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Asymmetric Transfer Hydrogenation of Aryl Ketones Catalyzed by Salt-Free Two Samarium Centers Supported by a Chiral Multidentate Alkoxy Ligand

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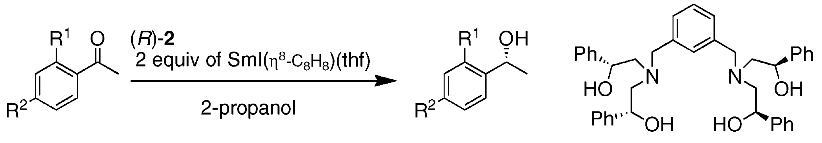
ABSTRACT



R^1 = Cl, R^2 = H
> 99% conversion
> 99% *ee*

(*R*)-**2**

We synthesized a chiral multidentate ligand, (*R*,*R*,*R*,*R*)-*N*,*N*,*N*′,*N*′-tetra(2-hydroxy-2-phenylethyl)-1,3-xylylene diamine [(*R*)-2], which can support two metals at adjacent positions. Asymmetric transfer hydrogenation of acetophenone and its derivatives was conducted by using salt-free bimetallic lanthanoid complexes of (*R*)-2, and the combination of two samarium atoms and (*R*)-2 was found to be the best catalyst system for asymmetric transfer hydrogenation of aryl ketones in high enantioselectivity (up to >99% ee).

Asymmetric transfer hydrogenation of ketonic substrates is an intriguing and useful synthetic methodology to yield chiral alcohols.[1] Trivalent samarium compounds supported by bi- and tridentate chiral auxiliaries have been utilized as catalysts for this purpose.[2] Among them, Evans et al. reported that a samarium species, which was in situ generated by treating the dilithio salt of a chiral tridentate ligand, (*R*)-**1**, with SmI_3, mediated the asymmetric reduction of aryl ketones.[2c] It is assumed likely that the interaction of the lithium salt with the catalytically active samarium center may play an important role in determining the activity and enantioselectivity because some ate lanthanoid compounds have been reported to show different catalytic performance compared with salt-free lanthanoid compounds.[3] The enantioselectivity and catalytic activity of the samarium species were quite sensitive to the purity of the lithiation reagent, such as *n*-BuLi. Additionally, the samarium catalyst system based on (*R*)-**1** exhibited a nonlinear amplification effect on the asymmetric transfer hydrogenation of *o*-chloroacetophenone,[2c] indicating that the catalytically active mononuclear samarium species was assumed to be in equilibrium with the dimmeric species.[4]

In contrast to the mononuclear metal complex, similar efforts have not been made for bimetallic and multimetallic

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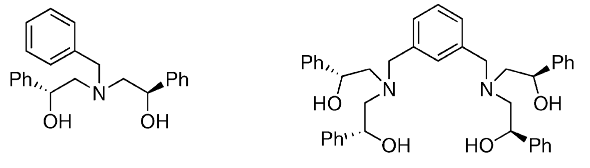
catalyst systems,[5] in which each metal center acts cooperatively and mutually not only to activate substrates but also to enhance any selectivities including enantioselectivity. Recent achievements were that bimetallic catalyst systems based on zinc, aluminum, and titanium with chiral auxiliary ligands catalyzed some asymmetric reactions such as aldol reaction[6] and carbonyl reduction.[7]

On the basis of these precedents, we could point out that two factors, presence or absence of salt and mononuclear or dinuclear status, are mainly responsible to the catalytic performance of lanthanoid compounds, and thus we anticipated that a salt-free, dinuclear compound of samarium bearing a new chiral multidentate ligand, (*R*,*R*,*R*,*R*)-*N*,*N*,*N*′,*N*′-tetra(2-hydroxy-2-phenylethyl)-1,3-xylylene diamine [(*R*)-**2**], could exhibit superior catalytic performance for asymmetric transfer hydrogenation of aryl ketones.

The multidentate ligand (*R*)-**2** was obtained as a pale yellow oil in 50% yield by the reaction of *m*-xylylenediamine with excess amounts of (*R*)-(+)-styrene oxide.[8] For preparing a salt-free samarium complex of (*R*)-**2**, we used the precursor SmI(η^8-cyclooctatetraene)(thf) (**3e**),[9] in which the cyclooctatetraene ligand acts as a dianion. Thus, the simple one-pot reaction of **3e** with the alcoholic parts of (*R*)-**2** resulted in the formation of the salt-free complex 1,3-$C_6H_4[CH_2N(CH_2CHPhO)_2SmI]_2$ (**4e**) along with release of cyclooctatetraene. Titration monitored by absorption spectroscopy indicated that 2 equiv of **3e** were consumed in the reaction with (*R*)-**2** to give the salt-free dinuclear samarium species **4e**.

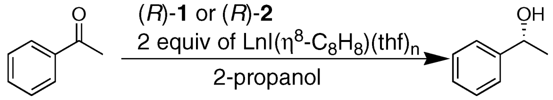


(*R*)-**1** (*R*)-**2**

Figure 1. Chiral multidentate ligands.

When the catalyst **4e** (5 mol %) was used for asymmetric transfer hydrogenation of acetophenone in 2-propanol at 25 °C for 24 h, (*R*)-1-phenylethanol was obtained in 95% ee and quantitative yield (Table 1, run 5). We found that the catalytic activity and enantioselectivity depended highly on the central metals, and the samarium catalyst **4e** was the best among the tested catalysts 1,3-$C_6H_4[CH_2N(CH_2CHPhO)_2LnI]_2$ (**4a**−**e**) (Table 1), which were derived by mixing (*R*)-**2** and 2 equiv of LnI(η^8-cyclooctatetraene)(thf)$_n$ (**3a**: Ln = La, n = 3; **3b**: Ln = Ce, n = 3; **3c**: Ln = Pr, n = 3; **3d**: Ln = Nd, n = 2; **3e**: Ln = Sm, n = 1).[9] The enantioselectivity of the product decreased in the order of the increased atomic radii, La ≈ Ce < Nd < Pr ≪ Sm, such a tendency being

Table 1. Asymmetric Transfer Hydrogenation of Acetophenone Using Catalyst Systems Derived from (*R*)-**2** and 2 Equiv of Lanthanide Complexes, LnI(η^8-cyclooctatetraene)(thf)$_n$ (**3a**−**e**)[a]



run	ligand	lanthanoid complexes	conversion (%)[b]	ee (%) (config)[c]
1	(*R*)-2	**3a**	5	18 (*R*)
2	(*R*)-2	**3b**	9	22 (*R*)
3	(*R*)-2	**3c**	46	79 (*R*)
4	(*R*)-2	**3d**	43	77 (*R*)
5	(*R*)-2	**3e**	>99	95 (*R*)
6	(*R*)-1	**3e**	77	82 (*R*)

[a] Reaction temperature, 25 °C; reaction time, 24 h; *S*/*C* = 20; 25 equiv of 2-propanol for substrate. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] Enantiomeric purity was determined by chiral HPLC. Absolute configuration was assigned by comparison of product rotations to the literature value.[11]

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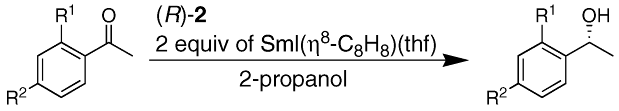
Table 2. Asymmetric Transfer Hydrogenation of Aryl Ketones by the Catalyst System Derived from (*R*)-**2** and SmI(η^8-cyclooctatetraene)(thf) (**3e**)[a]



run	substrate	time (h)	conversion (%)[b]	ee (%) (config)[c]
1	**6**	24	22	68 (*R*)
2		48	47	68 (*R*)
3	**7**	24	>99	>99 (*R*)
4	**8**	24	77	93 (*R*)
5	**9**	24	90	87 (*R*)
6	**10**	24	>99	89 (*R*)
7	**11**	24	83	78 (*R*)
8	**12**	24	98	>99 (*R*)
9	**13**	24	10	>99 (*R*)
10		48	40	>99 (*R*)
11	**14**	24	29	45 (*R*)
12		48	35	45 (*R*)
13	**15**	24	17	65 (*R*)
14	**16**	48	21	65 (*R*)

[a] Reaction temperature, 25 °C; reaction time, 24 h; *S/C* = 20; 25 equiv of 2-propanol for substrate. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] Enantiomeric purity was determined by chiral HPLC. Absolute configuration was assigned by comparison of product rotations to the literature value.[11]

consistent with the catalysts derived from the reaction of a dilithium salt of (*R*)-**1** ligand with LnI_3.[2c] The salt-free samarium species $C_6H_5CH_2N(CH_2CHPhO)_2SmI$ (**5**), in situ derived by treating (*R*)-**1** with 1 equiv of **3e**, catalyzed the asymmetric hydrogenation of acetophenone under the same condition to afford the alcohol in 82% ee and 77% conversion, whose values were less than the reported values (96% ee and 83% conversion) when the samarium catalyst system derived from the reaction of the dilithium salt of (*R*)-**1** with 1 equiv of SmI_3 was used.[2c]

We measured pseudo-first-order rate constants for the asymmetric transfer hydrogenation of acetophenone by using the dinuclear samarium species **4e** and the mononuclear samarium species **5**, both being salt-free catalysts, in the temperature range of −10 to 20 °C. The rate constant k_{obs} at 0 °C in the bimetallic catalyst system **4e** ($0.16\ s^{-1}$) was found to be 10 times larger than that in **5** ($0.012\ s^{-1}$), indicating that two metal centers cooperatively accelerated the reaction. Eyring plots afforded the thermodynamic parameters (**4e**: $\Delta H^\ddagger = 34(1)$ kJ/mol, $\Delta S^\ddagger = -170(1)$ J/mol·K, and $\Delta G^\ddagger =$ 81(2) kJ/mol (0 °C); **5**: $\Delta H^\ddagger = 71(6)$ kJ/mol, $\Delta S^\ddagger = -55$(7) J/mol·K, and $\Delta G^\ddagger = 86(5)$ kJ/mol (0 °C)), the larger negative value of $\Delta S^\ddagger$ found for **4e** suggesting that acetophenone was easily trapped by the mutual two samarium centers.

Table 2 summarizes the asymmetric transfer hydrogenation of various aryl ketones in 2-propanol at 25 °C. Catalytic activity and enantioselectivity are sensitive to the substituents on acetophenone. Enantioselectivity and conversion of the reduction of propiophenone (**6**) decreased (Table 2, run 1). For halogenated acetophenone derivatives **7**−**11**, we found that ortho-substituted derivatives were readily reduced compared with the corresponding meta- and para-substituted derivatives (Table 2, runs 3−7) with higher enantioselectivities (Table 2, runs 3 and 6). Such ortho-halogen substituent effects have been reported for asymmetric hydrogenation by using samarium reagents.[2b,10] A very effective ortho-substituent influence was observed for methoxy acetophenones **12** and **13** (Table 2, runs 8−10): **12** was almost consumed within 24 h to give (*R*)-(+)-2-methoxy-α-methylbenzyl alcohol in >99% ee, whereas **13** was converted in only 10%, though enantioselectivity was still very high (>99% ee). Reduction of cyclic ketones **14** and **15** resulted in slow conversion and low enantioselectivities (Table 2, runs 11−14).

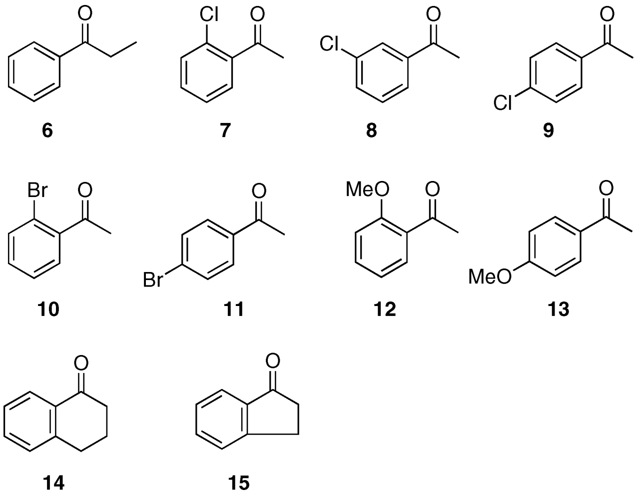


Figure 2. Ketonic substrates.

In summary, we have prepared a new chiral multidentate alkoxy ligand, (*R*)-**2**, capable of supporting two metal centers at adjacent positions. Salt-free samarium catalyst mediated asymmetric transfer hydrogenation of acetophenone and its derivatives to give the corresponding alcohols in high enantioselectivity (up to 99% ee).

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Supporting Information Available: Experimental details of the synthesis of chiral ligand (*R*)-**2** and catalytic transfer hydrogenation of ketonic substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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