Reduction of Carbonyl Compounds by Lanthanide Metal/2-Propanol: In-situ Generation of Samarium Isopropyloxide for Stereoselective Meerwein−Ponndorf−Verley Reduction

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The reduction of ketones and aldehydes with lanthanide metals (La, Ce, Sm, Yb) and a catalytic amount of iodine (5 mol %) in *i*PrOH proceeded smoothly to produce the corresponding alcohols as the major products in good yield, while in THF, methanol, and ethanol the pinacols were mainly produced. The yields of alcohols were improved most effectively by the use of Sm metal, the amount of pinacol produced thus being minimized. The actual reducing agent may be samarium isopropyloxide, which mediates the Meerwein–Ponndorf–Verley-type hydride-transfer reaction, since the reaction can be carried out catalytically with respect to samarium. The stereoselectivities of the reductions of the 2- and 4-substituted cyclohexanones with Sm/*i*PrOH were higher than those achieved with SmI_2/*i*PrOH or Sm/H_2O. The asymmetric reduction of acetophenone could be achieved to give the 1-phenylethanol in up to 95% *ee* in the presence of the chiral ligand **7**.

Introduction

The direct use of metallic lanthanides in organic synthesis has classically been reported as Grignard- and Reformatsky-type reactions involving organolanthanide species as intermediates.[1] As lanthanide metals have high reduction potentials, they have also been used as reducing agents for alkyl halides and carbonyl compounds. Yb metal mediates the Birch-type reduction of aromatic compounds in liquid ammonia[2] and the "Umpolung" of aromatic carbonyl compounds.[3] Metallic samarium mediates a Simmons−Smith-type cyclopropanation of allylic alcohol and the iodomethylation of carbonyl compounds with diiodomethane.[4] The diastereoselective Barbier-type reaction can also be performed with Sm.[5] The most typical and efficient reaction carried out with lanthanide metals such as La, Ce, Yb, and Sm is the pinacolic coupling reaction of carbonyl compounds.[6] The diastereoselective reductive coupling of chiral imines is promoted by Sm, to give the corresponding chiral vicinal diamines.[7] The direct use of metallic lanthanides in organic synthesis has been of some interest, but their application is still limited. On the other hand, samarium(II) iodide has been a popular reducing agent, applied to a wide range of functional groups.[8] Metallic lanthanides, including samarium, have advantages in terms of atom economy, however; samarium(II) iodide requires one mol of iodine in addition to one mol of samarium. A recent report demonstrated that samarium metal can be used in water and can mediate the pinacol coupling reaction of aromatic ketones and aldehydes.[9] More than ever, metallic lanthanides are now becoming attractive and promising reagents from the viewpoint of green chemistry. We are interested in the reductive coupling of carbonyl compounds with metallic lanthanides because this is one of the highest yielding and synthetically useful reactions.

Results and Discussion

We first re-examined the reductive coupling of acetophenone with lanthanum metal according to Nishiyama's method.[6a] Upon treatment of acetophenone with lanthanum metal (1 equivalent relative to acetophenone) in THF in the presence of a catalytic amount of iodine at room temperature, the solution gradually became dark gray to black. The solution was stirred at room temperature for 20 h, and worked up conventionally. GC/MS analysis of the organic solution showed the corresponding pinacol as a major product together with a small amount of the alcohol. The result was fairly consistent with Nishiyama's results, although our yield was lower. We then carried out the reaction in MeOH, EtOH, and *i*PrOH instead of THF. For the reactions in MeOH and EtOH, the proportion of the alcohol increased, but the pinacol was still formed in significant amounts. The reaction in *i*PrOH dramatically changed the product selectivity, the alcohol being mainly produced, unlike the reactions in THF and EtOH. These results are

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summarized in Table 1. The reaction hardly took place in *t*BuOH and H_2O.

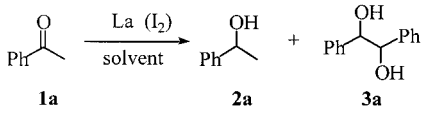


Table 1. Reduction of acetophenone with lanthanum metal

Entry	Reaction[a] Solvent	Yield (%)[b] Alcohol **2a**	Pinacol **3a**
1	THF	3	44
2	MeOH	28	26
3	EtOH	10	39
4	*i*PrOH	48	24
5	*t*BuOH	0	0
6	H_2O	0	0

[a] Acetophenone (1.0 mmol), La (1.0 mmol), iodine (0.04−0.06 mmol), solvent (3.0 mL); 25 °C, 20 h. [b] Yield was determined by GC by use of internal standard based on acetophenone.

We were interested in this preferential reduction of the ketone to the alcohol in *i*PrOH, and examined some representative lanthanide metals (i.e., La, Ce, Sm, and Yb metals). The results of the reaction with acetophenone are shown in Table 2. The reaction procedure was modified in order to improve the alcohol selectivity. Thus, lanthanide metal and a trace of iodine were stirred in *i*PrOH at room temperature for 1 h before the addition of acetophenone, during which time the metal powder almost dissolved and the solution became darker.[10] Acetophenone was then added to the solution, and the system was stirred at room temperature for 20 h. After conventional acidic workup of the solution, the organic extract was analyzed by GC/MS. As shown in Table 2, the use of samarium metal was the most effective way to improve the yield of the alcohol, thus minimizing the amount of the pinacol.

Table 2. Reduction of acetophenone with lanthanide metals in *i*PrOH

Entry	Reaction[a] Ln	Yield (%)[b] Alcohol **2a**	Pinacol **3a**
1	La	48	24
2	Ce	34	22
3	Sm	96	2
4	Yb	24	24

[a] Acetophenone (1.0 mmol), Ln (1.0 mmol), iodine (0.04−0.06 mmol), *i*PrOH (3.0 mL); 25 °C, 20 h. [b] Yield was determined by GC by use of internal standard based on acetophenone.

The above procedure with Sm/*i*PrOH was applied to the reduction of several ketones and aldehydes; typical results are shown in Table 3. Aromatic ketones such as 4-substituted acetophenones, propiophenone, or 1-acetonaphthones each underwent a simple reduction to form the corresponding alcohol, with little contamination originating from the pinacol coupling product. The reduction of 4-nitroacetophenone (**1d**) resulted in a low yield of 4′-nitrophenyl-1-ethanol, probably due to contamination by nitro group reduction (entry 4). The reduction of aldehydes such as cyclohexanecarboxaldehyde (**1j**) and 3-phenylpropanal (**1k**) yielded the corresponding primary alcohols in moderate to good yields; isopropyl 3-phenylpropionate, possibly resulting from a disproportionation reaction, was detected in the reaction with 3-phenylpropanal. Interestingly, the reaction with benzaldehyde (**1l**) gave not only benzyl alcohol but also the reductive aldol product with acetone, resulting from the oxidation of 2-propanol (entry 12); 4-phenyl-3-buten-2-ol was produced in 10% yield.

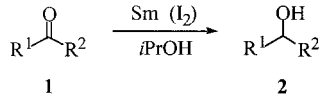


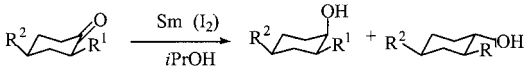
Table 3. Reduction of ketones and aldehydes (**1a**−**l**) with Sm in *i*PrOH

Entry	Ketone, aldehyde[a] R^1	R^2	Yield of **2** (%)[b]
1	Ph	Me (**1a**)	96
2	4-$MeOC_6H_4$	Me (**1b**)	82
3	4-F C_6H_4	Me (**1c**)	99
4	4-NO_2 C_6H_4	Me (**1d**)	33
5	Ph	Et (**1e**)	84
6	1-$C_{10}H_7$	Me (**1f**)	92
7	$PhCH_2$	$PhCH_2$ (**1g**)	95
8	Ph	*c*-C_3H_5 (**1h**)	60
9	$PhCH_2CH_2$	Me (**1i**)	78
10	*c*-C_6H_{11}	H (**1j**)	87
11	$PhCH_2CH_2$	H (**1k**)	60[c]
12	Ph	H (**1l**)	48[d]

[a] Ketone (1.0 mmol), Sm (1.0 mmol), iodine (0.04−0.06 mmol), *i*PrOH (3.0 mL); the ketone was added after 2 h stirring of a mixture of Sm(I_2 cat) and *i*PrOH at 25 °C. [b] Yield was determined by GC by use of internal standard based on a ketone. [c] Other product: isopropyl 3-phenylpropionate, 5%. [d] Other product: 4-phenyl-3-buten-2-ol, 10%.

The stereochemical outcome of the reduction was examined with 2- and 4-substituted cyclohexanones; these results are shown in Table 4. The results from the reaction with SmI_2/*i*PrOH[11] were also examined for comparison. Treatment of 2-methylcyclohexanone (**4a**) with Sm/*i*PrOH preferentially gave the *trans* alcohol (**6a**) (76% *de*), while treatment with SmI_2/*i*PrOH gave an almost 1:1 mixture of the *cis* and *trans* isomers (entries 1−2). The Sm/H_2O system has been reported to produce a stereochemical outcome similar to that of SmI_2/*i*PrOH in the reaction with **4a**.[9] The reaction with 2-phenylcyclohexanone (**4b**) preferably gave the *cis* alcohol (**5b**) with either Sm/*i*PrOH or SmI_2/*i*PrOH (entries 3−4). In the reaction with 2-methoxycyclohexanone (**4c**), Sm/*i*PrOH preferentially gave the *cis* alcohol (**5c**) in good yield, while SmI_2/*i*PrOH reductively removed

the methoxy group to produce cyclohexanol along with a poor yield of **5c** (entries 5−6).[12] These results showed the Sm/*i*PrOH system to provide higher stereoselectivity than SmI_2/*i*PrOH in the reduction with chiral ketones. This diastereoselectivity may be explained in terms of a less hindered equatorial attack of Sm/*i*PrOH on the carbonyl group. Chelation of the carbonyl group (and methoxy group) to the samarium atom should be involved in the stereoselective reduction. Sm/*i*PrOH gave a slightly better diastereoselectivity (*trans* major) than observed with SmI_2/*i*PrOH in the reaction with 4-*tert*-butylcyclohexanone (**4d**) (entries 7−8).[13]



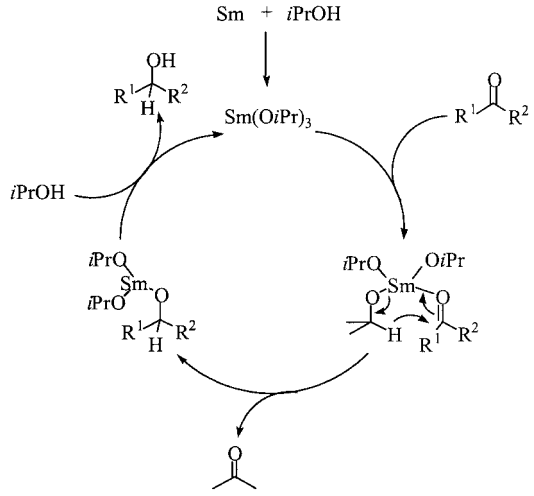
4a: R^1 = Me, R^2 = H
4b: R^1 = Ph, R^2 = H
4c: R^1 = OMe, R^2 = H
4d: R^1 = H, R^2 = *t*Bu

Table 4. Reduction of substituted cyclohexanones (**4a**−**d**) with Sm/*i*PrOH or SmI_2/*i*PrOH

Entry	Reaction[a] Ketone	Reagent	Total yield (%)	**5/6**[b] (*cis*/*trans*)
1	**4a**	Sm	> 99	12:88
2	**4a**	SmI_2	> 99	45:55
3	**4b**	Sm	> 99	91:9
4	**4b**	SmI_2	> 99	90:10
5	**4c**	Sm	90	70:30
6	**4c**	SmI_2	15[c]	70:30
7	**4d**	Sm	> 99	15:85
8	**4d**	SmI_2	> 99	28:72

[a] Ketone (1.0 mmol), Sm (1.0 mmol), iodine (0.05 mmol), *i*PrOH (3.0 mL) or SmI_2 (1.0 mmol), THF (20 mL), *i*PrOH (1.0 mL); 25 °C, 20 h. [b] Yield and isomer ratio were determined by GC by use of internal standard based on a ketone. [c] Other product, cyclohexanol, 81%.

The reaction can be carried out catalytically. It was thus carried out with 0.5 mmol of Sm and 5.0 mmol of acetophenone (10 mol %) in *i*PrOH (5 mL) under the stated conditions (Scheme 1), and 4.0 mmol of 1-phenylethanol was produced (80% yield). This result suggested that the reaction was not mediated by Sm metal itself, as otherwise 0.75 mmol (1.5 equivalent to Sm) of the ketone could be reduced at most; the reaction may not involve a single-electron transfer. The actual reducing agent may be samarium isopropyloxide, which mediates Meerwein−Ponndorf−Verley (MPV)-type hydride transfer from an isopropoxy group to a carbonyl group.[14] The observation of the aldol product of the benzaldehyde with acetone (Table 3, entry 12) may support this mechanism, the acetone being the result of the dehydrogenation of 2-propanol.[15] A catalytic amount of iodine initiates the reaction of the samarium metal with *i*PrOH to generate samarium isopropyloxide. Indeed, the samarium metal almost disappeared during the reaction and the solution darkened before the addition of the carbonyl compound.[10] The Sm/*i*PrOH-promoted reduction proceeded smoothly at room temperature, while the reaction with isolated samarium isopropyloxide proceeds at a higher temperature (30−80 °C). This in situ preparation of samarium isopropyloxide should provide a convenient and efficient method of MPV reduction without the use of a harmful mercury salt as an activator for samarium.[10] Furthermore, this method with metallic samarium has an advantage over SmI_2/*i*PrOH in terms not only of atom economy but also of stereoselectivity of the chiral ketones.



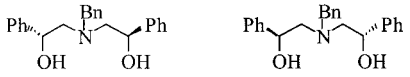
Scheme 1

We finally applied this reaction to the asymmetric reduction of acetophenone by screening some chiral ligands; (1*R*,5*R*)-3-benzyl-1,5-diphenyl-3-azapentane-1,5-diol (Evans' amino alcohol, **7**),[16] its (1*S*,5*S*)-enantiomer (**8**), (−)-sparteine (**9**), (2*R*,4*R*)-pentanediol (**10**), (*S*)-valinol (**11**), and (*R*)-BINOL (**12**) were examined as representative ligands. The reaction was usually carried out with a stoichiometric amount of Sm and the ligand relative to acetophenone. The results, shown in Table 5, show that **7** and **8** were the most efficient ligands for the asymmetric re-

Table 5. Enantioselective reduction of acetophenone with Sm/chiral ligand/*i*PrOH

Entry	Reaction[a] Ligand	Yield of **2a** (%)[b]	*ee* (%)[c] (configuration)
1	(1*R*,5*R*)-**7**	60	95 (*R*)
2[d]	(1*R*,5*R*)-**7**	20	75 (*R*)
3	(1*S*,5*S*)-**8**	55	94 (*S*)
4	(2*R*,4*R*)-**9**	86	12 (*S*)
5	(−)-sparteine (**10**)	79	0
6	(*S*)-valinol (**11**)	74	0
7	(*S*)-BINOL (**12**)	trace	−

[a] Acetophenone (0.5 mmol), Sm (0.5 mmol), iodine (0.05 mmol), ligand (0.5 mmol), *i*PrOH (3.0 mL), THF (1.0 mL); 25 °C, 20 h. [b] Yield was determined by GC by use of internal standard based on acetophenone. [c] Determined by GC on a chiral capillary column (Chiraldex G-TA). [d] Acetophenone (10 mmol) was used for each 1 mmol of Sm and a ligand.



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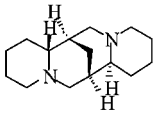

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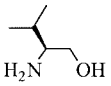

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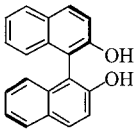

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duction; the use of **7** afforded a 60% yield of **3a** with 95% *ee* (*R*). The catalytic reaction with 10 mol % of **7** to acetophenone was not successful, giving only a 20% yield (based on the ketone) with lower enantioselectivity (75% *ee*).

Conclusion

This in situ preparation of samarium isopropyloxide should provide a convenient and efficient method of MPV reduction without the need for a harmful mercury salt as an activator for samarium. Furthermore, this method with metallic samarium has an advantage over SmI_2/*i*PrOH in terms not only of atom economy but also of stereoselectivity of the chiral ketones.

Experimental Section

General: The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR (300 MHz) spectrometer as solutions in $CDCl_3$. The chemical shifts are reported in δ units downfield from the internal reference (Me_4Si). The infrared spectra were obtained with a JASCO Herschel FT/IR-230A spectrometer. The HPLC analyses were carried out on a Hitachi L-7100 apparatus fitted with a UV detector and chiral columns. The GC/MS analyses were carried out on a Hewlett−Packard 5980/5972 instrument fitted with a capillary column (HP-5ms, 0.25 mm, 30 m) with helium as carrier gas. The optical rotations were determined on a JASCO DIP-370 apparatus. The elemental analyses were carried out with a Yanaco CHN CORDER MT-5. Preparative TLC was conducted on a 20 × 20 cm glass sheet coated with a 2-mm layer of Merck kieselgel 60 PF_{254}. All the lanthanide metals (99.9%) were purchased from Nippon Yttrium Co., Ltd. Lanthanum and cerium were obtained as powders. Samarium and ytterbium were obtained as ingots and scraped with a rasp and then used as powders (ca. 40 mesh). 2-Propanol was distilled from CaH_2 and stored over 4-Å molecular sieves (MS-4Å). Methanol and ethanol were distilled from magnesium alkoxides generated by addition of magnesium turnings. Commercial dry THF was used without further purification. All organic compounds were commercially available and were used without further purification.

Stoichiometric Reaction between Acetophenone (1a) and Samarium Metal in *i*PrOH: The following information provides a typical experimental procedure for the reduction of ketones with samarium metals. Under a nitrogen atmosphere, samarium powder (150 mg, 1.0 mmol) and a trace of iodine (10−15 mg, 0.04−0.06 mmol) were placed in a 50 mL Schlenk tube fitted with a magnetic stirring bar. Dry *i*PrOH (2.0 mL) was introduced by syringe through a septum at room temperature. An exothermic reaction started within a few minutes and the solution became dark purple to black; this observation may represent the formation of "samarium isopropyloxide". After the solution had been stirred for 1 h at room temperature, an *i*PrOH (1.0 mL) solution of acetophenone (120 mg, 1.0 mmol) was added. The mixture was stirred at the same temperature for 20 h, during which the color of the solution became dark brown. The solution was hydrolyzed with hydrochloric acid (0.1 mol/L, 25 mL), and the aqueous phase was extracted with three portions of ethyl acetate (15 mL). The organic phase was washed with aqueous sodium thiosulfate (to remove the liberated iodine) and brine, and was then dried with magnesium sulfate. GC/MS analysis of the organic solution revealed the presence of 1-phenylethanol as the major product and a small amount of the corresponding pinacol.

All products were known compounds and were characterized by GC/MS on a capillary column (HP-5ms) by use of authentic samples. The yields of products were determined by GC with biphenyl as an internal standard. Some compounds were isolated by preparative TLC (Merck Silica Gel 60 PF_{256}) and their structures were further confirmed by ^1H NMR (300 MHz).

Enantioselective Reaction between Acetophenone (1a) and Sm/Chiral Ligand in *i*PrOH: The "samarium isopropyloxide" (Sm, 0.5 mmol; *i*PrOH, 3.0 mL) was prepared by the same procedure as described above. After the solution had been stirred for 1 h at room temperature, a THF (1.0 mL) solution (1*R*,5*R*)-3-benzyl-1,5-diphenyl-3-azapentane-1,5-diol (**7**, 350 mg, 1.0 mmol) was added, and the mixture was stirred for 1 h. Acetophenone (120 mg, 0.5 mmol) was then added, and the resulting mixture was stirred at the same temperature for 20 h, during which the color of the solution changed to brown. The solution was hydrolyzed with hydrochloric acid (0.1 mol/L, 25 mL), and the aqueous phase was extracted with three portions of ethyl acetate (15 mL). The organic phase was washed with aqueous sodium thiosulfate (to remove the liberated iodine) and brine, and was then dried with magnesium sulfate. Chiral GC analysis (Chiraldex G-TA, 20 m, 80 °C) of the organic solution revealed the presence of (*R*)-1-phenylethanol (*Rt* = 15.5 min) as a major product and the (*S*)-alcohol (*Rt* = 14.2 min) as the minor product.

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[13] Our result differed from Kagan's report, in which the *cis* alcohol was the major product (*cis*/*trans* = 72:28) after repetition of several experiments. See ref.[11]

[14] Lanthanide isopropyloxide-mediated MPV reductions have been reported: J.-L. Namy, J. Souppe, J. Collin, H. B. Kagan, *J. Org. Chem.* **1984**, *49*, 2045; A. Lebrun, J.-L. Namy, H. B. Kagan, *Tetrahedron Lett.* **1991**, *32*, 2355; T. Okano, M. Matsuoka, S. Kinoshita, M. Kiji, *Nippon Kagaku Kaishi*, **1993**, 487.

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[16] It has been reported that the samarium alkoxide of the amino alcohol **7** is an efficient catalyst for asymmetric MPV reduction: D. A. Evans, S. G. Nelson, M. R. Gand, A. R. Muci, *J. Am. Chem. Soc.* **1993**, *115*, 9800.

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