (**1g**) has not been rationalized.

A typical experimental procedure is as follows: To a CH_2Cl_2 (1 ml) suspension of $ZnBr_2$ (11 mg, 0.05 mmol) was added a CH_2Cl_2 (1.5 ml) solution of 1-(1-methoxy-1-phenylethyl)-2-methyl-2-(trimethylsilylmethyl)-cyclobutane (**2a**) (145 mg, 0.5 mmol) at room temperature. After being stirred for 64 min, the reaction mixture was quenched by addition of saturated $NaHCO_3$ aqueous solution. The organic layer was extracted with CH_2Cl_2, and the extract was dried over Na_2SO_4. After removal of the solvent, the residue was purified by

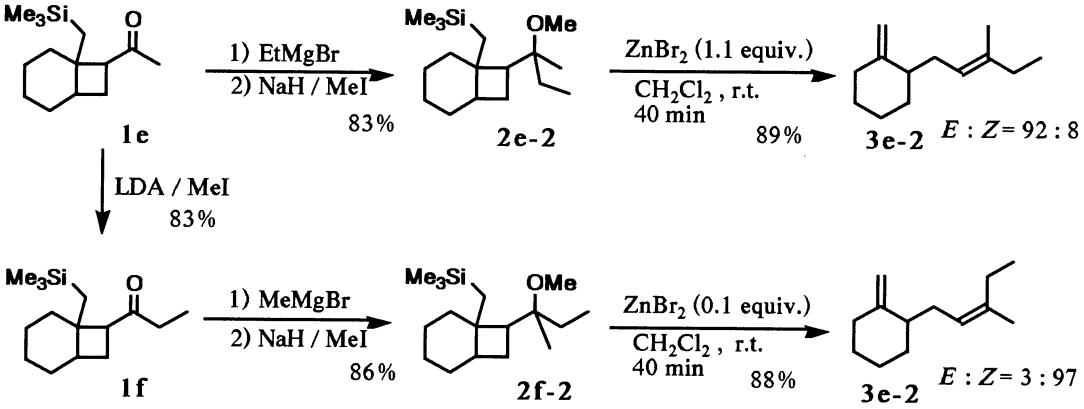
Table 1. Ring opening reaction of 1-methoxymethyl-2-(trimethylsilylmethyl)cyclobutanes (2)[a]

Entry	Cyclobutyl ketone (1)	PhLi or RMgBr (equiv.)	2[b,c] (Yield/%)	$ZnBr_2$ (equiv.)	Time min	Product (3)[b] (Yield/%)	$E:Z$[d]
1	 1a	PhLi (1.5)	2a (89)[e]	1.1	60		3a (94) 92 : 8
2				0.1	64		3a (95) 94 : 6
3	 1b	MeMgBr (1.5)	2b (97)[e]	1.1	90		3a (75) 3 : 97
4	 1c	PhLi (1.2)	2c (91)[f]	1.1	66		3c (86) 93 : 7
5				0.1	61		3c (91) 94 : 6
6		PhLi (2)	2d-1 (73)[f]	1.1	40		3d-1 (87) 93 : 7
7				0.1	64		3d-1 (91) 95 : 5
8	 1d	 (2)	2d-2 (73)[f]	0.1	80		3d-2 (84) 92 : 8[g]
9	 1e	PhLi (1.5)	2e-1 (84)[e]	1.1	60		3e-1 (95) 96 : 4
10			h) (89)[e]	1.1	90		3e-1 (85) 94 : 6
11				0.1	1200		3e-1 (83) 94 : 6
12[i]	 1f	PhLi (1.5)	2f-1 (85)[e]	1.1	60		3f-1 (94) 96 : 4

a) All reactions were performed with the same procedure as described in the text, unless otherwise noted. b) The structures of these compounds were supported by IR and NMR spectra. c) Overall yield from 1. d) Determined by NMR spectra. e) Ether was used as a solvent. f) THF was used as a solvent. g) Determined by capillary GLC analysis (SUPELCOWAX 10). h) 8-(1-Hydroxy-1-phenylethyl)-1-(trimethylsilylmethyl)-bicyclo[4.2.0]-octane. i) The starting material (1f) was prepared by methylation (MeI / 0 °C) of lithium enolate of 1e (LDA / THF / -78 – 0 °C) in 83% yield.

preparative TLC(hexane) and 2-methyl-6-phenyl-1,5-heptadiene (**3a**) (88 mg, 95%) was isolated. The stereoisomeric ratio (*E*: *Z*= 94 : 6) was determined by NMR spectrum.

Considering the facts that the nucleophilic attack of organometals to cyclobutyl ketones (**1**) is stereoselective and the 1,4-elimination of methyl ethers (**2**) is stereospecific, the both (*E*)- and (*Z*)-1,5-dienes (**3**) can be prepared by the present reaction as demonstrated in the following scheme.[5)]



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3) T. Fujiwara, A. Suda, and T. Takeda, *Chem. Lett.*, **1991**, 1619.

4) The configuration of the phenyl group substituted olefins was determined on the basis of their chemical shifts of vinyl protons. The configuration of **3e-2** was determined by the comparison of its NMR spectra with that of an authentic sample prepared by the allylation of cyclohexanone enolate followed by the Peterson olefination using (trimethylsilylmethyl)magnesium chloride. The (*E*)-allylic bromide used was prepared by Corey's method; E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967). The ^{1}H NMR chemical shifts of vinyl protons of these compounds (δ) in $CDCl_3$ were as follows; (*E*)-**3a**: 5.77 (tq, J = 7.0, 1.2 Hz); (*Z*)-**3a**: 5.44 (tq, J = 7.1, 1.5 Hz); (*E*)-**3c**: 5.68 (tq, J = 7.2, 1.2 Hz); (*Z*)-**3c**: 5.34 (t, J = 6.6 Hz); (*E*)-**3d-1**: 5.77 (tq, J =7.1, 1.5 Hz); (*Z*)-**3d-1**: 5.45 (tq, J = 6.6, 1.5 Hz); (*E*)-**3e-1**: 5.78 (t, J = 6.0 Hz); (*Z*)-**3e-1**: 5.46 (t, J = 6.1 Hz); (*E*)-**3e-2**: 5.12 (t, J = 7.1 Hz); (*Z*)-**3e-2**: 5.09 (t, J = 6.2 Hz); (*E*)-**3f**: 5.64 (t, J = 7.0 Hz); (*Z*)-**3f**: 5.42 (t, J = 7.0 Hz); (*E*)-**3g**: 5.78 (tq, J= 7.0, 1.2 Hz); (*Z*)-**3g**: 5.49 (tq, J= 7.5, 1.4 Hz). The configuration of **3d-2** was also assigned by the comparison with the authentic (*E*)- and (*Z*)-isomers prepared from geraniol and nerol in a similar manner described above. The ^{1}H NMR chemical shifts of allylic methyl protons (δ) in $CDCl_3$ were as follows; (*E*)-**3d-2**: 1.61 (s, 6H), 1.68 (s, 3H); (*Z*)-**3d-2**: 1.61(s, 3H), 1.69 (s, 6H).

5) The stereoisomeric ratios were determined by capillary GLC analysis (SUPELCOWAX 10).

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