A Chiral Samarium-Based Catalyst for the Asymmetric Meerwein–Ponndorf–Verley Reduction

David A. Evans,* Scott G. Nelson, Michel R. Gagné, and Alexander R. Muci

Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138

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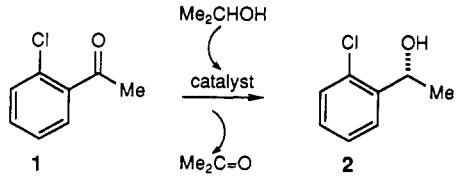
The Meerwein–Ponndorf–Verley (MPV) reduction enjoys a prominent historical position in synthesis methodology,[1] and milder variants of this process utilizing trivalent lanthanide catalysts continue to improve the utility of this reaction for the reduction of ketones.[2] The purpose of this communication is to report an enantioselective variant of the MPV reduction which is catalyzed by a chiral samarium(III) complex at ambient temperatures in 2-propanol.[3]

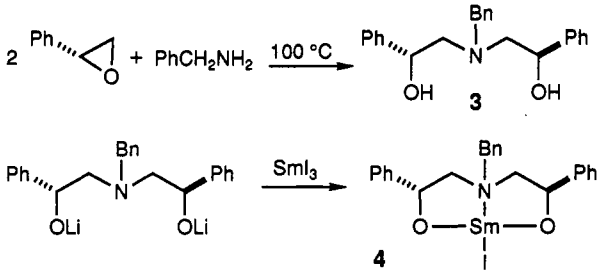
On the basis of precedent established by Kagan,[2] a range of Sm(III) complexes were generated from freshly prepared SmI_3 and chiral bi- and tridentate ligands. These complexes were screened as catalysts in the reduction of *o*-chloroacetophenone (25 equiv of 2-propanol, 25 °C) (eq 1). This screening process



(1)

revealed two important trends. First, contrary to expectation, complexed ligands containing chiral secondary alkoxides are not oxidized under the reaction conditions, an important consideration in ligand design since secondary alcohols are potential substrates in this reaction. Second, chiral bidentate ligands consistently afforded lower enantioselectivities than several tridentate ligands.[4] The most successful of these ligands and the use of the derived lanthanide complex in asymmetric MPV reductions are reported in the following discussion.

The ligand *(R,R)*-**3**, giving the highest selectivities for the MPV reduction of aryl methyl ketones, was synthesized in one step from commercially available (*R*)-styrene oxide and benzylamine (eq 2).[5] Generation of the 1:1 metal–ligand complex **4** was

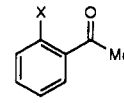
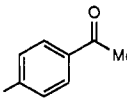
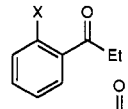
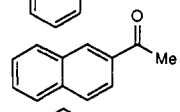
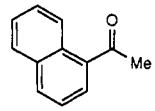


(2)

(3)

accomplished by double deprotonation of (*R,R*)-**3** with hydroxide-free *n*-BuLi and subsequent complexation with SmI_3 in THF (eq 3).[6] The resulting soluble catalyst, at 5 mol %, catalyzes the reduction of **1** by 2-propanol to give the (*R*)-alcohol **2**, in 97% ee and 96% yield at ambient temperatures over a 1–2-h period (eq 1). Interestingly, catalyst **3** is considerably more reactive than the previously reported *t*-$BuOSmI_2$ complex, which typically requires a temperature of 60 °C to catalyze the reduction of ketones.[2]

Table I. Enantioselective MPV Reduction of Aryl Methyl Ketones[a]

entry	substrate		% ee (config)[b]	% conversion[c]
1		X = Cl	97 (*R*)[d,e]	100 (96)
2		X = H	96 (*R*)[d]	83 (74)
3		X = OMe	96 (*R*)[f]	100 (95)
4		X = Cl	94 (*R*)[f]	91 (88)
5		X = OMe	92 (*R*)[d]	43 (36)
6		X = NO_2	94 (*R*)[g]	100 (77)
7		X = Cl	68 (*R*)[d,e]	95 (78)
8		X = H	73 (*R*)[f]	66 (63)
9			96 (*R*)[h]	84 (82)
10			97 (*R*)[e,f]	98 (95)

[a] Reactions were carried out on a 2-mmol scale using the conditions given in the text. Products were isolated after complete conversion or 24 h. [b] Absolute configuration assigned by comparison of product rotations to literature values except where noted. [c] Conversions were determined by GLC. Values in parentheses are isolated yields. [d] Enantiomeric purity was determined by chiral GLC assay (Chiraldex G-TA). [e] Absolute configuration was assigned by the method of Trost (Trost, B. M. *et al. J. Org. Chem.* **1986**, *86*, 2370–2374). [f] Enantiomeric purity was determined by chiral HPLC assay (Daicel Chiralcel-OD). [g] Enantiomeric purity was determined by ^1H NMR spectroscopic assay of the derived Mosher ester. [h] Enantiomeric purity was determined by chiral HPLC assay (Bakerbond, DNBPG).

Our initial efforts have been directed at the reduction of aryl ketones for which ligand *(R,R)*-**3** has been optimized (Table I). In general, simple aryl methyl ketones afford enantiomeric excesses ≥92% (entries 1–6, 9, 10). The aryl moiety may be varied with regard to the degree and position of substitution, and naphthyl methyl ketones also reduce with high selectivity (entries 9, 10). At the present time, reaction enantioselectivity appears to be quite sensitive to the alkyl substituent. For example, as the size of the alkyl group is increased (Me → Et), enantioselectivity decreases (entries 7, 8).

One of the critical characteristics of this MVP reduction variant is the special affinity exhibited by the catalyst for 2-propanol as the hydride source. For example, other alcohols such as 3-pentanol, cyclopentanol, or benzhydrol are not practical alternative reductants. As a corollary to this observation, product enantiomeric purity is maintained in all instances even after prolonged exposure to the catalyst system.

(1) (a) Wilds, A. L. *Org. React. (N.Y.)* **1944**, *2*, 178–223. (b) Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425–1429. (c) von E. Doering, W.; Aschner, T. C. *J. Am. Chem. Soc.* **1953**, *75*, 393–397.

(2) (a) Namy, J. L.; Souppe, J.; Collin, J.; Kagan, H. B. *J. Org. Chem.* **1984**, *49*, 2045–2049. (b) Lebrun, A.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1991**, *32*, 2355–2358.

(3) Limited success has been achieved using chiral Zr, Ru, Rh, and Ir complexes as catalysts: (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051–1069 and references cited therein. (b) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziger, D. *Helv. Chim. Acta* **1992**, *75*, 2171–2209.

(4) For example, the complex formed from (*S*)-lithium binaphthoxide and SmI_2 exhibited 24% ee in the reduction of **1**. More promising chiral catalysts derived from tridentate 2,6-bis(oxazolinyl)pyridines (Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306–4309) and *t*-$BuOSmI_2$, which afforded 58% ee in the indicated reduction (eq 1).

(5) (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769. (b) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343.

(6) Structure **4** is provided only to represent ligand–metal stoichiometry. Catalyst aggregation, alluded to by the nonlinear effects described below, may affect the exact nature of the catalytic species.

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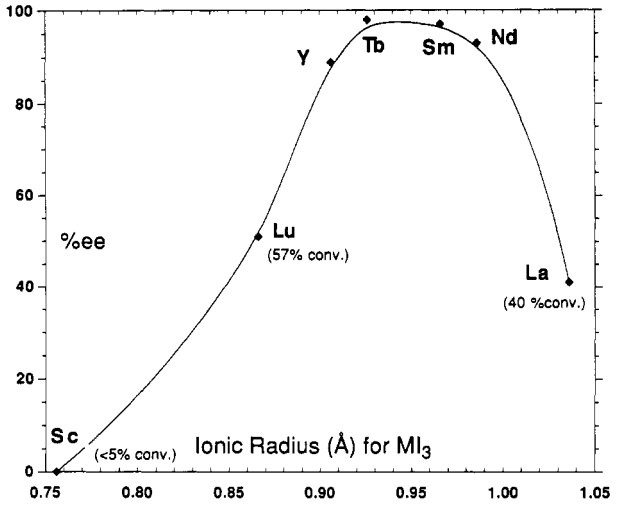

Figure 1. Enantioselective reduction of **1** by catalysts derived from **3** and MI_3 (2-propanol, 24 h, 25 °C).

The influence of electronic effects on reduction efficacy was also examined. Not unexpectedly, electron-withdrawing groups increase the reactivity of the ketone (entries 1, 4, 6, 7), whereas an electron-donating group (entry 5) attenuates substrate reactivity, with the exception of the *o*-methoxy substituent (entry 3). A competition experiment between *o*-methoxyacetophenone and acetophenone showed at least a 10-fold increase in rate of reduction of the *ortho*-substituted ketone. We attribute this rate enhancement to two-point binding of the substrate to the metal center. The increased reactivity effected by a proximal heteroatom may be general, and such two-point catalyst–substrate binding could be a promising attribute of these reductions.[7]

The effect of lanthanide metal size on the enantioselectivity of the reduction of *o*-chloroacetophenone reduction has also been investigated. As illustrated in Figure 1, lanthanide(III) complexes derived from NdI_3, SmI_3, and TbI_3 and ligand (*R*,*R*)-**3** showed optimum selectivities;[8] deviations to either larger or smaller ionic radii[9,10] exhibited diminished enantioselectivities and reduced catalytic competencies. For the most active lanthanide catalysts derived from the indicated metal halide (YI_3, TbI_3, SmI_3 and NdI_3) and ligand **3**, reduction times of 1.5–3 h were observed. These results, coupled with the higher reactivity of Sm for the reduction of acetophenone, implicated the complex derived from SmI_3 to be the optimal catalyst on both selectivity and reactivity considerations.

Nonlinear effects similar to those reported by Kagan[11] and Noyori[12] have been observed. When enantiomerically enriched (80% ee) ligand **3** was employed in the reaction, the product **2** was formed in 95% ee, the same enantiomeric excess as obtained using enantiomerically pure **3**. Such stereochemical amplification is consistent with, but not limited to, the scenario of a stable hetero dimer such as [(*S*,*S*)-**3**]SmI-[(*R*,*R*)-**3**]SmI sequestering the minor amounts of [(*S*,*S*)-**3**]SmI into an unreactive species, thereby allowing [(*R*,*R*)-**3**]SmI to kinetically dominate the reaction. This kinetic/mechanistic scheme is analogous to that proposed by Noyori in the catalyzed ethylation of aldehydes by Et_2Zn.

A typical experiment using 2 mmol of substrate is as follows:[13] under an argon or nitrogen atmosphere, 36 mg (0.1 mmol) of ligand **3** in 0.5 mL of THF is cooled to 0 °C and deprotonated with 1.9 equiv of *n*-BuLi.[14] The ligand solution is warmed to room temperature and transferred via cannula into a second flask containing a slurry of SmI_3 in THF which has been prepared from 1.0 mL of 0.1 M SmI_2 (0.1 mmol) and 15 mg (0.053 mmol) of diiodoethane.[15] After transfer of the residual ligand into the reaction flask with an additional 0.4 mL of THF, the homogeneous orange catalyst solution is stirred for 1 h at ambient temperature.[16] To the catalyst solution is added 3.8 mL of 2-propanol (50 mmol) followed by 2 mmol of the ketone (final 2-propanol:THF ratio = 2:1). The reaction is quenched by addition of a saturated aqueous solution of potassium sodium tartrate and then concentration of the resulting slurry *in vacuo*. The oil thus obtained is diluted with 1 M aqueous HCl and extracted with ethyl acetate. The organic extracts are concentrated *in vacuo*, and the resulting slurry is diluted with Et_2O, allowing the insoluble HCl salt of **3** to be collected by filtration. The ethereal layer is dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography affords the desired alcohol in the indicated yield and enantioselectivity (Table I).

In order to document the efficiency of this reduction on a larger scale, 100 mmol of 1-acetonaphthone was reduced using 5 mol % of **4** (25 °C, 66 h) and 25 equiv of 2-propanol to afford an 82% isolated yield of (*R*)-(+)-α-methyl-1-naphthalenemethanol (96% ee) while the HCl salt of **3** was recovered in 96% yield.[17]

Chiral lanthanide complexes have, thus, been demonstrated to effectively catalyze the asymmetric MPV reduction of aryl methyl ketones. Enantioselectivities in the reduction of aryl methyl ketones are competitive with enantioselective borane reductions[18] in both laboratory and larger scale applications. Current efforts are being directed toward exploring the generality of the reduction process in addition to the potential of heteroatom-directed MPV reductions.

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Supplementary Material Available: Experimental procedures and enantiomeric purity assays for all compounds (5 pages). Ordering information is given on any current masthead page.

(7) (a) In an earlier study we obtained circumstantial evidence that the Sm MPV reduction might be directed by heteroatom substituents: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031. (b) For a recent review on directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(8) In comparative reductions using *o*-chloroacetophenone and catalysts derived from MI_3 and ligand **3**, complete reductions were observed after 1.5–3 h for catalysts derived from YI_3,TbI_3,SmI_3,andNdI_3. The extent of conversion after 24 h for the other catalysts is recorded in Figure 1.

(9) Shannon, R. D. *Acta. Crystallogr.* **1976**, *A32*, 751–767.

(10) The lanthanide triiodides other than SmI_3 were purchased from Cerac Incorporated, Milwaukee, WI.

(11) Puchot, C.; Samuel, O; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353–2357.

(12) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49–69 and references cited therein.

(13) A typical experimental procedure involves the use of dry, degassed THF, ketone, and 2-propanol. Where possible, substrates were distilled from CaH_2.

(14) The use of hydroxide-contaminated *n*-BuLi was deleterious to both enantioselectivities and rates; optimum results were obtained using new bottles (Aldrich Chemical Co.).

(15) Imamoto, T.; Ono, M. *Chem. Lett.* **1987**, 501–502.

(16) The presence of Cl^- impurities was found to inhibit the reaction.

(17) On a 100-mmol scale, optimum results were obtained using 1.6 equiv of *n*-BuLi; see supplementary material for full procedural details.

(18) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429–3430 and references cited therein.