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Stereoselective Synthesis of (*E*)- and (*Z*)-γ,δ-Unsaturated Ketones Using *trans*-2-Phenylthiocyclobutyl Ketones

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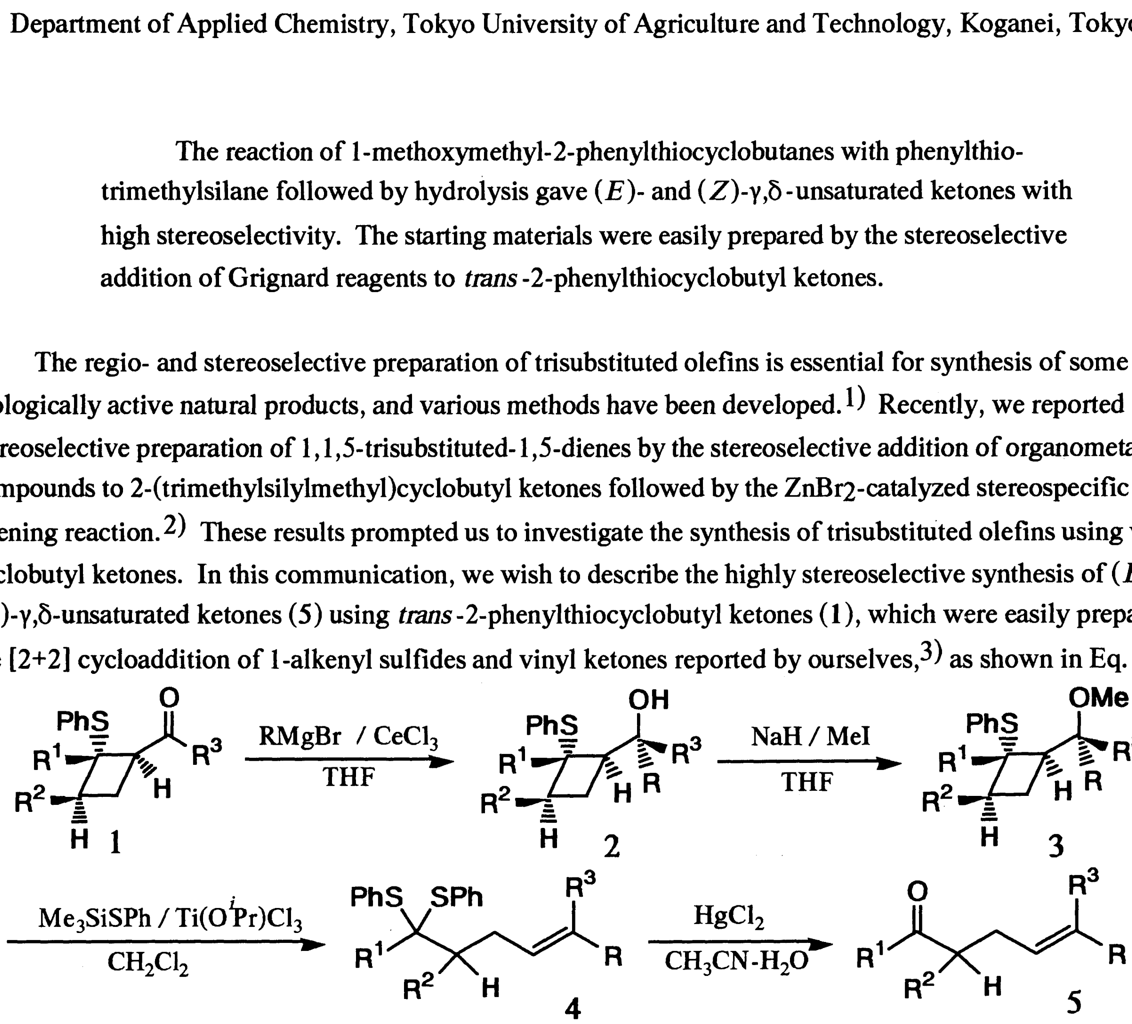
The reaction of 1-methoxymethyl-2-phenylthiocyclobutanes with phenylthiotrimethylsilane followed by hydrolysis gave (*E*)- and (*Z*)-γ,δ-unsaturated ketones with high stereoselectivity. The starting materials were easily prepared by the stereoselective addition of Grignard reagents to *trans*-2-phenylthiocyclobutyl ketones.

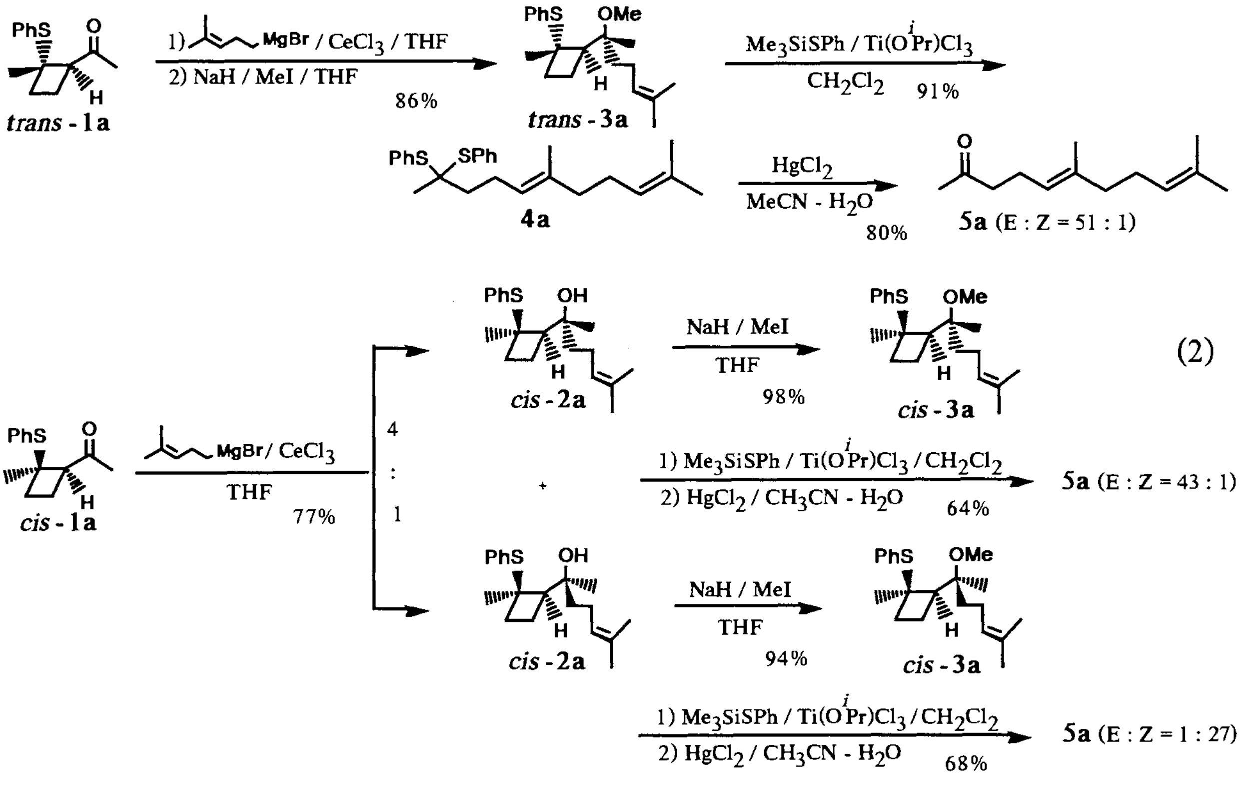
The regio- and stereoselective preparation of trisubstituted olefins is essential for synthesis of some biologically active natural products, and various methods have been developed.[1] Recently, we reported the stereoselective preparation of 1,1,5-trisubstituted-1,5-dienes by the stereoselective addition of organometallic compounds to 2-(trimethylsilylmethyl)cyclobutyl ketones followed by the $ZnBr_2$-catalyzed stereospecific ring-opening reaction.[2] These results prompted us to investigate the synthesis of trisubstituted olefins using various cyclobutyl ketones. In this communication, we wish to describe the highly stereoselective synthesis of (*E*)- and (*Z*)-γ,δ-unsaturated ketones (**5**) using *trans*-2-phenylthiocyclobutyl ketones (**1**), which were easily prepared by the [2+2] cycloaddition of 1-alkenyl sulfides and vinyl ketones reported by ourselves,[3] as shown in Eq. 1.



(1)

First we examined the synthesis of trisubstituted olefin (**5**) using both stereoisomers of 1-acetyl-2-methyl-2-phenylthiocyclobutane (*cis*- and *trans*-**1a**) (Eq. 2). It was found that the methyl ether (*trans*-**3a**) was obtained with high stereoselectivity (40%, the ratio of stereoisomers = 39 : 1) by the reaction of *trans*-**1a** with 4-methyl-3-pentenylmagnesium bromide (1.5 equiv. / THF / -78 – 0°C) followed by methylation (NaH / MeI / THF / 0 °C – room temperature). Furthermore, the use of cerium(III) chloride (1.5 equiv.) in the reaction with Grignard reagent as an additive increased the yield of *trans*-**3a** and diastereoselectivity of the reaction (86%, the ratio of stereoisomers = 68 : 1).[4] On the contrary, the reaction of *cis*-**1a** with 4-methyl-3-pentenylmagnesium bromide gave the considerable amounts of both diastereomers of hydroxymethylcyclobutane (*cis*-**2a**), which were transformed to the methyl ethers (*cis*-**3a**) after they were separated each other by TLC. The high stereoselectivity observed in the reaction of *trans*-**1a** is well accounted for by the attack of Grignard reagent from less hindered side of the most stable conformer of six-membered chelate (A) formed by the coordination of *trans*-**1a** to cerium(III) chloride as shown in Fig. 1. In the reaction of *cis*-**1a**, the two relatively stable conformers (B and C) would be responsible for the formation of each of the diastereomers.

Next, the ring-opening reaction of 1-methoxymethyl-2-phenylthiocyclobutanes (**3a**) was examined. The treatment of the methyl ether (*trans*-**3a**) with trichloroisopropoxytitanium(IV) in the presence of phenylthiotrimethylsilane gave the thioacetal (**4a**) which, in turn, was hydrolyzed with mercury(II) chloride[5] to afford geranylacetone ((*E*)-**5a**) in good yields. The similar transformation of each of the diastereomers of the methyl ether (*cis*-**3a**) gave (*E*)-**5a** and nerylacetone ((*Z*)-**5a**), respectively. These results suggest that the ring-opening reactions of **3a** proceed via the chair-like six-membered cyclic transition states; Fig. 2, for example, illustrates the



(2)

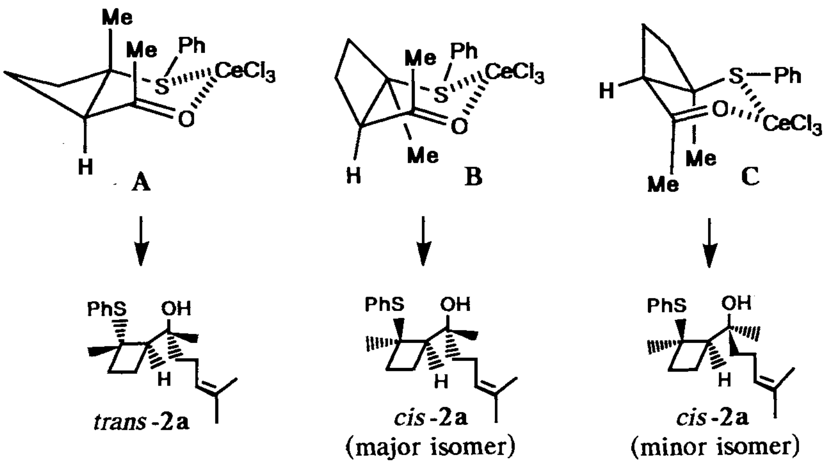


Fig. 1.

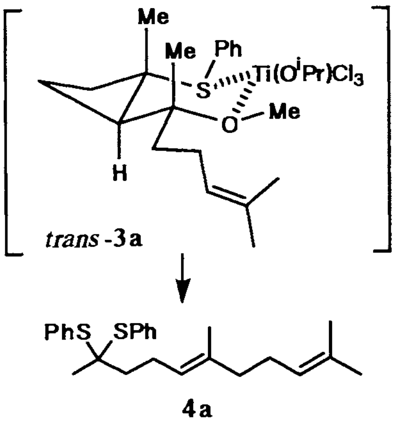
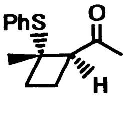
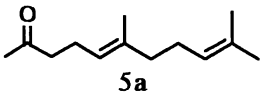
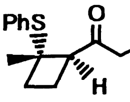
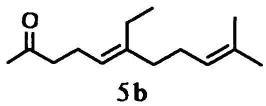
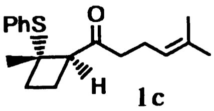
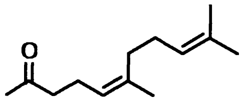
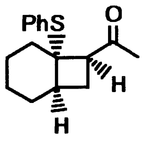
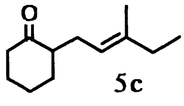
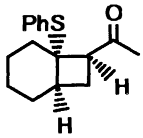
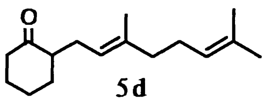
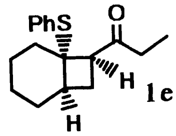
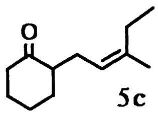
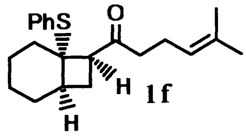
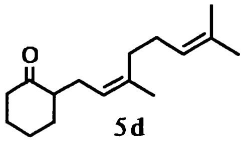


Fig. 2.

Table 1. The stereoselective synthesis of (*E*)- and (*Z*)-γ, δ-unsaturated ketones (5)[a]

Entry	2-Phenylthiocyclobutyl ketone (1)	RMgBr	Products (Yield / %)[b] 3	4	5		*E* : *Z*[c]
1	 1a		3a (86)	4a (91)	 5a	(80)	51 : 1
2	 1b		3b (88)	4b (90)[d]	 5b	(94)	93 : 1
3	 1c	MeMgBr	3c (73)	4c (89)	 5a	(91)	1 : 40
4	 1d	EtMgBr	3d-1 (86)	4d-1 (94)	 5c	(87)	100 : 0[e]
5	 1d		3d-2 (93)	4d-2 (94)	 5d	(80)	137 : 1
6	 1e	MeMgBr	3e (86)	4e (82)	 5c	(94)	0 : 100[e]
7	 1f	MeMgBr	3f (94)	4f (94)	 5d	(81)	1 : 74

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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, ^{1}H NMR, and ^{13}C NMR spectra. c) Determined by capillary GLC analysis (SUPELCOWAX 10). d) The reaction was carried out at -78 – -50 °C for 5.5 h. e) The minor isomer could not be detected by capillary GLC analysis after the Peterson olefination of 5c using (trimethylsilylmethyl)magnesium chloride.[2)] transition state for the reaction of *trans*-**3a**.

Using *trans*-2-phenylthiocyclobutyl ketones (**1**) as starting materials, the synthesis of various γ, δ-unsaturated ketones (**5**) was performed. As shown in the Table 1, all these reactions gave the ketones (**5**) in high yields with high stereoselectivity. In all cases examined, the ketones (**5**) in which the substituent originated from Grignard reagents occupied a *trans*-position were produced.[6]

A typical experimental procedure for the transformation of methoxymethylcyclobutanes (**3**) to γ, δ-unsaturated ketones (**5**) is as follows. To a CH_2Cl_2 (1.9 ml) solution of $Ti(O^iPr)Cl_3$ (prepared from $TiCl_4$ (0.56 mmol) and $Ti(O^iPr)_4$ (0.19 mmol) at 0 °C for 10 min) was added a CH_2Cl_2 (0.78 ml) solution of phenylthiotrimethylsilane (0.74 mmol) at -78 °C, and the mixture was stirred for 10 min. Then a CH_2Cl_2 (2 ml) solution of 8-(1-methoxy-1-methylpropyl)-1-phenylthiobicyclo[4.2.0] octane (**3d-1**) (150 mg, 0.49 mmol), which was prepared from **1d** and ethylmagnesium bromide, was added. After being stirred for 1 h at -78 °C, the reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution. The reaction mixture was filtered through celite and the organic materials were extracted with CH_2Cl_2. The extract was washed with 1M NaOH aqueous solution and dried (Na_2SO_4). After removal of the solvent, the residue was purified by preparative TLC (hexane) and 1-[2,2-bis(phenylthio)cyclohexyl]-3-methyl-2-pentene (**4d-1**) (177 mg, 94%) was isolated. To a MeCN - H_2O (8 : 1) (4.5 ml) solution of the thioacetal (**4d-1**) thus obtained was added $HgCl_2$ (504 mg, 1.85 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with brine and filtered through celite. The organic materials were extracted with pentane, and the usual work-up and purification by TLC (hexane : AcOEt = 95 : 5) gave 2-(3-methyl-2-pentenyl)cyclohexanone (**5c**) (73 mg, 87%).

Since the *trans*-2-phenylthiocyclobutyl ketones (**1b** (93%), **1c** (44%), **1e** (87%), and **1f** (43%)) were easily prepared by alkylation (MeI (4 equiv.) or prenyl bromide (3 equiv.) / 0 °C) of lithium enolates of *trans*-**1a** or **1d** (LDA / -78 - 0 °C / THF / 6 h) as well as the [2+2] cycloaddition of alkenyl sulfides with vinyl ketones (**1a** (90%; *trans*: *cis* = 94 : 6), **1c** (66%; *trans*: *cis* = 83 : 17), **1d** (72%; *trans*: *cis* = 89 : 11), **1f** (66%; *trans*: *cis* = 95 : 5))[7], it should be noted that both (*E*)- and (*Z*)-γ, δ-unsaturated ketones (**5**) can be synthesized stereoselectively using the same starting materials (Entries 1 and 3, 4 and 6, 5 and 7).

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References

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3) T. Takeda, T. Fujii, K. Morita, and T. Fujiwara, *Chem. Lett.*, **1986**, 1311.
4) T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, **111**, 4392 (1989).
5) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).
6) The configurations of **5a**, **c**, and **d** were determined by comparison of their NMR spectra and GLC retention times with those of the authentic samples. The stereoisomeric mixtures of authentic samples (**5c** and **d**) were prepared by the alkylation of lithium enolates of acetone and cyclohexanone with the stereoisomeric mixtures of the corresponding allylic halides. The authentic (*E*)-**5a**,**c**, and **d** were synthesized using geranyl bromide and (*E*)-3-methyl-2-pentenyl bromide prepared by Corey's method; E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967). The stereoisomeric mixture of **5a** is commercially available. The stereochemistry of **5b** was identified by comparison of its ^{13}C NMR chemical shift of C-5 nuclei with that of **5a**. The chemical shifts of these carbons in $CDCl_3$ are as follows; (*E*)-**5a**, 122.6; (*Z*)-**5a**, 123.4; (*E*)-**5b**, 122.1; (*Z*)-**5b**, 122.6.
7) The stereoisomers were easily separated each other by silica gel chromatography, and the stereochemistry of **1a** was determined by NOE experiment.

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