

1,2-Regioselective Reduction of α,β -Unsaturated Carbonyl Compounds with Lithium Aluminium Hydride in the Presence of Lanthanoid Salts

Shin-ichi Fukuzawa,* Tatsuo Fujinami, Shoji Yamauchi, and Shizuyoshi Sakai

Department of Applied Chemistry, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

An α,β -unsaturated carbonyl compound when reduced by lithium aluminium hydride in the presence of lanthanoid chloride, bromide, iodide, or acetylacetonate gives, selectively, an allylic alcohol, while in its absence saturated alcohol formation predominates. Such reactions can be applied to various α,β -unsaturated carbonyl compounds such as aldehydes, ketones, esters, and lactones. In addition to its wide applicability, this reagent appears to be easier to use, than other known reducing reagents.

Although much attention has been paid to the use of organo-lanthanoid derivatives in organic synthesis,¹ less attention has been paid to the similar use of inorganic lanthanoid salts;² their use as an n.m.r. shift reagent {[Ln(fod)₃], Ln = Eu, Yb}, in mediated spiroannellation³ or Diels-Alder reactions,⁴ in the acetalization of aldehydes with a lanthanoid chloride (LnCl₃),⁵ the selective reduction of α -enones with sodium borohydride-LnCl₃,⁶ and carbon-carbon bond formation between α -halogeno ketones and aldehydes by CeI₃ have been reported.⁷ A common feature of these reactions is the high substrate specificity shown, a characteristic which may be explained by the lanthanoid ion being a weak Lewis acid and having a high affinity for oxygen.⁸ In connection with our interest in the selective activation of functional groups by lanthanoid salts, we have studied the regioselective 1,2-reduction of α,β -unsaturated carbonyl compounds with lithium aluminium hydride (LiAlH₄) and lanthanoid salts to give allylic alcohols. Saturated alcohol formation predominates in the absence of lanthanoid salts. Whilst the LnCl₃-NaBH₄/MeOH brings about the 1,2-reduction of α -enones, it does not affect other α,β -unsaturated carbonyl compounds such as aldehydes, esters, and carboxylic acids.† In contrast the LiAlH₄-LnX₃ reaction is effective for such compounds. In addition to its wide applicability, this reagent has the advantage of being simpler to use than the more conventional 1,2-regioselective reducing agents such as diisobutylaluminium hydride and 9-borabicyclononane.⁹

Results and Discussion

Treatment of cinnamaldehyde (**1a**) with 1 equivalent of LiAlH₄ in tetrahydrofuran (THF) at room temperature produced 3-phenylpropan-1-ol (**1c**) quantitatively.¹⁰ In contrast, addition of LiAlH₄ to a THF solution of (**1a**) and cerium chloride (1 equiv. each), gave cinnamyl alcohol (**1b**) (99%) together with a trace of compound (**1c**). As shown in Table 1, the regioselectivity still remained high for [CeCl₃]/[cinnamaldehyde] ratios > 0.2, but decreased for lower values (0.1). This result illustrates the catalytic activity of CeCl₃. Other cerium salts such as CeBr₃, CeI₃, or cerium acetylacetonate [Ce(acac)₃] are similarly effective for high 1,2-selectivity, but CeF₃ and cerium acetate are not (see Table 1). It has been reported that the addition of LiAlH₄ to cinnamaldehyde (**1a**) (0.25:1.0) at -10 °C produces a high yield of cinnamyl alcohol (**1b**).¹¹ However, our procedure is easier since it requires neither adjustment of temperature or quantity of LiAlH₄.

Table 1. Reduction of cinnamaldehyde (**1a**) with LiAlH₄ in THF in the presence of cerium salts^a

Cerium salts (equiv.)	% of Conversion ^b	Ratio of selectivity ^b	
		Allylic alcohol	Saturated alcohol
CeCl ₃ (1)	100	0:100	
(0.1)	100	24:76	
(0.2)	100	87:13	
(0.3)	100	92:8	
(0.5)	100	98:2	
(1.0)	100	99:1	
CeF ₃ (1.0)	100	10:90	
CeBr ₃ (1.0)	99	99:1	
CeI ₃ ^c (1.0)	90	95:5	
Ce(OAc) ₃ (1.0)	100	30:70	
Ce(acac) ₃ ^d (1.0)	100	98:2	

^a **1a** (1 mmol), LiAlH₄ (1 mmol), THF (7 ml); 10 min at room temperature. ^b Determined by g.l.c. ^c Prepared *in situ* from cerium metal and iodine. ^d Cerium acetylacetonate.

Table 2. Solvent effect on the reduction of (**1a**)^a

Solvent (ml)	% of Conversion ^b	Ratio of selectivity ^b	
		Allylic alcohol	Saturated alcohol
Hexane (7)	100	0:100	
Benzene (7)	100	0:100	
Et ₂ O (7)	100	75:25	
THF (1)	100	94:6	
(2)	100	99:1	
(7)	100	99:1	
(15)	100	99:1	

^a CeCl₃, LiAlH₄, (**1a**); 1 mmol each, 10 min at room temperature. ^b Determined by g.l.c.

The choice of solvent was an important factor to achieve a high selectivity, THF proving the best and then Et₂O; non-coordinative solvents such as hexane and benzene, produced no 1,2-selectivity (see Table 2). The overall concentration in THF was not critical for selectivity, which remained > 90% in 1–15 ml of THF (Table 2).

The results of the reduction of cinnamaldehyde in the presence of various metallic salts are shown in Table 3. Analysis of the results indicates that cinnamaldehyde (**1a**) reduction to yield cinnamyl alcohol (**1b**) is related to the nature of the lanthanoid salts. For reasons of economy cerium salts, were chosen for investigation. Thus the LiAlH₄-CeCl₃ reagent with methyl cinnamate (**2a**), cinnamic acid (**3a**), benzylideneacetone

† We have checked independently that the carbonyl group of cinnamaldehyde is not reduced by NdCl₃-NaBH₄ in MeOH, the acetalized compound being the major product (90%).^{5,6}

Table 3. Reduction of (1a) with LiAlH₄ in THF in the presence of metallic salts^a

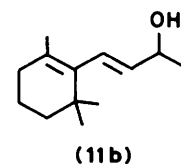
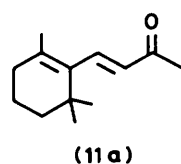
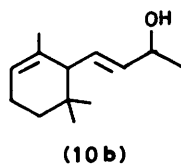
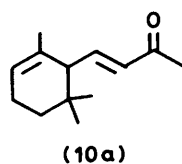
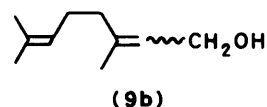
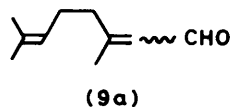
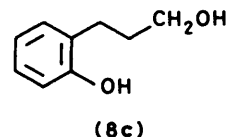
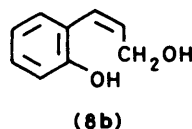
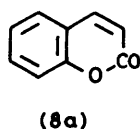
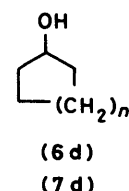
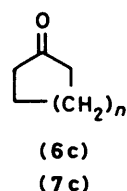
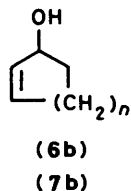
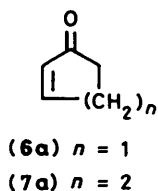
M in MCl ₃	% of Conversion ^b	Ratio of selectivity ^b	
		Allylic alcohol	Saturated alcohol
La	95	99:1	
Ce	100	99:1	
Pr	75	100:0	
Nd	98	100:0	
Sm	99	95:5	
Eu	100	98:2	
Yb	86	99:1	
Fe	98	51:49	
Co ^c	75	34:66	
Ni ^d	100	1:99	

^a MCl₃, LiAlH₄, (1a); 1 mmol each in THF (7 ml), 10 min at room temperature. ^b Determined by g.l.c. ^c CoCl₂. ^d NiCl₂.

(4a), and chalcone (5a) gave excellent yields of the corresponding allylic alcohols, (1b), (1b), (4b), and (5b), respectively contaminated with a slight amount of the saturated alcohols. In the absence of CeCl₃ parallel reductions afforded the corresponding saturated alcohols exclusively.

PhCH=CHCOR (1a) R=H (2a) R=OMe (3a) R=OH (4a) R=Me (5a) R=Ph	PhCH=CHCH(OH)R (1b) R=H (4b) R=Me (5b) R=Ph	PhCH ₂ CH ₂ CH(OH)R (1c) R=H (4c) R=Me (5c) R=Ph
---	--	---

CeCl₃ was also effective for the 1,2-reduction of cyclic enones such as cyclopent-2-en-1-one (6a) and cyclohex-2-en-1-one (7a) which, in its presence, the allylic alcohols (6b) and (7b) were formed in higher selectivity. Lack of regioselectivity in the

**Table 4.** Reduction of various α,β-unsaturated carbonyl compounds with LiAlH₄-CeCl₃ in THF^a

Carbonyl compound	Products (% of yield) ^b	% of Selectivity ^b	
		Allylic alcohol (without CeCl ₃) ^f	Saturated alcohol
(1a)	(1b), (1c) (99) (1)	99:1	(0:100)
(2a) ^d	(1b), (1c) (75) (25)	83:17	(0:100)
(3a)	(1b), (1c) (56) (14)	80:20	(0:100)
(4a)	(4b), (4c) (98) (1)	99:1	(1:99)
(5a)	(5b), (5c) (98) (1)	99:1	(1:99)
(6a)	(6b), (6c), (6d) (63) (2) (34)	64:36 ^e	(15:85 ^e)
(7a)	(7b), (7c), (7d) (98) (1) (1)	98:2 ^e	(83:17 ^e)
(8a) ^d	(8b), (8c) (50) (50)	50:50	(0:100)
(9a)	(9b) (50) (50) ^f	50:50	
(10a)	(10b) (100)	100:0	(100:0)
(11a)	(11b) (100)	100:0	(100:0)
	(100)	100:0	(100:0)

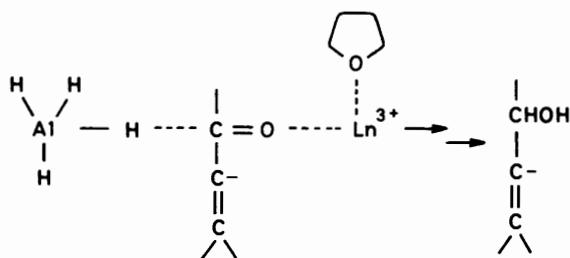
^a Carbonyl compound, LiAlH₄, CeCl₃; 1 mmol each in THF (7 ml), 10 min at room temperature. ^b Determined by g.l.c. ^c The reaction proceeded quantitatively. ^d LiAlH₄; 2 mmol. ^e Including a saturated ketone. ^f NdCl₃ was used. ^g Determined by ¹H n.m.r. ^h LiAlH₄; 4 mmol, CeCl₃; 2 mmol.

reduction of coumarin (8a) produced a 1:1 mixture of compounds (8b) and (8c); although the replacement of CeCl₃ by NdCl₃ gave no improvement in selectivity both still affected the reaction since in their absence no compound (8b) was formed.

Unexpectedly, from citral (**9a**), α -(**10a**) and β -ionone (**11a**), compounds (**9b**), (**10b**), and (**11c**) respectively were produced in excellent yields, both in the presence and absence of CeCl_3 (see Table 4).

The mechanism for the above reaction is unclear, the existence of reducing species requiring examination: the divalent lanthanoid species Ln^{2+} may be excluded on the basis of their absence in pinacol coupling reactions.¹⁰ Although lanthanoid hydride (LnH_3) or lanthanoid aluminium hydride species [$\text{LnCl}_n(\text{AlH}_4)_3$] may be one possibility for the reaction, if present such species, on the addition of a carbonyl compound to a mixture of LiAlH_4 and LnCl_3 in THF, should give the same result as the general procedure mentioned. An alternative procedure, however, resulted in a much lower yield of 1,2-reduction product, suggesting such hydride species are unlikely to be the reducing agent.

As stated above, the lanthanoid ion, Ln^{3+} has a strong affinity for oxygen and complex formation between LnX_3 and a carbonyl group may occur. Luche *et al.* have shown in the selective reduction of compounds (**6a**) to (**6b**) with $\text{NaBH}_4\text{-SmI}_3$ or $\text{NaBH}(\text{OMe})_3\text{-ErI}_3$, that the complexation effect of lanthanoid ion on the conjugated system was important in an aprotic medium.⁶ Under conditions of complexation control, *i.e.* a carbonyl group being activated by Ln^{3+} , attack of the conjugated system at a carbonyl carbon would be enhanced and the reduction rate should be accelerated. From our results, a similar complexation effect seems to be plausible. Consequently, we tentatively propose the reaction mechanism shown in the following scheme:



Scheme.

Experimental

¹H N.m.r. spectra were recorded with Hitachi R-24 (60 MHz) and Hitachi R-600 (60 MHz) instruments on solutions with SiMe_4 as an internal standard. I.r. spectra were taken in CHCl_3 solution with a JASCO-A1. G.l.c. analyses were carried out by using a Shimadzu 6AM apparatus on EGSS-X (3%)—Chromosorb-W (1 and 3 m), PEG 20 M (20%)—Celite (2 m), and Casterwax (10%)—Neopack 1A (2 m) columns (N_2 as carrier gas).

THF and diethyl ether were dried over sodium and then distilled under a nitrogen atmosphere. Lithium aluminium hydride was purchased from Metalgesellschaft AG. Anhydrous lanthanum chloride was commercially available (Nakarai Chemicals). Other lanthanoid chlorides, CeCl_3 , PrCl_3 , NdCl_3 , SmCl_3 , EuCl_3 , and YbCl_3 , were obtained by drying the corresponding commercial hydrates with SOCl_2 .¹² All starting α,β -unsaturated carbonyl compounds were commercially available and used without further purification. Such commercial organic compounds as cinnamyl alcohol, 3-phenylpropan-1-ol, geraniol, citronellol, cyclohexanol, cyclohexanone, cyclohex-2-enol, cyclopentanol, cyclopentanone, and cyclopent-2-enol were used as authentic samples for g.l.c. analyses.

General Procedure for the Reduction.—Cinnamaldehyde (**1a**; 132 mg, 1 mmol) and LnCl_3 (1 mmol) were dissolved in THF (7

ml). The lanthanoid salt LnCl_3 failed to dissolve in THF and the solution was heterogeneous. After the mixture had been stirred for a few minutes* (4–5 min), LiAlH_4 (37 mg, 1 mmol) was then added at room temperature. A vigorous gas evolution continued for 10 min before the solution was neutralized with dilute HCl, and then extracted with diethyl ether (20 ml \times 3); the combined extracts were then dried (MgSO_4). G.l.c. analyses of the ethereal solution revealed the presence of cinnamyl alcohol (**1b**) (132 mg, 0.99 mmol) and a trace of 3-phenylpropan-1-ol (**1c**) by using methyl cinnamate as an internal standard.

Reduction of benzylideneacetone (4a). In the presence of CeCl_3 , (**4b**) was obtained in 99% yield; δ_{H} (60 MHz) 1.20 (d, 3 H), 3.5 (br s, 1 H, OH), 4.0–4.5 (m, 1 H), 6.10 (dd, 1 H, *J* 5 and 15 Hz), 6.41 (d, 1 H, *J* 15 Hz), and 6.9–7.3 (m, 5 H). In the absence of CeCl_3 , (**4c**) was formed quantitatively; δ_{H} (60 MHz) 1.09 (d, 3 H), 1.5–1.8 (m, 2 H), 2.4–2.7 (m, 2 H), 3.66 (set, 1 H), 4.0 (br s, 1 H, OH), and 6.9–7.3 (m, 5 H).

Reduction of chalcone (5a). In the presence of CeCl_3 (**5b**) was obtained in 99% yield; δ_{H} (60 MHz) 5.1 (m, 1 H), 6.2–6.5 (m, 1 H), 6.60 (d, 1 H, *J* 15 Hz), 7.0–7.5 (m, 10 H). In the absence of CeCl_3 , (**5c**) was formed quantitatively; δ_{H} (60 MHz) 2.4–2.7 (m, 2 H), 3.3–3.7 (m, 2 H), 4.49 (t, 1 H, *J* 6 Hz), and 6.9–7.4 (m, 10 H).

Reduction of coumarin (8a). Two equimolar amount of LiAlH_4 (2 equiv.) and CeCl_3 (1 equiv.) were used for the reduction of (**8a**) to (**8b**); the ¹H n.m.r. spectrum revealed the presence of a mixture of (**8b**) and (**8c**); (**8b**) δ_{H} (60 MHz) 4.20 (d, 2 H, *J* 7 Hz), 5.5–6.0 (m, 1 H), 6.30 (d, 1 H, *J* 10 Hz), and 6.8–7.2 (m, 4 H). (**8c**); δ_{H} (60 MHz) 1.7–2.0 (m, 2 H), 2.66 (t, 2 H, *J* 6 Hz), 3.53 (t, 2 H, *J* 6 Hz), and 6.8–7.2 (m, 4 H).

Reduction of α -ionone (10a). Compound (**10b**) δ_{H} (60 MHz) 0.81 (s, 3 HO), 0.90 (s, 3 H), 1.20 (d, 3 H, *J* 7 Hz), 1.58 (s, 3 H), 1.8–2.2 (m, 5 H), 3.35 (br s, 1 H, OH), 4.0–4.4 (m, 1 H), and 5.2–5.5 (m, 3 H).

Reduction of β -ionone (11a). Compound (**11b**) δ_{H} (60 MHz) 0.92 (s, 6 H), 1.20 (d, 3 H, *J* 8 Hz), 1.61 (s, 3 H), 1.4–2.2 (m, 6 H), 3.2 (br s, 1 H, OH), 4.0–4.4 (m, 1 H), 5.35 (dd, 1 H, *J* 16 and 8 Hz), and 5.95 (d, 1 H, *J* 16 Hz).

* When this process was omitted, 1,2-selectivity was sometimes reduced. We consider this time necessary for the induction of Ln^{3+} ion complexation with a carbonyl group.

References

- For reviews; (a) T. Imamoto, Y. Tawarayama, T. Kusumoto, and M. Yokoyama, *J. Synth. Org. Chem. Jpn.*, 1984, **42**, 143; (b) Y. Fujiwara, *Kagaku, Zokan* (Kyoto), 1985, **105**, 111; (c) H. B. Kagan, 'Fundamental and Technological Aspects of Organo-f-Element Chemistry,' T. J. Marks and I. L. Fraga Ed., NATO ASI, Dordrecht, 1985, pp. 49–76; (d) H. Schuman, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 474.
- For Examples (a) T. Kano and H. Yanagida Eds., 'Rare Earth-Properties and Applications,' Gihodo Press Co., Tokyo, 1982, ch. 1 and ch. 3. N. E. Topp, 'Chemistry of Rare-Earth Elements,' Elsevier, Amsterdam, 1965, ch. 1 and ch. 4.
- B. M. Trost and M. J. Bogdanwicz, *J. Am. Chem. Soc.*, 1973, **95**, 2038; *ibid.*, 1973, **95**, 5321.
- M. Bendarski and S. Danishefsky, *J. Am. Chem. Soc.*, 1983, **105**, 3716; *ibid.*, 1983, **105**, 6968; *Tetrahedron Lett.*, 1983, **24**, 3451; *ibid.*, 1985, **26**, 2507.
- J.-L. Luche and A. L. Gemal, *J. Chem. Soc., Chem. Commun.*, **1978**, 976; *J. Am. Chem. Soc.*, 1979, **101**, 5848; *J. Org. Chem.*, 1979, **44**, 4187.
- (a) J.-L. Luche, *J. Am. Chem. Soc.*, 1978, **100**, 2226; (b) J.-L. Luche, L. R. Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, **1978**, 601; (c) A. L. Gemal and J.-L. Luche, *J. Am. Chem. Soc.*, 1981, **103**, 5454.

- 7 S. Fukuzawa, T. Fujinami, and S. Sakai, *J. Chem. Soc., Chem. Commun.*, **1985**, 777.
- 8 G. Klopman, *J. Am. Chem. Soc.*, 1968, **90**, 223.
- 9 A. Hajos, 'Complex Hydride,' Elsevier, Amsterdam, 1979, ch. 3 and ch. 4.
- 10 (a) J. L. Namy, J. Soupe, and H. B. Kagan, *Tetrahedron Lett.*, 1983, **24**, 765; (b) J. Soupe, L. Danon, J. L. Namy, and H. B. Kagan, *J. Organomet. Chem.*, 1983, **250**, 227.
- 11 F. A. Hochstein and W. G. Brown, *J. Am. Chem. Soc.*, 1948, **70**, 3484.
- 12 A. R. Pray, *Inorg. Synth.*, 1957, **5**, 153.

Received 17th December 1985; Paper 5/2224