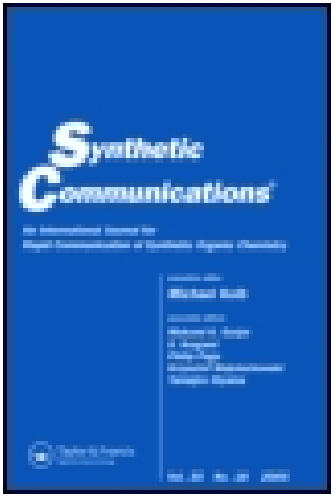

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Cyclodimerization of α, β-Unsaturated Ketones Promoted by Samarium Diiodide

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CYCLODIMERIZATION OF α, β-UNSATURATED KETONES PROMOTED BY SAMARIUM DIIODIDE

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Abstract: Samarium (II) iodide has been successfully utilized as a strong one-electron transfer reducing agent for the cyclodimerization of α, β-unsaturated ketones. The absence of any alcohol as proton source is essential. The reaction is regioselective over the competitive carbon-carbon double bond reduction and stereocontrolled. The configuration of the cyclodimerization products, has been confirmed by X-ray analysis.

Since its introduction by Kagan and his group,[2] SmI_2 has been extensively investigated as a mild, neutral, selective and versatile single electron transfer reductant in synthetic chemistry.[3] Furthermore, the Sm (III) Lewis acid generated during the course of the reaction can be used as a template to control stereochemistry in appropriately designed substrates. Carbon-carbon bond formation is the essence of organic synthesis and the reductive dimerization of carbonyl derivatives is a most valuable method for establishing carbon-carbon bonds. In previous papers, we reported SmI_2 is an effective agent for the

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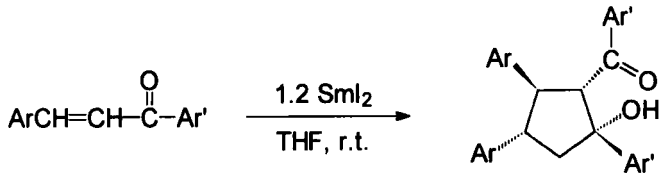
cyclodimerization of arylmethylidenemalonitriles and arylmethylidenecyanoacetates in the absence of alcohol.[4] In the presence of proton source, the dimers and carbon-carbon double bond reduction product were obtained, however, cyclodimerization product was not found. Inanaga et al. reported that the reaction of α, β-unsaturated esters and amides with SmI_2 and an alcohol in THF gave hydrodimerization products in the presence of HMPA as copromoter,[5] and that the system yielded conjugate reduction products when HMPA was replaced by N,N-dimethylacetamide (DMA) as additive.[6] The analogous 1,4-reduction was also reported by Alper et al.[7] When ketones were used as the substrates, several other differences were observed. Fukuzawa reported the intermolecular coupling reaction of α, β-unsaturated esters with carbonyl compounds afforded complex unidentified products in the absence of alcohol.[8] While in the presence of alcohol, the same system gave cross reductive coupling product γ-lactones in good yields.[9] Recently, the synthesis of chiral γ-lactones has been achieved by the SmI_2 in the presence of alcohol in extremely high enantioselectivity.[10] Otera reported that some conjugated enones underwent reduction of the carbon-carbon double bond in the presence of an alcohol,[11] while Kagan found that there was competition between carbonyl group or carbon-carbon double bond and no attempt was made to improve selectivity under the same reaction condition.[2] Cabrera reported SmI_2 promoted the hydrodimerization of cyclic α, β-unsaturated ketones in the absence of alcohol as a proton source.[12] These results show that whether the presence of alcohol as proton source has an evidence influence on the reaction. Herein we wish to report the results on the stereocontrolled cyclodimerization of α, β-unsaturated ketones promoted by SmI_2 in the absence of alcohol as proton source, which is undergo a different pathway than that previously reports.

Results and discussion

When α, β-unsaturated ketones were treated with 1.2 equiv. SmI_2 in THF in the absence of alcohol at room temperature the cyclodimerization products were obtained (**Scheme 1**).



1 2

Scheme 1

Table 1 Reaction of α, β-unsaturated ketones promoted by SmI_2

Entry	Ar	Ar'	Isolated Yield (%)
1	C_6H_5	C_6H_5	82
2	4-ClC_6H_4	C_6H_5	87
3	2-ClC_6H_4	C_6H_5	77
4	3,4-$OCH_2OC_6H_3$	C_6H_5	70
5	4-$CH_3C_6H_4$	C_6H_5	73
6	C_6H_5	4-$CH_3C_6H_4$	74
7	3,4-$OCH_2OC_6H_3$	4-$CH_3C_6H_4$	68

Table 1 summarized the results on the reaction of a number of substrates. In the reactions, the cleavage takes place at the carbon-carbon and carbon-oxygen double bond. The chloro, alkoxy groups of the substrates could not be reduced under the reaction conditions. The reaction was completed within about 20 min. and afforded the corresponding substituted cyclopentanol in good yield. There are several reports on the cyclodimerization of the α, β-unsaturated ketones induced by metal system, such as Zn-$TiCl_4$,[13] Yb,[14] tributyltin hydride[15] and $NdCl_3$-lithium naphthalide.[16] However, our results has the advantages than the literature's in yield and selectivity.

The relative stereochemistry of products was assigned by a 2D NMR study as shown in **Fig. 1**. The NOESY experiment of compound **2a**, which is performed

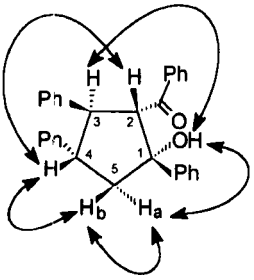


Fig. 1 Observed NOEs of **2a**.

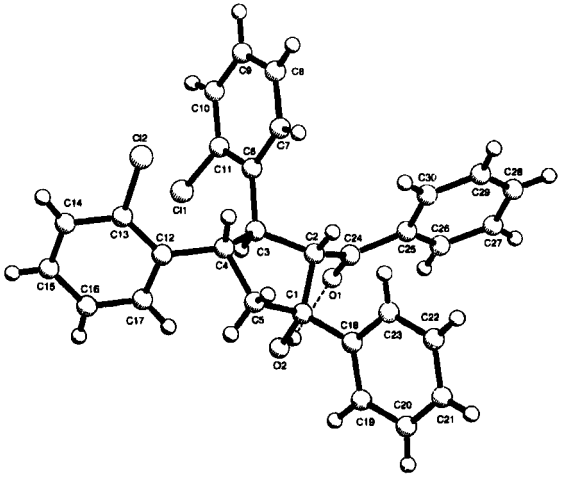
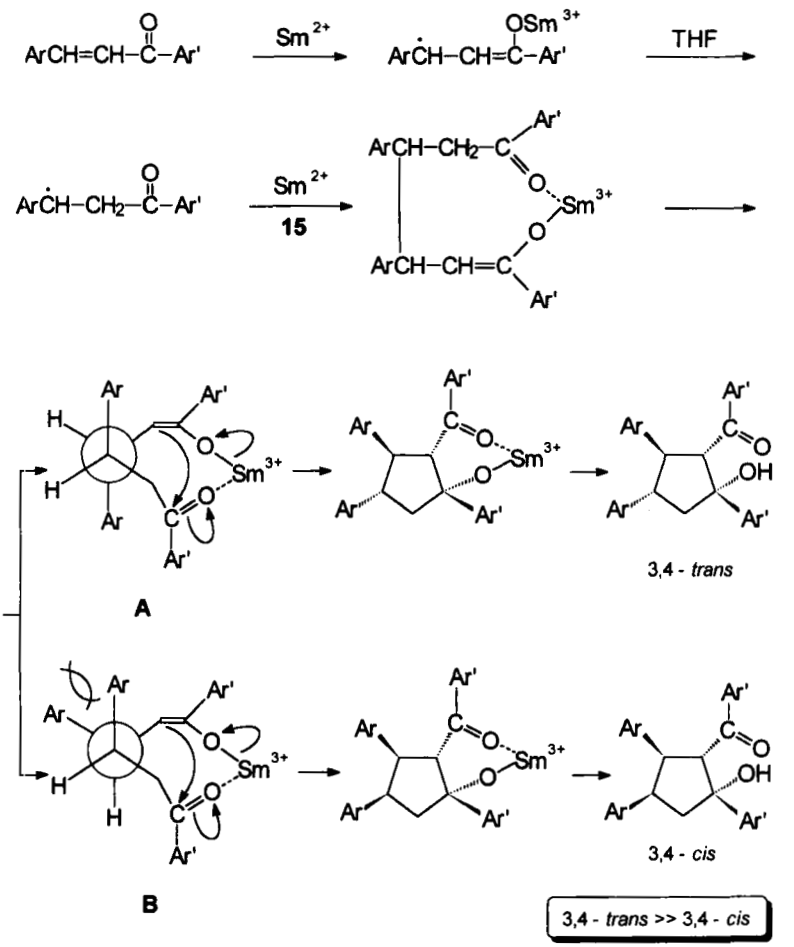


Fig. 2 ORTEP diagram of **2c**

on a Brucker 500 instrument, give us clear evidences of the *cis*-positions of C^5-H_b with C^4-H, C^5-H_a with the hydrogen atom of OH group. We observed the evidence NOE effects between C^2-H with C^4-H and C^3-H with the hydrogen atom of OH group. These observations led us capable of establishing the relative stereochemistry of compound **2a**, which is 1,2-*cis*-2, 3-*trans*-3,4-*trans* relations. The configuration of the product **2** was determined by X- ray diffraction of **2c**. **Fig. 2** shows the ORTEP diagram of compound **2c** as atypical example of the structure. The stereochemistry of compound **2a** is in agreement with that of the same compound by Takaki[14] using Yb-HMPA-THF and Zhou[13] using $TiCl_4$-Zn system. However, Fournier reported that the stereochemistry at C(3) and C(4) positions was different,[17] when the cyclodimerization product prepared with same substrate by electronreduction.

Although the detailed mechanism of the above reaction has not been clarified yet, the cyclopentanol formation could be explained by the possible mechanism presented in **Scheme 2**.



Scheme 2

The observed selectivity of the cyclodimerization based on the different conformation for the anions can be explained by two important conformations **A** and **B**, which come from the attack of the radical enolate on the enone. Form **A**, which is non-eclipsed conformation, may be favored due to the steric hindrance effects are minimized (the two aryl groups being in anti-positions) and if the cycle is generated, the 3,4 - *trans* configuration product is obtained. In addition, the

Sm^{3+}species resulting from SmI_2 can stabilize the neighboring carbonyl group and enol form by coordination. However, the eclipsed conformation **B**, a less favored due to the steric interactions are maximized (the two aryl groups being syn-positions), forms the 3,4 - *cis* configuration product difficulty.

Experimental

Tetrahydrofuran (THF) was distilled from sodium — benzophenone immediately prior to use. All reactions were performed under a nitrogen atmosphere, using syringes and Schlenk-type techniques.

Melting points are uncorrected. Infrared spectra were recorded on FTIR-8101 spectrometers in KBr with absorptions in cm^{-1}. NMR spectra were determined in Brucker 500 or JEOL FT-90Q spectrometers. *J* values are in Hertz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on HP 5989A spectrometers. Microanalysis was carried out on a Carlo-Erba 1106 instrument.

General procedure for the SmI_2-promoted cyclodimeriztion of α,β-unsaturated ketones

To Sm (1.2 mmol) in dry THF (12 ml) was added I_2 (1.2 mmol). The resultant orange slurry was stirred vigorously for 2h at room temperature. The resulting SmI_2 solution had a deep blue-green color. A solution of α, β-unsaturated ketones (1 mmol) in the anhydrous THF(15 ml) was added at room temperature under dry nitrogen atmosphere. The reaction mixture was then stirred at room temperature for 20 min.. After the reaction was completed, the reaction was quenched with dilute hydrochloric acid (5% HCl, 2 ml). The solution was extracted with diethyl ether (3 × 40 ml) and the combined extracts were washed with saturated solution of $Na_2S_2O_3$ (15 ml), saturated solution of NaCl (15 ml), and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the crude product purified by preparative thin layer chromatography on silica gel using ethyl acetate-benzene-cyclohexane (1:4:8) as eluent.

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-benzoyl-1,3,4-triphenyl cyclopentanol 2a

2a was obtained from chalcone as a white solid in 82 % yield. mp 192 - 194 ℃; ν_{max} / cm^{-1} (KBr) 3440 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.58 (1 H, dd, *J* 14.4, 6.1, C^5 - H_a), 3.00 (1 H, dd, *J* 14.4, 10.7, C^5 - H_b), 3.77 (1 H, ddd, *J* 10.7, 10.2, 6.1, C^4 - H), 4.10 (1 H, dd, *J* 11.7, 10.2, C^3 - H), 4.55 (1 H, d, *J* 11.7, C^2 - H), 5.25 (1 H, s, OH), 7.10 – 7.65 (20 H, m, ArH). *m/z* 400 (M - H_2O, 1), 209 (100), 131 (8), 105 (34), 77 (5); (Found: C, 86.39; H, 6.23. $C_{30}H_{26}O_2$ requires C, 86.09; H, 6.26 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-benzoyl-1-phenyl-3,4-di(4-chlorophenyl)cyclopentanol 2b

2b was obtained from 4-chlorochalcone as a white solid in 87 % yield. mp 192 - 194 ℃; ν_{max} / cm^{-1} (KBr) 3440 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.48 (1 H, dd, *J* 14.4, 6.1, C^5 - H_a), 2.97 (1 H, dd, *J* 14.4, 10.7, C^5 - H_b), 3.63 (1 H, ddd, *J* 10.7, 10.0, 6.1, C^4 - H), 4.02 (1 H, dd, *J* 11.7, 10.0, C^3 - H), 4.50 (1 H, d, *J* 11.7, C^2 - H), 5.01 (1 H, s, OH), 6.90 – 7.75 (18 H, m, ArH). *m/z* 488 (M + 2, 0.6), 486 (M^+, 0.9), 470 (M+2 - H_2O, 3), 468 (M-H_2O, 5), 245 (11), 243 (34), 105 (100), 77 (32); (Found: C, 74.06; H, 4.86 $C_{30}H_{24}Cl_2O_2$ requires C, 73.92; H, 4.96 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-benzoyl-1-phenyl-3,4-di(2-chlorophenyl)cyclopentanol 2c

2c was obtained from 2-chlorochalcone as a white solid in 77 % yield. mp 192 - 193 ℃; ν_{max} / cm^{-1} (KBr) 3450 (OH), 1650 (C=O); δ_H ($CDCl_3$) 2.37 (1 H, dd, *J* 14.4, 5.0, C^5-H_a), 3.07 (1 H, dd, *J* 14.4, 10.9, C^5-H_b), 4.67 - 4.79 (3 H, m, C^2 - H, C^3 - H, C^4 - H), 5.60 (1 H, s, OH), 6.92 – 8.11 (18 H, m, ArH). *m/z* 488 (M + 2, 1), 486 (M^+, 1.5), 470 (M + 2 - H_2O, 5), 468 (M - H_2O, 7), 245 (36), 243 (73), 105 (100), 77 (32); (Found: C, 73.70; H, 4.79. $C_{30}H_{24}Cl_2O_2$ requires C, 73.92; H, 4.96 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-benzoyl-1-phenyl-3,4-di(3,4-methylenedioxylphenyl) cyclopentanol 2d

2d was obtained from 3,4-methylenedioxychalcone as a white solid in 70 % yield. mp 183 - 184 ℃; ν_{max} / cm^{-1} (KBr) 3480 (OH), 1650 (C=O); δ_H ($CDCl_3$)

2.52 (1 H, dd, *J* 14.3, 6.1, C^5-H_a), 2.98 (1 H, dd, *J* 14.3, 10.5, C^5-H_b), 3.67 (1 H, ddd, *J* 10.5, 9.9, 6.1, C^4 - H), 4.05 (1 H, dd, *J* 11.5, 9.9, C^3 - H), 4.41 (1 H, d, *J* 11.5, C^2 - H), 5.20 (1 H, s, OH), 5.79 (2 H, s, OCH_2O), 5.89 (2 H, s, OCH_2O), 6.54 – 7.55 (16 H, m, ArH). *m/z* 506 (M^+, 1), 389 (19), 253 (38), 105 (100), 77 (27); (Found: C, 75.94; H, 5.06. $C_{32}H_{26}O_6$ requires C, 75.88; H, 5.17 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-benzoyl-1-phenyl-3,4-di(4-methylphenyl)cyclopentanol 2e

2e was obtained from 4-methylchalcone as a white solid in 73 % yield. mp 188 - 190 ℃; ν_{max} / cm^{-1} (KBr) 3440 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.15 (3 H, s, CH_3), 2.27 (3 H, s, CH_3), 2.50 (1 H, dd, *J* 14.4, 6.6, C^5 - H_a), 2.98 (1 H, dd, *J* 14.4, 10.7, C^5 - H_b), 3.68 (1 H, ddd, *J* 10.7, 10.2, 6.6, C^4 -H), 4.13 (1 H, dd, *J* 11.7, 10.2, C^3 - H), 4.48 (1 H, d, *J* 11.7, C^2 - H), 5.20 (1 H, s, OH), 6.83 – 7.58 (18 H, m, ArH). *m/z* 447 (M + 1, 3), 429 (M +1 - H_2O, 19), 325 (21), 322 (19), 223 (52), 105 (100), 77 (22); (Found: C, 85.85; H, 6.75 $C_{32}H_{30}O_2$ requires C, 86.06; H, 6.77 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-(4-methylbenzoyl)-1-(4-methylphenyl)-3,4-diphenylcyclo -pentanol 2f

2f was obtained from 4'-methylchalcone as a white solid in 74 % yield. mp 170 - 171.5 ℃; ν_{max} / cm^{-1} (KBr) 3450 (OH), 1640 (C=O); δ_H ($CDCl_3$) 2.24 (3 H, s, CH_3), 2.26 (3 H, s, CH_3), 2.58 (1 H, dd, *J* 14.4, 6.1, C^5 - H_a), 2.92 (1 H, dd, *J* 14.4, 10.5, C^5 - H_b), 3.75 (1 H, ddd, *J* 10.5, 9.5, 6.1, C^4 - H), 4.09 (1 H, dd, *J* 11.5, 9.5, C^3 - H), 4.50 (1 H, d, *J* 11.5, C^2 - H), 5.26 (1 H, s, OH), 6.89 – 7.67 (18 H, m, ArH). *m/z* 429 (M +1 - H_2O, 3), 223 (100), 131 (18), 119 (67), 91 (27); (Found: C, 85.86; H, 6.85 $C_{32}H_{30}O_2$ requires C, 86.06; H, 6.77 %).

1,2-*cis*-2,3-*trans*-3,4-*trans*-2-(4-methylbenzoyl)-1-phenyl-3,4-di(3,4-methylenedioxy-phenyl) cyclopentanol 2g

2g was obtained from 3,4-methylenedioxy-4'-methylchalcone as a white solid in 68 % yield. mp 171 - 172 ℃; ν_{max} / cm^{-1} (KBr) 3440 (OH), 1640 (C=O);

δ_H ($CDCl_3$) 2.25 (3 H, s, CH_3), 2.26 (3 H, s, CH_3), 2.48 (1 H, dd, *J* 14.4, 6.1, C^5 - H_a), 3.02 (1 H, dd, *J* 14.4, 10.7, C^5 - H_b), 3.65 (1 H, ddd, *J* 10.7, 10.0, 6.1, C^4 - H), 3.99 (1 H, dd, *J* 11.6, 10.0, C^3 - H), 4.37 (1 H, d, *J* 11.6, C^2 - H), 5.21 (1 H, s, OH), 5.80 (2 H, s, OCH_2O), 5.85 (2 H, s, OCH_2O), 6.49 – 7.45 (14 H, m, ArH). *m/z* 516 (M - H_2O, 3), 399 (11), 267 (28), 223 (15), 119 (100), 91 (33); (Found: C, 76.24; H, 5.53 $C_{34}H_{30}O_6$ requires C, 76.39; H, 5.66 %).

X-ray Crystal structure determination of compound 2c

Crystals suitable for X-ray analysis were obtained by crystallization from the ethanol solution of **2c**. $C_{30}H_{24}Cl_2O_2$, M = 487.32, triclinic, space group $P\bar{1}$, a = 9.700(2), b = 16.754(4), c = 7.686(2) Å, α = 96.92(2), β = 100.13(2), γ = 91.61(2)°, V = 1219.1(5) $Å^3$, Z = 2, D_C = 1.328 gcm^{-3}, F (000) = 508.00, μ (M_o-K_α) = 2.92 cm^{-1}, colorless prismatic crystals, crystal size 0.20 × 0.20 × 0.30 mm.

Intensity data were collected at 293K on a Rigaku AFC7R diffractometer with graphite - monochromated M_o-K_α radiation (λ = 0.71069 Å). 2655 independent reflections were collected using ω - 2θ scan mode in the range of 6°< 2θ < 45°, of which 1756 intensity data with ($I > 2\sigma(I)$) were observed. The corrections for *Lp* factors were applied. The structure was solved by direct methods[18] and expanded using Fourier techniques.[19] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. A full-matrix least-squares refinement give final R = 0.039 and R_w = 0.044 with $w = 1/\sigma^2(F_0)$, S = 1.43. The maximum peak in the final difference Fourier map is 0.27 e / $Å^3$ and the minimum peak is -0.20 e / $Å^3$. In the final circle refinement the largest parameter shift ($\Delta/\sigma)_{max}$ is 0.00. All calculations were performed using TEXSAN program package.[20]

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