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Lanthanoid(III) Trichloride-Tin(II) Chloride Mediated Cycloaddition Reaction of α,α′-Dibromo Ketones with 1,3-Dienes or Enamines

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The reaction of α,α′-dibromo ketones with 1,3-dienes in the presence of $CeCl_3$–$SnCl_2$ in tetrahydrofuran is found to give the corresponding [3+4] cycloadduct in fair to good yields under mild conditions. Furan and cyclopentadiene serve as highly efficient receptors of the oxyallyl intermediate to give bicyclic cycloadducts. The reaction of 2,4-dibromo-3-pentanone with isoprene gives both [3+4] and [3+2] cycloadducts. [3+2] Cycloaddition proceeds similarly with enamines to afford 2-cyclopenten-1-ones after treatment with 3% ethanolic NaOH solution.

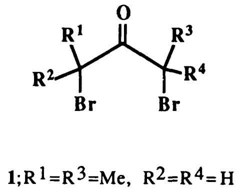
Organic synthesis using lanthanoid compounds has been of current interest.[1] Lanthanoid(III) trichloride ($LnCl_3$) has appeared to be one of the attractive reagent for organic synthesis. The combination with $NaBH_4$[2] or $LiAlH_4$[3] is efficient for 1,2-regioselective reduction of α,β-unsaturated carbonyl compounds, organic halides, and phosphine oxide. They can also be employed together with Grignard reagents or organolithium reagents for regio- and stereoselective alkylation of carbonyl compounds.[4] The characteristic of these reactions may be explained by the lanthanoid ion being a weak Lewis acid and having a high affinity for oxygen.[5] These combined reagents have recently been accepted into the repertoire of standard synthetic methodology. Lanthanoid(III) trichloride has been used as a Lewis acid catalyst for Friedel–Crafts reaction,[6] aldol reaction of silyl enol ether,[7] and ring opening reaction of oxirane.[8] Other trivalent lanthanoid reagents than $LnCl_3$ are also found to be useful for organic synthesis. For example, lanthanoid perchlorate and triflate are good catalyst for preparation of 4-substituted 2,6-dimethylpyrimidines from amines and nitriles.[9] Lanthanoid triflate can also be used with alkyllithium for the conversion of tertiary amines to ketones.[10] Lanthanoid tris[bis(trimethylsilyl)amide] has been developed for regioselective alkylation of epoxides with alkyllithium, where $LnCl_3$ poorly works.[11]

On the other hand, we previously reported a facile aldol synthesis from α-halo ketones and carbonyl compounds by using the combined reagent of $CeCl_3$–$SnCl_2$; a cerium enolate was assumed to be an intermediate.[12] The success of this reaction is due to activation of carbonyl group by cerium(III) ion promoting the reduction of the halogen group by $SnCl_2$. When we applied this combined reagent to a reaction of α,α′-dibromo ketone with furan and cyclopentadiene, the bicyclooctenones, i.e., [3+4] cycloadducts were produced in high yields. As α,α′-dibromo ketone has been recognized as a suitable building block for preparation of five- and seven-membered carbocycles by reaction with alkenes and 1,3-dienes, respectively,[13] the following reagents so far been developed for the reaction: Cu/NaI,[14] Zn/Cu,[15] Fe/graphite,[16] and $Fe_2(CO)_9$.[17] The former three reagents requires some activations and reaction system is heterogeneous. $Fe_2(CO)_9$ is toxic and expensive, and it requires long reaction time and high reaction temperature, although it appears to be an excellent reagent for both [3+4] and [3+2] cycloadditions. $CeCl_3$–$SnCl_2$ reagent can be more conveniently used for the cycloaddition reaction of some α,α′-dibromo ketones, and the reaction procedure is quite simple. The reaction is homogeneous, needs no activation, and is carried out at room temperature in the air. Both $CeCl_3$ and $SnCl_2$ are easily kept with a little care of moisture, non toxic, and inexpensive.

We would like to report here a facile [3+4] and [3+2] cycloaddition reaction of α,α′-dibromo ketones with 1,3-dienes and enamines by $CeCl_3$–$SnCl_2$, respectively.

Results and Discussion

Reaction of α,α′-Dibromo Ketones with Furans in the Presence of the Combined Reagent of $LnCl_3$–$SnCl_2$: The reaction of 2,4-dibromo-3-pentanone (**1**) with furan in tetrahydrofuran (THF) proceeded smoothly at 0 °C to room temperature to afford the cycloadduct (**4**) in good yield when the combined reagent of $CeCl_3$–$SnCl_2$ was employed. The results are shown in Table 1. One equivalent of $SnCl_2$ to **1** was sufficient for the reaction (Run 1), but an excess of $SnCl_2$ gave a more satisfactory yield of **4**; a three-fold excess of $SnCl_2$ was enough to obtain a reasonable

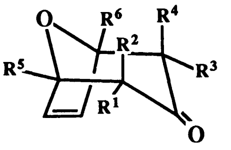


1; $R^1=R^3=Me$, $R^2=R^4=H$
2; $R^1=R^2=R^3=R^4=Me$
3; $R^1=R^2=Me$, $R^3=R^4=H$

Table 1. Cycloadduct Synthesis from **1** and Furan by $LnCl_3$-$SnCl_2$$^{a)}$

Run	Ln in $LnCl_3$	Isolated yield (%) of **4**$^{b)}$
1	Ce$^{c)}$	76
2	Ce$^{d)}$	81
3	Ce	90
4	Ce$^{e)}$	90
5	Ce$^{f)}$	0
6	Ce$^{g)}$	0
7	Ce$^{h)}$	0
8	—$^{i)}$	0
9	La	74
10	Sm	90
11	Eu	69
12	Er	72

a) **1** (4 mmol), furan (40 mmol), $LnCl_3$ (4 mmol), $SnCl_2$ (12 mmol), THF (15 cm^3); 0 °C, 2 h then rt, 3 h. b) A mixture of **4a**, **4b**, and **4c**. c) $SnCl_2$ (4 mmol). d) $SnCl_2$ (8 mmol). e) 0 °C, 2 h then rt, 22 h. f) Without $SnCl_2$. g) SnF_2 (12 mmol) was used. h) $PbCl_2$ (12 mmol) was used. i) Without $CeCl_3$.



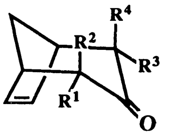
4a;R^1=R^3=Me, R^2=R^4=R^5=R^6=H
4b;R^2=R^4=Me, R^1=R^3=R^5=R^6=H
4c;R^1=R^4=Me, R^2=R^3=R^5=R^6=H
5a;R^1=R^3=R^5=Me,R^2=R^4=R^6=H
5b;R^1=R^3=R^6=H, R^2=R^4=R^5=Me
6a;R^1=R^3=R^5=R^6=Me, R^2=R^4=H
6b;R^1=R^3=H, R^2=R^4=R^5=R^6=Me
7;R^1=R^2=Me, R^3=R^4=R^5=R^6=H
8;R^1=R^2=R^3=R^4=Me, R^5=R^6=H

result (Run 3). No reaction took place in the absence of either $CeCl_3$ or $SnCl_2$ (Run 5,8). The use of SnF_2 or $PbCl_2$ (lead and tin are both 4B element) instead of $SnCl_2$ results in no reaction with the recovery of starting **1**. It may be concluded that the combination of $CeCl_3$ and $SnCl_2$ is essential to the reaction. Cycloadduct **4** was a mixture of three stereoisomers with respect to the two methyl groups (**4a**, **4b**, and **4c**).[18] The isomer ratio was determined by ^{1}H NMR integration of the bridgehead protons and olefinic protons after addition of the shift reagent [Eu(dpm)$_3$] according to the literature.[17b] The isomer ratio did not change when the reaction was carried out for a longer time (Run 4), indicating that the isomerization in **4** was not involved in the system and the configuration must be determined at a cycloaddition step.

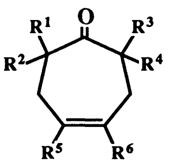
Other lanthanoid trichloride such as $LaCl_3$, $SmCl_3$, $EuCl_3$, and $ErCl_3$ can be used for the reaction; the yields and isomer ratios were virtually the same despite variation of the lanthanoid metal. For reasons of economy $CeCl_3$ was chosen for investigation.

The cycloadducts of **1** with the substituted furans such as 2-methylfuran and 2,5-dimethylfuran were also obtained as mixtures of two types of cis adducts in good yields, no trans isomers being produced. The reaction of the other dibromide (**2** and **3**) with furan similarly gave 1:1 adduct (**7** and **8**, respectively) in high yields. The results are summarized in Table 2 (Runs 2, 3, 7, and 10).

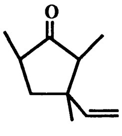
Reaction with Cyclopentadiene: The reaction of the dibromides with 1,3-dienes including furans are also shown in Table 2. The $CeCl_3$-$SnCl_2$ promoted the reaction of the dibromides (**1**—**3**) and cyclopentadiene gave the bicyclic ketones (**9**—**11**) in high yields (Runs 4, 8, 11). The cycloadduct derived from **1** was two types of cis adducts (**9a** and **9b**) in a ratio of **9a**:**9b**=72:28. No trans isomer was discernible in this reaction. The structural determination of the adduct was carried out by ^{1}H NMR by reference to the literature.



9a;R^1=R^3=Me, R^2=R^4=H
9b;R^1=R^3=H, R^2=R^4=Me
10;R^1=R^2=Me, R^3=R^4=H
11;R^1=R^2=R^3=R^4=Me



12;R^1=R^3=R^5=R^6=Me, R^2=R^4=H
13;R^1=R^3=R^5=Me, R^2=R^4=R^6=H
15;R^1=R^2=R^5=R^6=Me, R^3=R^4=H
16;R^1=R^2=R^3=R^4=R^5=R^6=Me



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Reaction with Open-Chain 1,3-Dienes: Reaction of **1**—**3** with open-chain 1,3-dienes were examined by using 1,3-butadiene, isoprene, and 2,3-dimethyl-1,3-butadiene. With 2,3-dimethyl-1,3-butadiene the corresponding 4-cycloheptenones (**12**, **13**, **15**, and **16**) were obtained in moderate yields, but less than that with cyclic dienes (Table 2, Runs 5, 9, and 12). It is interesting that the reaction of **1** with isoprene gave **14** as [3+2] cycloadduct in addition to the expected [3+4] cycloadduct **13** (Run 6). A similar result is reported in the reaction of α-bromo silyl enol ether with isoprene.[18] Unfortunately, the cycloadduct with 1,3-butadiene could not be isolated and many products were formed. As a [3+2] cycloadduct with isoprene was obtained, we tried the reaction of **1** with monoalkenes such as styrene and α-methylstyrene, but results was no reaction.

Reaction with Enamines: Although the reaction of an α,α′-dibromo ketone with alkenes did not produce

Table 2. Cycloadducts Synthesis from **1**—**3** and 1,3-Dienes by CeCl$_3$-SnCl$_2$[a]

Run	α,α′-Dibromo ketone	1,3-Diene	Product and isolated yield (%)
1	**1**	Furan	**4a**, **4b**, **4c**, 90 (**4a**:**4b**:**4c**=62:28:10)[b]
2	**1**	2-Methylfuran	**5a**, **5b** 78 (**5a**:**5b**=70:30)[b]
3	**1**	2,5-Dimethylfuran	**6a**, **6b** 91 (**6a**:**6b**=63:37)[b]
4	**1**	Cyclopentadiene	**9a**, **9b** 88 (**9a**:**9b**=72:28)[b]
5	**1**	2,3-Dimethyl-1,3-butadiene[c]	**12**, 48
6	**1**	Isoprene	**13**, 37; **14**, 33
7	**2**	Furan	**7**, 77
8	**2**	Cyclopentadiene	**10**, 70
9	**2**	2,3-Dimethyl-1,3-butadiene	**15**, 30
10	**3**	Furan	**8**, 78
11	**3**	Cyclopentadiene	**11**, 71
12	**3**	2,3-Dimethyl-1,3-butadiene	**16**, 37

a) **1**—**3** (4 mmol), 1,3-diene (40 mmol), CeCl$_3$ (4 mmol), SnCl$_2$ (12 mmol), THF (15 cm^3); 0 °C, 2h then rt, 3 h. b) Determined by ^{1}H NMR with Eu(dpm)$_3$. c) 1,3-Diene (12 mmol).

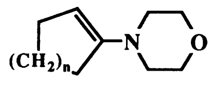
Table 3. Cycloadducts Synthesis from **1**—**2** and Enamines by CeCl$_3$-SnCl$_2$[a]

Run	α,α′-Dibromo ketone	Enamine	Product isolated yield (%)	Isomer ratio[b] (trans:cis)
1	**1**	**17**	**21**, 54	95:5
2	**1**	**18**	**22**, 55	94:6
3	**1**	**19**	**23**, 55	93:7
4	**1**	**20**	**24**, 48	—
5	**2**	**18**	**25**, 28[20]	—

a) **1**, **2** (4 mmol), enamine (12 mmol), CeCl$_3$ (4 mmol), SnCl$_2$ (12 mmol), THF (15 cm^3); rt, 5 h then treated with 3% NaOH/EtOH (3 cm^3) for 30 min. b) Determined by GLC.

[3+2] cycloadducts, the cycloadducts with activated alkenes such as enamines could be obtained. For example, when a mixture of **1** and 1-morpholinocyclopentane (**17**) were reacted in the presence of CeCl$_3$-SnCl$_2$ in THF at 0 °C and subsequently treated with 3% ethanolic NaOH, 2-cyclopenten-1-one (**21**) was produced in a moderate yield as a mixture of cis and trans isomers in a ratio of cis:trans=6:94. The other examples are given in Table 3.[20]

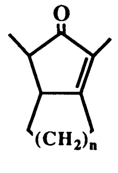
Reaction Mechanism: Treatment of **1** with 1 equiv of CeCl$_3$-SnCl$_2$ (1:1) followed by with D$_2$O in THF gave 2-bromo-4-deuterio-3-pentanone (**26**). This result may suggest that the first step of the reaction of α,α′-dibromo ketone with CeCl$_3$-SnCl$_2$ involves a single debromination just like a Reformatsky reaction to afford a corresponding cerium α-bromo enolate (**27a**).[12] The enolate **27a** suffers further elimination of bromide ion by way of S$_N$1 like reaction to give the oxyallyl cation (**28a**) which undergoes [3+4] and [3+2] cycloadditions with 1,3-dienes and enamines, respectively.[15b,17a] α-Halo silyl enol ether (**27b**) is an isolated metal α-halo enolate and has been designed for the synthetic equivalent of an oxyallyl cation.[19] Then the



17;n=1

18;n=2

19;n=3

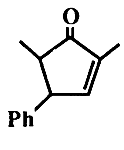


21;n=1

22;n=2

23;n=3

20



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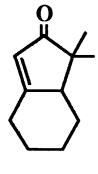

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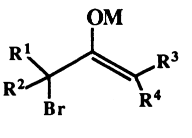
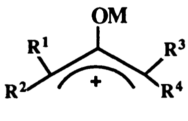


27a;M=CeCl$_2$

27b;M=SiMe$_3$



28a; M=CeCl$_2$

28b;M=SiMe$_3$

plausible key intermediate of the oxyallyl cation seems to be the ceruim α-bromo enolate.

Experimental

^{1}H NMR spectra were recorded with Hitachi R-24 (60 MHz) and Hitachi R-600 (60 MHz) instrument in $CDCl_3$ solutions with $SiMe_4$ as an internal standard. IR spectra were taken with Shimadzu IR 410. GLC analyses were carried out by using a Shimadzu 8A apparatus on EGSS-X(3%)-Chromosorb-W(2 m) and Silicone DC QF-1(5%)-Chromosorb-W(2 m) columns (N_2 as carrier gas).

Frash column chromatography was performed by EYELA EF-10 apparatus by using Merck Kieselgel 60 (230—400 mesh) or Wako C-300. Preparative TLC separation was conducted using 20×20 cm glass plates coated with a 2.0 mm thick layer of Merck Kieselgel PF_{254} gipsphaltig.

Tetrahydrofuran was distilled from sodium benzophenone ketyl under nitrogen. Anhydrous $LaCl_3$, $CeCl_3$, $SmCl_3$, $EuCl_3$, and $ErCl_3$ were obtained by drying the commercial hydrate with $SOCl_2$.[13] Anhydrous tin(II) chloride was purchased from Wako Pure Chemicals Co. and further dried at 200 °C in vacuo before use.

α,α'-Dibromo ketones (**1**, **2**, and **3**) were prepared by a dibromination of the corresponding ketones with bromine in diethyl ether catalyzed by phosphorus tribromide.[15a] Furan, 2-methylfuran, and 2,5-dimethylfuran were distilled over potassium hydroxide. Cyclopentadiene was distilled by thermolysis of commercial dicyclopentadiene at 200 °C just prior to use. Enamines were prepared from the corresponding ketones and morpholine in the presence of a catalytic amount of p-toluenesulfonyl chloride in refluxing benzene.

Reaction of α,α'-Dibromo Ketones with 1,3-Dienes in the Presence of $CeCl_3$-$SnCl_2$. General Procedure: Anhydrous $CeCl_3$ (1.00 g, 4 mmol) and $SnCl_2$ (2.27 g, 12 mmol) were placed in a 50 cm^3 two-neck round bottom flask containing a magnetic stirrer bar. To this THF (10 cm^3) was introduced followed by addition of a mixture of α,α'-dibromo ketone (4 mmol) and 1,3-diene (12—40 mmol) in 5 cm^3 of THF at 0 °C with stirring. The mixture was stirred at 0 °C for 2 h and then at room temperature for additional 3 h. The solution was poured into diluted HCl, extracted with chloroform (20 cm^3×3), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was passed through a short alumina column (2 cm×3 cm) eluted with chloroform to remove a polymeric product. Removal of the solvent by a rotary evaporator left the almost pure adduct by ^{1}H NMR analysis, which was further subjected to preparative TLC or flash column chromatography on silica gel (hexane–ethyl ehter=10:1 as eluent). All the cycloadducts were known compounds, then the identification and isomer ratio of the products were carried out by ^{1}H NMR and IR by reference to the literature.[15,17b] The spectra data of all the products were satisfied with the structure of the reported ones. The isomer ratio of the products, **4a**:**4b**:**4c**, **5a**:**5b**, and **6a**:**6b** were determined by ^{1}H NMR integration of the bridge head protons and olefinic protons with the shift reagent, $Eu(dpm)_3$.

Reaction of α,α'-Dibromo Ketone with Enamine by $CeCl_3$-$SnCl_2$: Anhydrous $CeCl_3$ (1.00 g, 4 mmol) and $SnCl_2$ (2.27 g, 12 mmol) were placed in a 50 cm^3 two-neck round bottom flask containing a magnetic stirrer bar. THF (10 cm^3) was introduced to the flask followed by addition of THF (5 cm^3) solution of α,α'-dibromo ketone (4 mmol) and enamine (12 mmol) at room temperature with stirring. The mixture was stirred at room temperature for 5 h, then diluted with ethyl acetate (50 cm^3), treated with saturated $NaHCO_3$ (30 cm^3), and filtered. The filtrate was washed with brine (30 cm^3×2), and dried ($MaSO_4$), After evaporation of the solvent the residue (the undeaminated adduct) was treated with 3% ethanolic NaOH solution (3 cm^3) at room temperature for 30 min. The solution was diluted with ethyl acetate (50 cm^3), neutralized with dilute HCl (20 cm^3), washed with brine (30 cm^3×2), then dried over $MgSO_4$. Evaporation of the solvent left a yellow oil which was passed through a short alumina column (2 cm×3 cm) with chloroform. The adduct (cyclopentenone derivative) was isolated by flash column chromatography on silica gel (hexane–ethyl acetate =10:1 as eluent). The cyclopentenone was obtained as a mixture of cis and trans (except for **24** and **25**). The stereoisomers was separated by preparative TLC (hexane–ethyl acetate=10:1). ^{1}H NMR and IR spectra of the products were identical with those of the reported ones.[17c] The isomer ratio was determined by GLC.

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18) The cycloaddition with furan by zinc also gives the three stereo isomers and explanation for the preferential formation of **4a** is discussed.[15b)]

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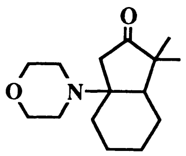
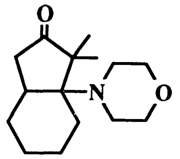
20) The reaction of **2** with **18** should give two regioisomers, **29** and **30**, but only **29** could be suffered from deamination to form **25**; **30** does not have an α-proton from the carbonyl group. We did not isolate the products as undeaminated forms.



29



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