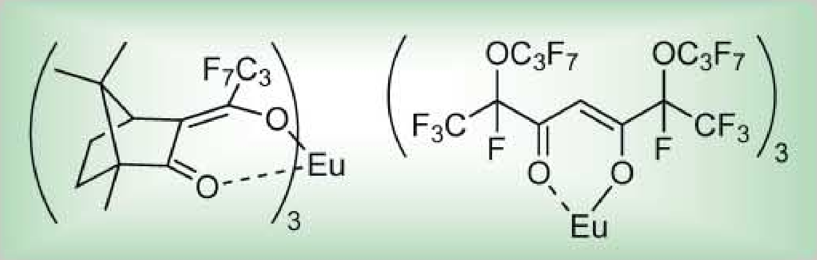
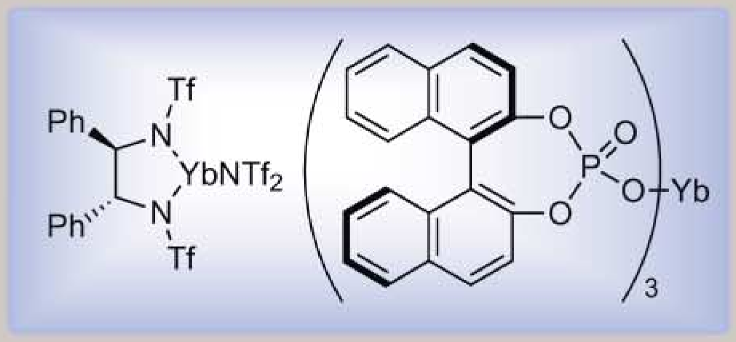
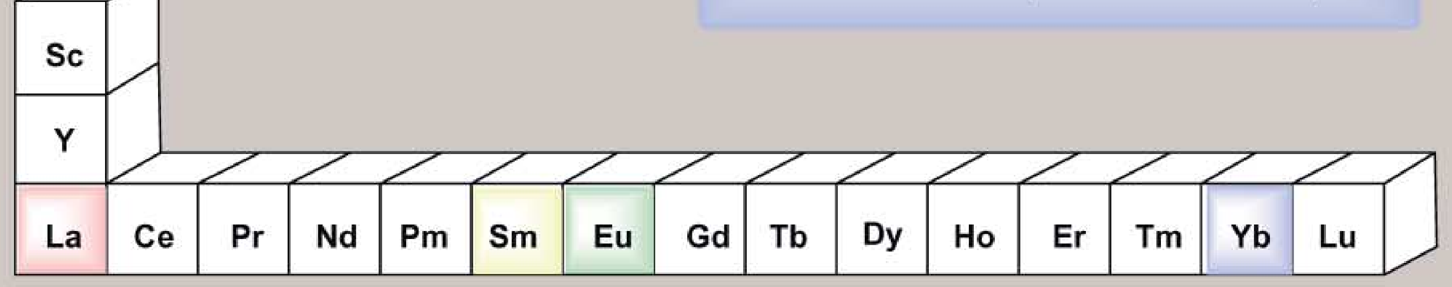
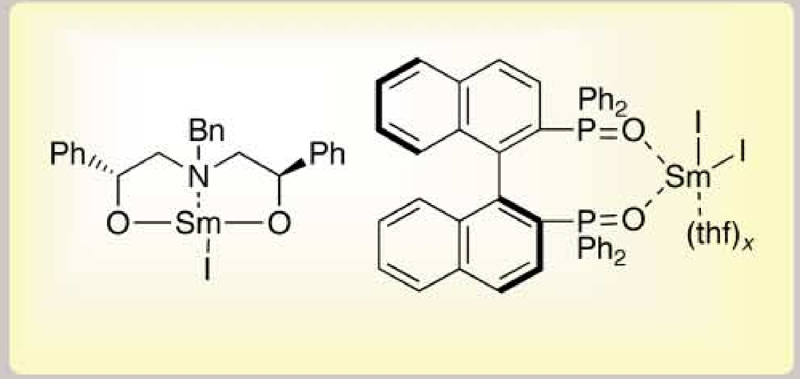
Asymmetric Catalysis by Lanthanide Complexes









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“Asymmetric” Catalysis by Lanthanide Complexes

Koichi Mikami,* Masahiro Terada, and Hiroshi Matsuzawa

Catalysis with lanthanide (Ln) complexes has been underestimated for long time, although Ln^{III} complexes have great advantages as Lewis acid catalysts for “asymmetric” carbon–carbon bond-forming reactions. Lanthanide complexes are highly active in ligand-substitution reactions, especially with hard ligands. The association with substrates and dissociation of products are achieved fast enough for high catalyst efficiency. The asymmetric catalysis of organic reactions can be greatly advanced by the use of Ln complexes with chiral ligands such as binaphthol (binol). Ln^{II} complexes are good reducing agents, which can be used in a wide variety of synthetically important reactions; when chiral ligands are used, many of these reactions are highly stereoselective. In the context of “green chemistry”, the development of asymmetric Ln catalysts, and their recyclable use, is of increasing importance. This review gives an overview of the most recent developments in catalysis with lanthanide(II) and lanthanide(III) complexes.

Keywords: asymmetric catalysis • enantioselectivity • coordination chemistry • lanthanides • Lewis acids

1. Introduction

“Asymmetric” catalysis of organic reactions is an important subject in modern science and technology.[1] Regarding the unique coordination chemistry of the f-block elements (“lanthanide” complexes),[2] particularly high coordination numbers are an advantage as organic reactions can be promoted catalytically rather than stoichiometrically.[3] The following characteristics are typical of lanthanide complexes: 1) The lanthanide cations, generally in the oxidation states $+2-+4$, have an extended Xe-core electronic configuration; they have $5s^25p^6$ outer-shell electrons and $4f^n$ deep-lying electrons ($n=1-14$; Table 1). 2) The inert 4f shell lies inactive, deep in the interior of the cation and is well-shielded by the filled $5s^2$ and $5p^6$ orbitals. The character of these f-block elements is in sharp contrast to that of d-block elements, in which the outer d orbital is filled sequentially. Ln^{3+} ions are commonly thought to have a tripositively charged, closed shell with a noble-gas electronic configuration. Therefore, no σ-donor–π-acceptor bonding mode occurs. 3) f-Block elements lack orbital restrictions, so there is no need to maximize orbital overlap as in d-block transition-metal chemistry. 4) Poor overlap of 4f orbitals with the ligand orbitals and the lanthanide contraction contribute to the predominantly ionic character of organolanthanide complexes. According to the HSAB classification of Pearson,[4] lanthanide cations are considered to be hard acids, ranked between Sr^{II} and Ti^{IV}. The ionic-bonding contributions cause lanthanide cations to be strongly oxophilic, which can be expressed in terms of the dissociation energy (D_0) of Ln–O bonds (Figure 1).[+, 5] 5) Table 2 represents the trend in effective ionic radii of these multiply charged cations, which prefer high coordination numbers between 6–12.[6] As shown in Figure 1, the atomic and ionic radii decrease linearly with increasing atomic number (“lanthanide contraction”). Therefore, metal–ligand interactions are determined by electrostatic factors and thus lanthanide cations preferentially interact with hard ligands. 6) Ln^{2+} complexes are strong reducing agents, for example, Sm^{2+}, Eu^{2+}, Tm^{2+},[7] and Yb^{2+} have oxidation potentials of $+1.55$, $+0.35$, $+2.3$, and $+1.15$ V, respectively.[8] 7) Lanthanide complexes are active in ligand substitution reactions and attainment of the association–dissociation equilibrium is fast.

The Lewis acidity (Z/r^3; $Z=$ charge and $r=$ ionic radius), is particularly low in complexes derived from the large Ln^{3+} cations.[9] Hence these systems are considered in organic synthesis to be mild Lewis acidic catalysts. However the Sc^{3+} ion, as the smallest rare-earth-metal cation, is the most Lewis acidic and lies on the borderline between lanthanide–early transition metal–aluminum. The Yb^{3+} ion is the second smallest lanthanide cation (after Lu^{3+}) and is hence the most

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[+] The elements specified in Figure 1 include scandium and yttrium, which are not formally defined as lanthanide elements, but as rare earth metals. For the sake of simplicity, in this review these two elements are also abbreviated to Ln.

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Table 1. Characteristic features of lanthanide elements.

	Configuration of outer electron shell						
Element	Atom	Ln^{2+}	Ln^{3+}	Ln^{4+}	E^0 (Ln $\rightarrow$ Ln^{3+} + 3e$^-$) [V]	E^0 (Ln^{2+} $\rightarrow$ Ln^{3+} + e$^-$) [V]	E^0 (Ln^{3+} $\rightarrow$ Ln^{4+} + e$^-$) [V]
La	$5d^{1}6s^{2}$	$5d^{1}$	[Xe]	–	+2.52		
Ce	$4f^{2}6s^{2}$	$4f^{2}$	$4f^{1}$	[Xe]	+2.48		−1.74
Pr	$4f^{3}6s^{2}$	$4f^{3}$	$4f^{2}$	$4f^{1}$	+2.46		ca. −3.2
Nd	$4f^{4}6s^{2}$	$4f^{4}$	$4f^{3}$	$4f^{2}$	+2.43		
Pm	$4f^{5}6s^{2}$	$4f^{5}$	$4f^{4}$	–	+2.42		
Sm	$4f^{6}6s^{2}$	$4f^{6}$	$4f^{5}$	–	+2.41	+1.55	
Eu	$4f^{7}6s^{2}$	$4f^{7}$	$4f^{6}$	–	+2.41	+0.35	
Gd	$4f^{7}5d^{1}6s^{2}$	$4f^{7}5d^{1}$	$4f^{7}$	–	+2.40		
Tb	$4f^{9}6s^{2}$	$4f^{9}$	$4f^{8}$	$4f^{7}$	+2.39		
Dy	$4f^{10}6s^{2}$	$4f^{10}$	$4f^{9}$	$4f^{8}$	+2.35		
Ho	$4f^{11}6s^{2}$	$4f^{11}$	$4f^{10}$	–	+2.32		
Er	$4f^{12}6s^{2}$	$4f^{12}$	$4f^{11}$	–	+2.30		
Tm	$4f^{13}6s^{2}$	$4f^{13}$	$4f^{12}$	–	+2.28	ca. +2.3	
Yb	$4f^{14}6s^{2}$	$4f^{14}$	$4f^{13}$	–	+2.27	+1.15	
Lu	$4f^{14}5d^{1}6s^{2}$	–	$4f^{14}$	–	+2.26		

Lewis acidic rare earth metal but one (Sc^{3+}). The higher Lewis acidity of the Yb^{3+} ion over the Lu^{3+} ion may originate from an incomplete 4f orbital. The Yb^{3+} ion is one electron short of a fully occupied 4f orbital, which increases its electron affinity over the Lu^{3+} ion. A similar argument can be extended to the anomaly of the Lewis acidities of Gd^{3+} and Eu^{3+} ions (half-filled 4f orbital).

The stability of ligands is ordered according to their tendency to hydrolyze, in the case of organolanthanide complexes, or to compete with the solvent, in the case of inorganic complexes, because fast acid–base ligand exchange is characteristic of organolanthanide chemistry (Figure 2). Organolanthanide complexes containing σ bonds to, for example, alkyl and alkoxides groups, readily hydrolyze with moisture to form the hydroxides.[2d] Even ligands with lower pKa values than water, such as OAr, tend to hydrolyze because of the formation of insoluble hydroxides. However, the presence of hard conjugate bases or chelating anions

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Koichi Mikami was born in 1953 in Bousou, Chiba, Japan. He received his Ph.D. in 1982 under the supervision of Professor Takeshi Nakai and Professor Nobuo Ishikawa and became an Assistant Professor then an Associate Professor in 1987 at the Tokyo Institute of Technology. In 1982–1983 he was a postdoctoral fellow at Yale University with Professor Frederick E. Ziegler. He has received the Tejima award on "Stereocontrol based on [2,3] Sigmatropic Rearrangements", the Chemical Society of Japan Award (Shinpo-Sho) on "Asymmetric Transmission and Asymmetric Synthesis based on the [2,3] Wittig Rearrangements", the Society of Synthetic Organic Chemistry Japan Award (Asahi-Kasei Award) on "Asymmetric Synthesis based on Carbonyl-Ene Reactions", the IBM award on "Highly Efficient Asymmetric Catalysis", the Ichimura science award on "Development of Asymmetric Catalytic Friedel–Crafts Reactions and their Industrial Application"; he was the Bristol-Myers-Squibb Lecturer (Colorado State University), Lilly Research Laboratories Lecturer (Ohio State University), the Boehringer Ingelheim Award Lecturer (University of Montreal), and Visiting Professor in the Université Paris-Sud and Taiwan.

Masahiro Terada, born in 1964 in Tokyo, Japan, became a research associate in 1989 in the Department of Applied Chemistry, Tokyo Institute of Technology. He received his Ph.D. in 1993 from this university under the direction of Professor Koichi Mikami. He was rewarded by the Inoue and Tejima foundations in 1995 for his Ph.D. thesis. In 1999–2000 he was a postdoctoral fellow at Harvard University with Professor Matthew D. Shair. He has now been an Associate Professor of Tohoku University since 2001.

Hiroshi Matsuzawa was born in 1975 in Kanagawa, Japan. He received his Masters degree from Chuo University. He is now a graduate student in the Graduate Course of Applied Chemistry, Tokyo Institute of Technology under the supervision of Professor Koichi Mikami.

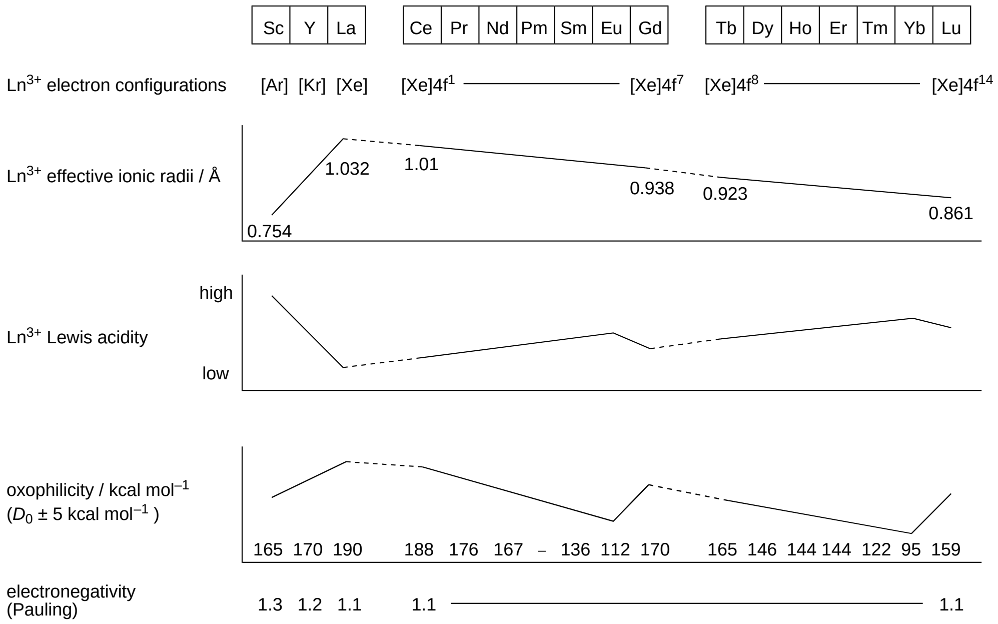


Figure 1. Characteristic features of lanthanide ions and elements. D_0 = dissociation energy of the Ln−O bond.

Table 2. Effective ionic radii (Å) of Ln^{3+}, Ln^{2+}, and Ln^{4+} ions.

	Coordination number					
Ln^{n+}	6	7	8	9	10	12
Sc^{3+}	0.754		0.870			
Y^{3+}	0.900	0.96	1.019	1.075		
La^{3+}	1.032	1.10	1.160	1.216	1.27	1.36
Ce^{3+}	1.01	1.07	1.143	1.196	1.25	1.34
Pr^{3+}	0.99		1.126	1.179		
Nd^{3+}	0.983		1.109	1.163		1.27
Pm^{3+}	0.97		1.093	1.144		
Sm^{3+}	0.958	1.02	1.079	1.132		1.24
Eu^{3+}	0.947	1.01	1.066	1.120		
Gd^{3+}	0.938	1.00	1.053	1.095		
Tb^{3+}	0.923	0.98	1.040	1.095		
Dy^{3+}	0.912	0.97	1.027	1.083		
Ho^{3+}	0.901		1.015	1.072	1.12	
Er^{3+}	0.890	0.945	1.004	1.062		
Tm^{3+}	0.880		0.994	1.052		
Yb^{3+}	0.868	0.925	0.985	1.042		
Lu^{3+}	0.861		0.977	1.032		
Sm^{2+}		1.22	1.27	1.32		
Eu^{2+}	1.17	1.20	1.25	1.30	1.35	
Tm^{2+}	1.03	1.09				
Yb^{2+}	1.02	1.08	1.24			
Ce^{4+}	0.87		0.97		1.07	1.14
Tb^{4+}	0.76		0.88			

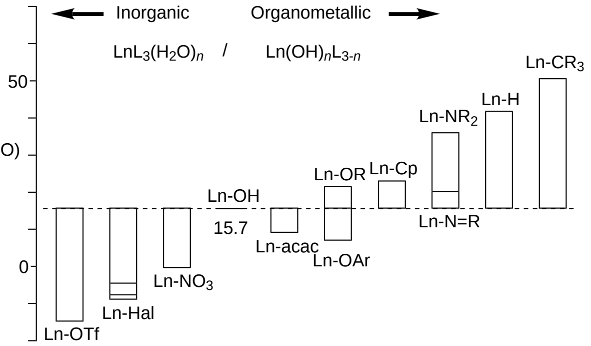


Figure 2. Hydrolysis of organolanthanide and inorganic lanthanide complexes.

(e.g. acac = acetylacetonate) can afford water-stable complexes. These complexes can be effective Lewis acids in alcoholic, water, and even in amine solvents.

Lanthanide trihalides, LnX_3, are generally prepared from lanthanide oxide, Ln_2O_3, as hydrates. The dehydration of $LnCl_3/(H_2O)_x$ ($x = 6, 7$) using NH_4Cl or $SOCl_2$ is the laboratory method of preparing anhydrous lanthanide chlorides [Eq. (1) and (2)].[10] In the case of X = Cl, thermal dehydration leads to the formation of undesirable lanthanide oxychlorides. Lanthanide carbonate can be used as a precursor for LnX_3 with evolution of carbon dioxide [Eq. (3)–(5), Tf = triflyl].[11]

$$Ln_2O_3 \quad + \quad aq.\ HX \longrightarrow \left[LnX_3(H_2O)_x\right] \quad x = 6, 7 \tag{1}$$

$$\xrightarrow[X\,=\,Cl]{SOCl_2 \text{ or } NH_4Cl} \text{anhydrous } LnCl_3 \tag{2}$$

$$Ln_2(CO_3)_3 \quad + \quad HOTf \longrightarrow \left[Ln(OTf)_3(H_2O)_x\right] + CO_2\uparrow \tag{3}$$

$$HNTf_2 \longrightarrow \left[Ln(NTf_2)_3(H_2O)_x\right] + CO_2\uparrow \tag{4}$$

$$HCTf_3 \longrightarrow \left[Ln(CTf_3)_3(H_2O)_x\right] + CO_2\uparrow \tag{5}$$

Lanthanide dihalides, LnX_2, are the only precursors for Ln^{II}-organometallic compounds [Eq. (6)–(9)]. SmI_2 is widely employed as a THF solution in organic synthesis.[3a,c–e, 12]

$$Sm \quad + \quad ICH_2CH_2I \xrightarrow[THF]{} \left[SmI_2(thf)_2\right] \tag{6}$$

$$SmI_3 \quad + \quad Sm \xrightarrow[THF]{} SmI_2 \tag{7}$$

$$\begin{tikzcd} Sm_2O_3 + aq.\ HBr \arrow[rr] & & SmBr_3\cdot 6H_2O \arrow[d, "CH(OMe)_3"] \\ & \left[SmBr_2(thf)_x\right] & SmBr_3 \arrow[l, "Li", "THF"'] \end{tikzcd} \tag{8}$$

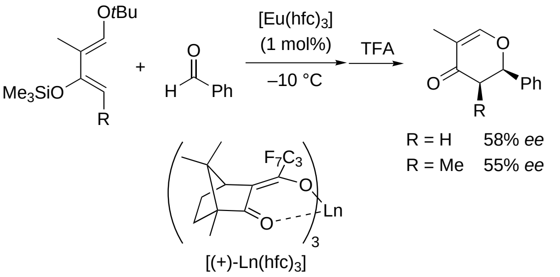
$$Yb \quad + \quad BrCH_2CH_2Br \xrightarrow[THF]{} \left[YbBr_2(thf)_2\right] \tag{9}$$

2. Asymmetric Catalysis with Ln^{III} Complexes

2.1. Initial Experiments

Because the metal–ligand interaction is of electrostatic origin, optimal charge balance of the Ln^{III} cations should be achieved by three stable anionic ligands. Identical anions form either neutral homoleptic complexes (MX_n) or ate complexes $[MX_n]^{z-}[Y]^{z+}$. Chelating anions are useful in synthesizing heterometallic complexes.

Bednarski, Maring, and Danishefsky reported the first example of asymmetric catalysis with an Ln^{III} complex, using a homoleptic chiral NMR shift reagent, [Eu(hfc)$_3$] (hfc = heptafluoropropylhydroxymethylene) [Eq. (10) TFA = trifluoroacetic acid].[13] They clarified the mechanism of the asymmetric hetero-Diels–Alder reaction (Figure 3).[14] Generally, Lewis acid complexes such as $BF_3 \cdot OEt_2$ or $TiCl_4$ provide first the Mukaiyama aldol product and then the cyclized product upon acidic workup (Figure 3a). However, lanthanide-catalyzed hetero-Diels–Alder reactions proceed in a concerted manner (Figure 3b).



(10)

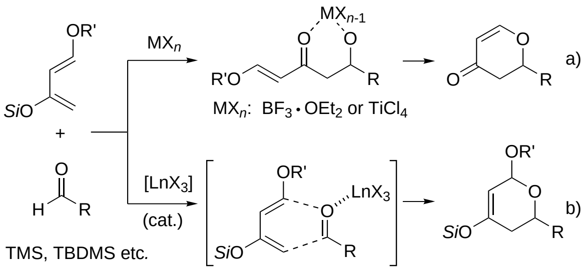


Figure 3. The dichotomous mechanisms of the hetero-Diels–Alder reactions promoted by a) stoichiometric or b) catalytic Lewis acid. TMS = trimethylsilyl, TBDMS = *tert*-butyldimethylsilyl.

The major problem associated with the catalysis of the Mukaiyama aldol reaction of silyl enol ethers by the standard Lewis acid complexes such as $BF_3 \cdot OEt_2$ or $TiCl_4$ is the transmetalation of the starting silyl enol ether to give eventually the β-metalloxycarbonyl chelate intermediate stoichiometrically (Figure 4a). We tested lanthanide complexes as Lewis acid catalysts for the synchronous aldol reaction (Figure 4b). First, we examined a chiral shift reagent[15] with a C_2-symmetric polyfluoro ligand, (+)- or (−)-dppm (see Equation (11) for the structure of dppm) for the catalysis of the aldol reaction of a variety of silyl enol ethers derived from esters or ketones, with aldehydes, acetals, and ketones. Unfortunately, the enantioselectivity of the (+)-[Eu(dppm)$_3$]-catalyzed aldol reaction is low. However, the Eu catalysts provided remarkable levels of recognition between carbonyl electrophiles and silyl enol ether nucleophile partners.

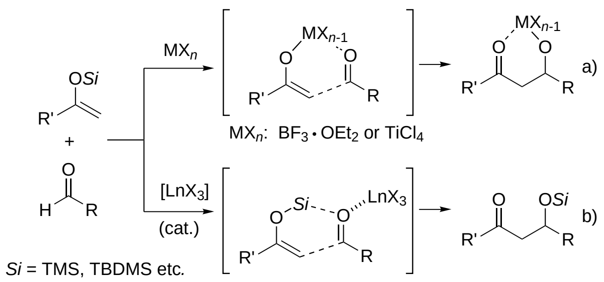
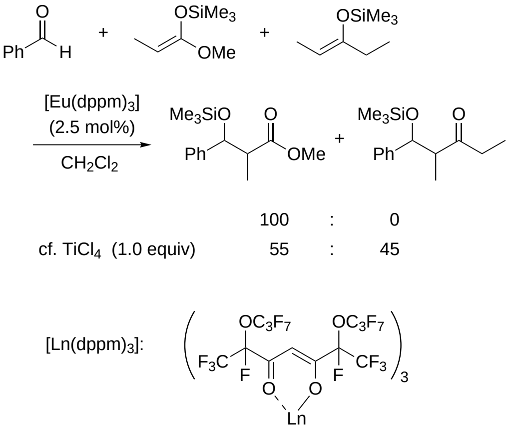


Figure 4. The envisaged mechanisms of aldol reaction catalyzed by a) standard Lewis acids and b) Ln^{III} complexes.



(11)

2.2. Aldol Reactions

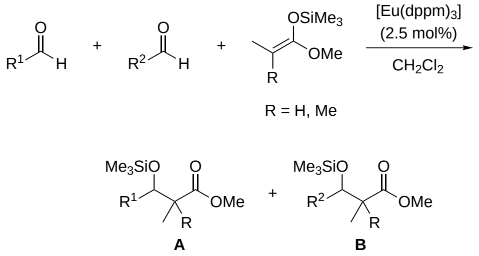
2.1. Molecular Recognition

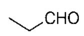
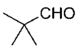
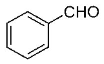
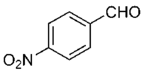
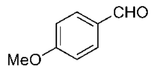
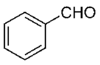
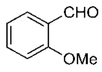
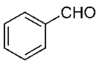
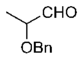
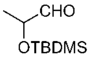
The [Eu(dppm)$_3$] catalysis exhibits remarkable levels of chemoselectivity in terms not only of carbonyl electrophiles but also of their silyl enol ether nucleophile partners [Eq. (11)].[16]

The [Eu(dppm)$_3$] catalyst was effective only for the reactions of aldehydes or α,β-unsaturated ketones with ketene silyl acetals, but totally ineffective for the reaction of acetals with ketene silyl acetal, ketones with ketene silyl acetal, and aldehydes with ketone-derived silyl enol ethers. This unique selectivity in catalysis is exemplified by a competitive aldol reaction of benzaldehyde with a ketene silyl acetal and a silyl enol ether. The Eu^{III} catalyst gave the ketene silyl acetal-derived aldol product exclusively [Eq. (11)]. In sharp contrast, a nearly 1:1 mixture of aldol products was obtained by stoichiometric use of $TiCl_4$.

In addition, the Eu^{III} catalysis shows high level of aldehyde discrimination in competitive aldol reactions (Table 3). First, the Eu^{III} catalysts are more sensitive to the steric demand in aldehydes than the stoichiometric use of $TiCl_4$ (entry 1). Second, the Eu^{III} catalysts can recognize the subtle difference in electronic effects on benzaldehyde derivatives (entry 2–4). Interestingly, *p*-nitrobenzaldehyde ($\sigma_{p\text{-}NO2} = +0.78$)[17] is less reactive than benzaldehyde in the Eu^{III}-catalyzed process

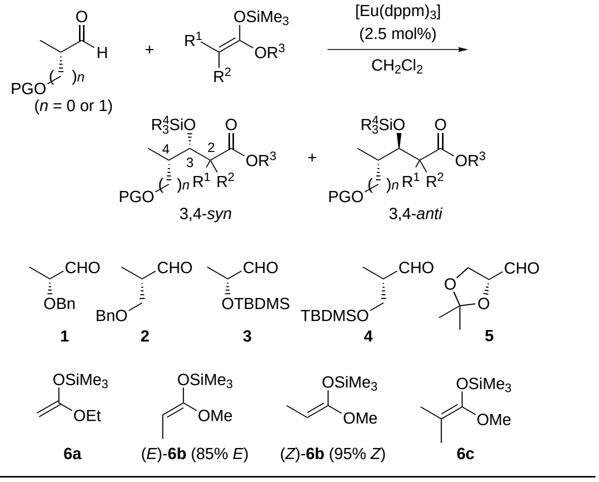
Table 3. Competitive aldol reaction between aldehydes.



Entry	R^1CHO	R^2CHO	**A**:**B**
1[a]			> 98:2 (77:23)[b]
2[a]			> 95:5
3[a]			87:13
4[a]			95:5 (68:32)[b]
5[c]			97:3

[a] R = H in ketene siyl acetal. [b] Stoichiometric amount of $TiCl_4$. [c] R = Me in ketene silyl acetal.

Table 4. Eu^{III}-catalyzed aldol reaction of alkoxyaldehydes with ketene silyl acetals **6**.



Entry	Aldehyde	**6**	Yield [%]	3,4-*syn*:3,4-*anti*
1	**1**	**6a**	75	> 99: < 1 (98:2)[a]
2		(*E*)-**6b**	78	89:11 (> 99:1)[a]
3		(*Z*)-**6b**	100	96:4
4		**6c**	80	92:8 (> 99:1)[a]
5	**2**	**6a**	35	68:32 (68:32)[a]
6		**6c**	30	36:64 (> 99:1)[a]
7	**3**	**6a**	90	74:26
8		(*E*)-**6b**	80	5:95
9		(*Z*)-**6b**	90	19:81
10		**6c**	55	29:71
11	**4**	**6a**	65	45:55
12		**6c**	62	19:81

[a] Stoichiometric amount of $TiCl_4$.

(entry 2). Similarly, *p*-methoxybenzaldehyde is more reactive than benzaldehyde (entry 3). More significantly, the Eu^{III} catalyst shows remarkable preference for *o*-methoxybenzaldehyde ($\sigma_{o\text{-OMe}} = -0.27$ to -0.67)[17] over benzaldehyde (entry 4), although the former is sterically more hindered. These results suggest that the relative reactivity of aldehydes in the Eu^{III}-catalyzed process is determined almost solely by the coordinating ability of aldehydes to the Eu^{III} complex, not by the electrophilicity of the aldehydes themselves. A similar argument can be extended to explain the high levels of molecular recognition of α-benzyloxy aldehyde and α-silyloxy aldehyde (entry 5); the former is preferentially complexed as a chelate ligand. Indeed, the 3,4-*syn* diastereomer is the major product (see Section 2.2.2).

2.2.2. Diastereoselective Catalysis by Induced Stereochemical Fit

Diastereoselectivity in the Eu^{III}-catalyzed aldol reaction is not high with a simple aldehyde such as benzaldehyde. However, the catalytic reaction of alkoxy aldehydes **1**–**5** with ketene silyl acetal **6** exhibited excellent stereoselectivity (Table 4).[18] The Eu^{III} catalyst recognizes the difference not only in the different protecting groups of the aldehydes (PG) but also the different steric demands of **6**, and hence dictates either chelation (3,4-*syn*) or nonchelation (3,4-*anti*) selections[19] in the catalytic aldol reactions of the α- and β-alkoxy aldehydes **1**–**4**. In Table 4, the results indicate that not only the degree but also the sense of 3,4-diastereofacial selection (chelation vs. nonchelation) is critically induced by the steric bulk of **6**. The characteristic features are as follows: 1) 3,4-*syn*/*anti* selectivities are primarily dependent on the kind of alkoxy protecting groups. Benzyl-protected aldehydes **1** and **2** gave the predominantly 3,4-*syn* product (entries 1–6) through chelation control. In contrast, the sterically hindered silyl protection (**3**, **4**) leads mainly to the 3,4-*anti* product through the nonchelate mode (entries 7–12). 2) The reaction of the α-alkoxy aldehydes **1** and **3** gave a higher distribution of 3,4-*syn* products (entries 1–4 and 7–10) than that of the β-alkoxy aldehydes **2** and **4** (entries 5, 6, 11, and 12). 3) The bulkier ketene silyl acetal **6c** tends to give 3,4-*anti* products, even with the α-benzyloxyaldehyde **1**. In particular, a changeover of the 3,4-selectivity from *syn* to *anti* was observed in the reaction with the aldehydes **2** and **3** (entries 5, 6, and 7–10). Of particular interest is that the degree of 3,4-*syn* selectivity decreases with increasing steric bulkiness of **6** in the order **6a** > **6b** > **6c** (entries 1–4). These results are in direct contrast to the general trend that "the more bulky ketene silyl acetals are therefore the more selective"[19] as observed by a stoichiometric use of $TiCl_4$ (entries 1–6).

This unique trend in the stereoselectivity of Eu^{III}-catalyzed aldol reactions is likely to reflect the complexation state of the Eu^{III} ion with the aldehydes, namely chelation versus nonchelation. In fact, LIS (lanthanide-induced shifts) NMR spectroscopic analysis qualitatively indicated that the order of chelate complexation ability to the aldehyde was **1** ≫ **2** > **3** > **4**.[20] The stereochemical control of the Eu^{III} catalysis is rationalized by the dichotomous catalytic cycles and the equilibrium between chelate and nonchelate complexes with aldehydes (**1**–**4**; Figure 5). In view of the Curtin-Hammett

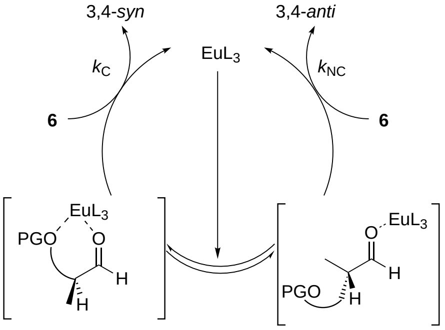
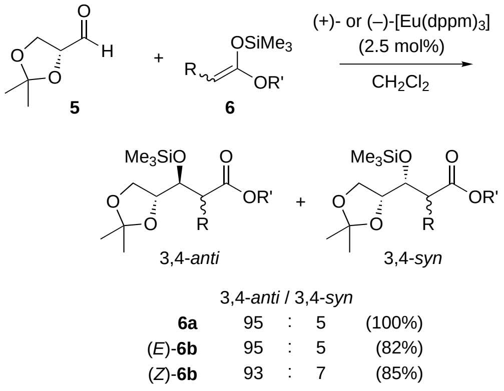


Figure 5. Catalytic cycles for chelation (k_C) versus nonchelation (k_{NC}) reactions. L = ligand.

principle,[21] the diastereofacial selectivity in the Eu^{III}-catalyzed aldol reaction is sensitive to the size of the ketene silyl acetal; sterically demanding ketene silyl acetals tend to react preferentially via the nonchelate complex rather than through the congested chelate complex.

An interesting and general problem lies in the reaction with the glyceraldehyde acetonide (**5**) which arises from the competition between α and β chelation to the metal complexes involved [Eq. (12)].[22] A high level of 3,4-*anti*-diastereofacial selectivity was observed in the Eu^{III}-catalyzed reaction, which can be explained by β-chelation control.[23]



	3,4-*anti* / 3,4-*syn*	
6a	95 : 5	(100%)
(*E*)-**6b**	95 : 5	(82%)
(*Z*)-**6b**	93 : 7	(85%)

(12)

However, our high 3,4-*anti* selectivity should not be interpreted by β chelation, because the β-chelation ability of Eu^{III} catalysts is not high (Table 4). Therefore the high 3,4-*anti* selectivity is rationalized by tridentate chelation caused by the high coordination number (commonly 6–9) of lanthanides (Figure 6).

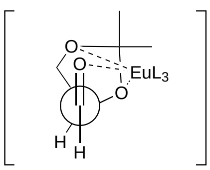
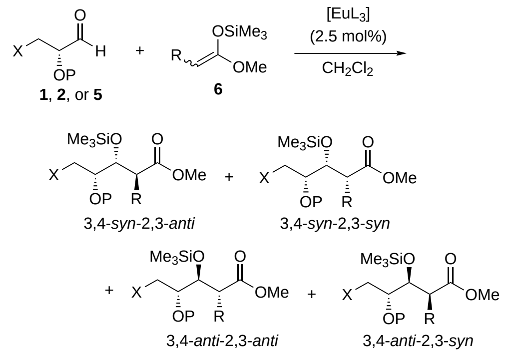


Figure 6. Tridentate chelation model.

Table 5. Eu^{III}-catalyzed aldol reactions of aldehyde (**1**, **3**, or **5**) and ketene silyl acetal **6**.



Entry	Aldehyde	R	3,4-*syn* [%] 2,3-*anti*		3,4-*syn* [%] 2,3-*syn*		3,4-*anti* [%] 2,3-*anti*		3,4-*anti* [%] 2,3-*syn*	Yield [%]
1	**3**	Me (95% *Z*)	5	:	14	:	1	:	80	90
2	**3**	Me (85% *E*)	2	:	3	:	1	:	94	80
3	**3**	OBn (100% *Z*)	2	:	5	:	0	:	93	58
4	**1**	Me (95% *Z*)	73	:	23	:	0	:	4	95
5	**1**	Me (85% *E*)	40	:	49	:	1	:	10	78
6	**1**	Et (95% *Z*)	92	:	8	:	0	:	0	83
7	**1**	OBn (100% *Z*)	98	:	2	:	0	:	0	93
8	**1**	OMe (100% *Z*)	97	:	3	:	0	:	0	81
9	**1**	OSiMe$_3$ (85% *Z*)	98	:	2	:	0	:	0	75
10	**5**	Me (95% *Z*)	6	:	1	:	14	:	79	85
11	**5**	Me (85% *E*)	3	:	2	:	33	:	62	82
12	**5**	OBn (100% *Z*)	33	:	18	:	0	:	49	53

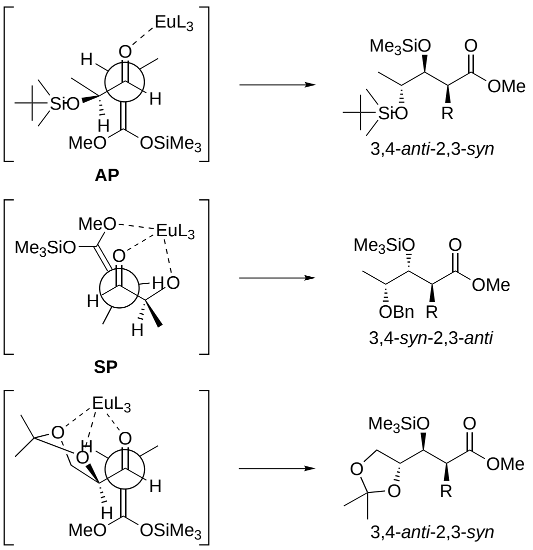
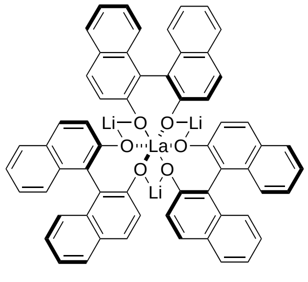


Figure 7. Antiperiplanar (**AP**: nonchelation, **AP'**: chelation) versus synperiplanar (**SP**) transition states in the aldol reaction.

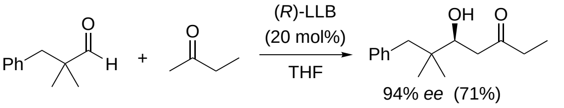
2,3-diastereoselectivity is also observed in the Eu^{III}-catalyzed aldol reaction.[24] Inspection of Table 5 reveals several significant features of the Eu^{III} catalysis. Aldehyde **3** afforded the 3,4-*anti*-2,3-*syn* product selectively (nonchelation/*syn*) via the well-accepted antiperiplanar transition state (**AP**; entries 1–3 and Figure 7). In contrast, aldehyde **1** predominantly gave the 3,4-*syn*-2,3-*anti* product (α chelation →*anti*), but the 2,3-diastereoselectivity depends on the geometry of the ketene silyl acetal **6** (entries 4–9). Most striking is the high 2,3-*anti* diastereoselectivity observed with (*Z*)-ketene silyl acetals, in direct contrast to the high 2,3-*syn* selectivity widely observed for aldol reactions under chelation control with a stoichiometric amount of Lewis acid, such as TiCl$_4$.[25] The unusual stereoselectivity reflected in the prodcuts is best rationalized by assuming the rarely observed synperiplanar transition state (**SP**),[26] which is favored by the additional coordination of the methoxy group in (*Z*)-ketene silyl acetal to the Eu^{III} complex that is chelated by the α-benzyloxyaldehyde **1**. The aldehyde **5**, binding in a tridentate chelation mode to the Eu^{III} catalyst, provided preferentially 3,4-*anti*-2,3-*syn* product (*α,β*-chelation →*syn*) through the antiperiplanar transition state (**AP′**). Thus, the stereocontrol by Eu^{III} catalysis is a result of the induced stereochemical fit in the complexation state of aldehyde–Eu^{III}, which dictates the transition state geometry and thus the stereochemistry of the products.

2.2.3. Enantioselective Catalysis

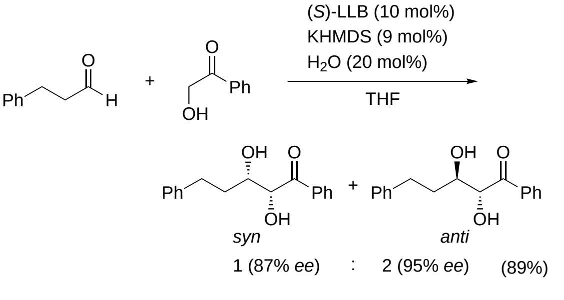
The asymmetric aldol reaction is one of the most powerful carbon–carbon bond-forming reactions. However, an unavoidable drawback in the asymmetric catalysis of this reaction is the necessity to preconvert the ketone moiety into a more reactive species such as a silyl enol ether or ketene silyl acetal.[27] Shibasaki reported that the chiral heterobimetallic complex,[28] LaLi$_3$-tris(binaphthoxide) (LLB), is an efficient asymmetric catalyst for direct aldol reactions of aldehydes and unmodified ketones. The LLB catalyst functions not only as a base to remove an α-proton of the ketone, but also as an acid in the final step of the reaction, giving the aldol product in high yield and with high enantioselectivity [Eq. (13)].[29]



(*R*)-LLB



(13)



(14)

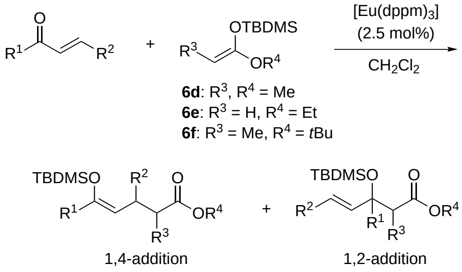
The LLB catalyst also works well for the direct aldol reaction of aldehydes with α-hydroxy ketones to provide 1,2-dihydroxy ketones in high enantiomeric excess [Eq. (14); KHMDS = potassium hexamethyldisilazane].[30]

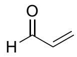
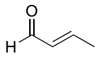
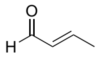
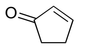
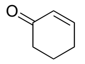
2.3. Michael Addition

2.3.1. Molecular Recognition

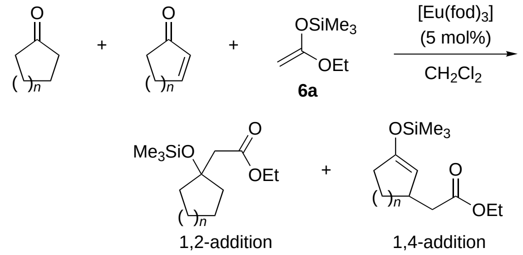
Eu^{III} catalysts exhibit unique recognition in their reaction with α,β-unsaturated carbonyl compounds, in which the competition between aldol (1,2-addition) and Michael (1,4-addition) reaction arises (Table 6).[16] The Eu^{III} catalyst is sensitive to the steric parameters not only in the α,β-unsaturated carbonyls but also in the ketene silyl acetals **6**. The β-unsubstituted enal ($R^1 = R^2 = H$) preferentially afforded the 1,4-addition product in a silyl enol ether form (entry 1), whereas the β-substituted enal ($R^2 = Me$) reacted with **6d** to deliver both 1,2- and 1,4-addition products (entry 2). The former product predominated over the 1,4-addition product with the sterically less demanding ketene silyl acetal **6e** (entry 3). In contrast, the Eu^{III}-catalyzed reaction with α,β-unsaturated ketones such as cyclopentenone afforded the 1,4-addition product exclusively, even when a less bulky ketene silyl acetal **6e** was used (entry 4 and 5).

Table 6. Selectivity of 1,4-addition versus 1,2-addition in Eu^{III}-catalyzed reactions.



Entry	Enone	6	Yield [%]	1,4:1,2
1		**6d**	85	>95:5
2		**6d**	65	44:56
3		**6e**	85	15:85
4		**6e**	85	100:0
5		**6f**	100	100:0

A significant discrimination between saturated and α,β-unsaturated ketones was observed in the Eu^{III}-catalyzed reactions with **6a** [Eq. (15); fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione].[31] The competition of the cyclic ketone and enone led to the exclusive formation of the 1,4-addition product. This discriminating ability of the Eu^{III} catalysis is remarkable when compared with the poor ability of stoichiometric TiCl$_4$.

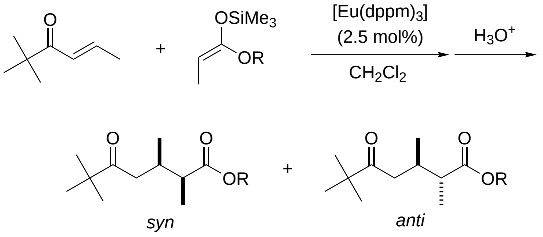


(15)

	1,2 : 1,4
$n = 1$	<1 : 99
$n = 1$ ($TiCl_4$, 1 equiv)	32 : 68
$n = 2$	5 : 95

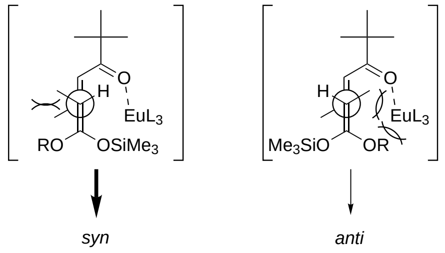
2.3.2. Diastereoselective Catalysis by Induced Stereochemical Fit

The diastereoselectivity in Eu^{III}-catalyzed Michael additions is generally not high. Both cyclic and acyclic enones gave low to moderate levels of *syn* selectivity, regardless of the geometry of the ketene silyl acetal.[32] However the extremely high level of *syn* selectivity was observed with the sterically congested *tert*-butyl (*E*)-propenyl ketone when an equally sterically bulky ketene silyl acetal was employed [Eq. (16)].

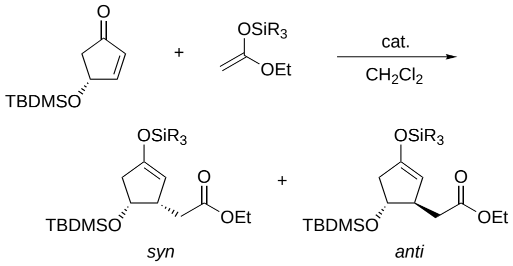


(16)

R		syn / anti	
R = *t*Bu	(>95% *E*)	95 : 5	(68% yield)
R = *i*Pr	(86% *E*)	87 : 13	(74% yield)



The principal advantage of Eu^{III}-catalyzed Michael addition is that the product is obtained as a silyl enol ether form, which is synthetically useful for further transformations. Michael addition to 4-silyloxycyclopentenone delivered the silyl enol ether product as a synthetic key intermediate for prostanoids with high *syn* selectivity [Eq. (17)].[33] This high *syn* selectivity contrasts with the extremely high *anti* selectivity observed in the tris(diethylamino)sulfonium difluoromethylsilicate (TASF)-catalyzed reaction. The stereochemical reversal generally found in Lewis acid catalysis (for example, with HgI_2),[34] is explained in terms of stereoelectronic effects based on the Cieplak model.[35]

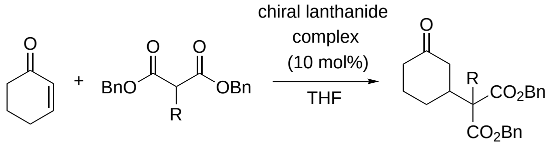


(17)

			syn / anti	
R = Me	[Eu(fod)$_3$]	(5 mol%)	74 : 26	(99%)
Et	HgI_2	(10 mol%)	95 : 5	(74%)
Me	TASF	(5 mol%)	0 : 100	(87%)

2.3.3. Enantioselective Catalysis

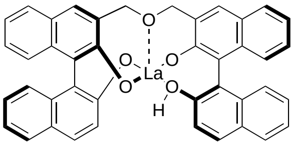
Shibasaki and co-workers reported that LaNa$_3$tris(binaphthoxide) (LSB) is ineffective for the asymmetric nitroaldol reaction.[36] However it is an effective catalyst for the enantioselective Michael addition of various enones with malonates, affording the Michael adducts in up to 92 % *ee* and in nearly quantitative yield [Eq. (18)].[37] The highly enantioselective catalysis of LSB thus observed contrasts directly with the ineffectiveness of LLB (described in Section 2.2.3) in the asymmetric Michael addition.



(18)

chiral lanthanide complex	R		
(*R*)-LSB	H	88% *ee*	(97%)
(*R*)-LLB	H	2% *ee*	(78%)
(*R*)-LSB	Me	92% *ee*	(91%)
(*R*,*R*)-La-linked-binaphthol*	H	>99% *ee*	(94%)

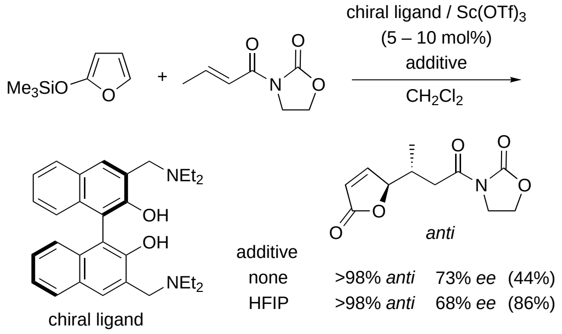
* in DME



alkali-metal free (*R*,*R*)-La-linked-binaphthol

Recently, a highly efficient and stable asymmetric catalyst, an La-linked–binol complex, was also developed[38] for the enantioselective Michael addition reaction [Eq. (18)], which gives the Michael adduct in an enantioenriched form. The notable advantage of the La-linked-binol complexes emphasized here is their high stability and, hence, can be stored even under air.

Kitajima and Katsuki reported an enantioselective Michael addition catalyzed by a chiral Sc^{III} complex prepared from $Sc(OTf)_3$ and binol derivatives bearing a tertiary aminomethyl group [Eq. (19)].[39] They achieved excellent diastereoselectivity and good enantioselectivity, but the yield was moderate. The addition of hexafluoroisopropanol (HFIP) suppressed the undesired Diels–Alder-type product, and improved the yield of the Michael reaction.



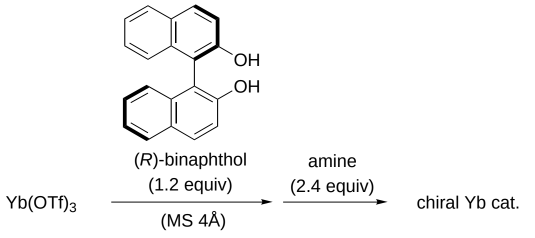
(19)

additive			
none	>98% *anti*	73% *ee*	(44%)
HFIP	>98% *anti*	68% *ee*	(86%)

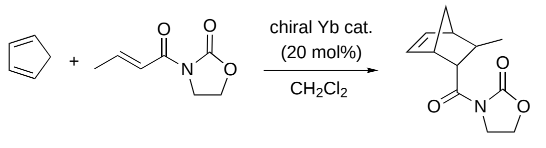
2.4. Diels–Alder Reaction

2.4.1. Diels–Alder Reactions with Chiral Lanthanide Complexes

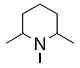
Kobayashi et al. succeeded in the chiral modification of the water-stable Lewis acid complex $Ln(OTf)_3$[40] with binaphthol [Eq. (20)].[41] Significantly, the use of a bulky amine led to an increase in the enantioselectivity [Eq. (21)], the sense of which depends critically on the kind of additive used [Eq. (22)].[42][43]



(20)

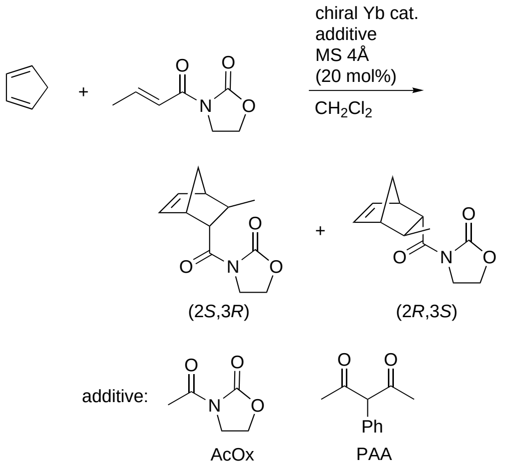


(21)

Amine	MS	*T* [°C]	Yield [%]	*endo* / *exo*	*ee* [%]
Et_3N	-	23	87	76 : 24	33
iPr_2EtN	-	23	82	85 : 15	70
iPr_2EtN	MS 4Å	23	88	87 : 13	83
	MS 4Å	23	91	86 : 14	90
	MS 4Å	0	77	89 : 11	95

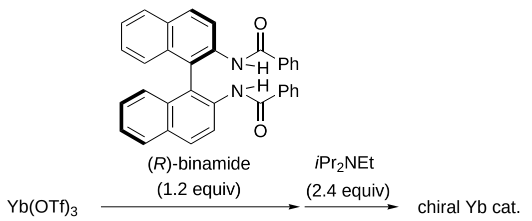
Nakagawa and co-workers synthesized 1,1′-(2,2′-bisacylamino)binaphthalene (binamide) and examined the function of this ligand in the asymmetric Diels–Alder reaction using the chiral ytterbium catalyst [Eq. (23) and (24)].[44] Screening various bulky amines with diisopropylethylamine led to the best result in this reaction. Qian and co-workers also described complexes of $Ln(OTf)_3$ and binaphthyl derivatives, and their use in asymmetric reactions.[45]

Collin and co-workers synthesized the enantiopure samarium binaphthoxides by the reaction of the dipotassium salts of binaphthol and 3,3′-bis(2-methoxyphenyl)binaphthol with samarium triiodide.[46] In the asymmetric Diels–Alder reaction, samarium 3,3′-bis(2-methoxyphenyl)binaphthoxide gave a higher enantioselectivity than the samarium binaphthoxide (81% *ee* (−28°C) vs. 28% *ee* (−25°C), respectively) [Eq. (25)]. The 3,3′-bis(2-methoxyphenyl)binaphthol is more sterically hindered than binaphthol and is capable of tri- or tetracoordination to the samarium center.

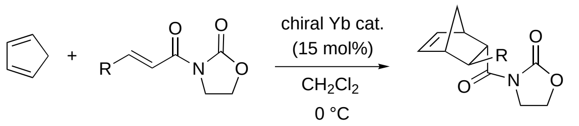


(22)

additive	Y [%]	*endo* / *exo*	*ee* [%]
AcOx	77	89 : 11	93 (2*S*,3*R*)
PAA	83	93 : 7	81 (2*R*,3*S*)

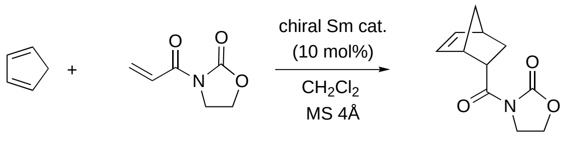


(23)



(24)

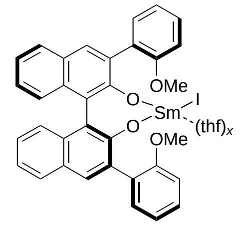
R = H 99% yield *endo*/*exo* = 91 (88% *ee*) :9
Me 97% yield *endo*/*exo* = 91 (>98% *ee*) :9



(25)

100% conversion
81% *ee*

chiral Sm cat. =



2.4.2. *Lanthanide Fluorous "Super" Lewis Acid*

In the mid-1990s, the concept of fluorous biphasic catalysis (FBC) was introduced for use as an environmentally benign recycling process (Figure 8).[47] Phosphane or phosphite ligands with fluorous "ponytails" and hydrocarbon spacers have been developed to immobilize late-transition-metal catalysts for hydroformylation, hydride reduction, hydrogenation, alkene epoxidation, and hydroboration in nonpolar media.[48] The design and immobilization of strong Lewis acid catalysts in this unorthodox nonpolar media for Lewis acid catalysis[49] remain a challenge.[50] We have reported that numerous (nine) fluorous "ponytails" of sufficient length (perfluorooctyl, C_8F_{17}) can be employed for fluorous-phase immobilization of lanthanide catalysts. The key to the success of the catalysts is the powerful electron-withdrawing effect of the perfluoroalkanesulfonylmethide group[51] without a hydrocarbon spacer.

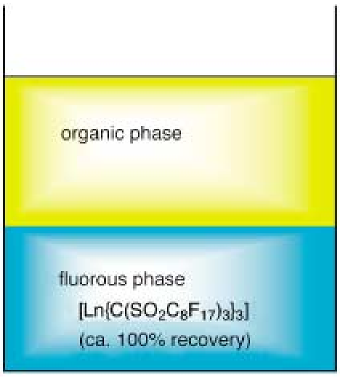
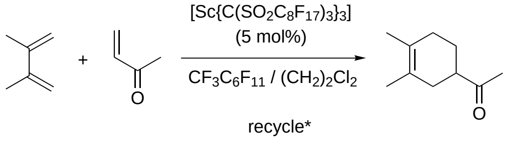


Figure 8. Catalysis in fluorous/organic biphasic system.

We have reported the "super" Lewis acidities and the complete recovery of the Ln^{III} tris(perfluorooctanesulfonyl)methide complexes for the Diels – Alder reaction in a fluorous phase [Eq. (26)].[52] The Diels – Alder reaction was carried out at 35 °C, in the presence of a catalytic amount (5 mol%) of Sc^{III} complex. The two heterogeneous phases were separated to give acetylcyclohexene, which was isolated in a good yield. The Sc^{III} methide complex was completely (>99.9%) recovered and reused. Sc^{III} and Yb^{III} tris(perfluorooctanesulfonyl)methide complexes can be immobilized in recyclable fluorous phases and are extremely efficient Lewis acid catalysts for alcohol acylation, Friedel – Crafts acylation, and Mukaiyama aldol reaction, by virtue of the highly electron-withdrawing effect of tris(perfluorooctanesulfonyl)methide ponytails without a hydrocarbon spacer. In addition, these lanthanide complexes could be reused as solid catalysts in organic solvent without the addition of fluorous solvent (Figure 9).[51b, 53]



(26)

recycle*	
1st	95
2nd	94
3rd	95
4th	95

*The catalyst in the fluorous phase was recycled

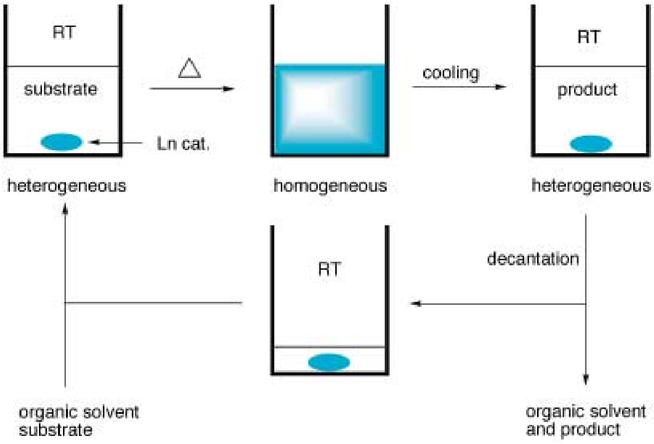
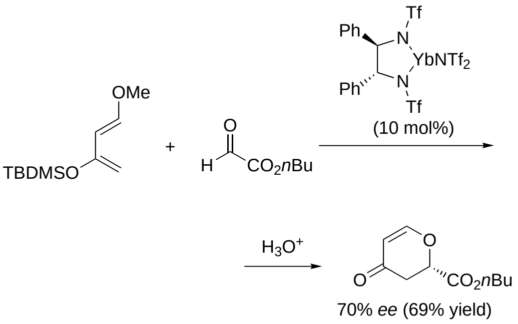


Figure 9. Use and reclamation of lanthanide complexes from organic solvents.

2.5. Hetero-Diels – Alder Reactions[20, 54]

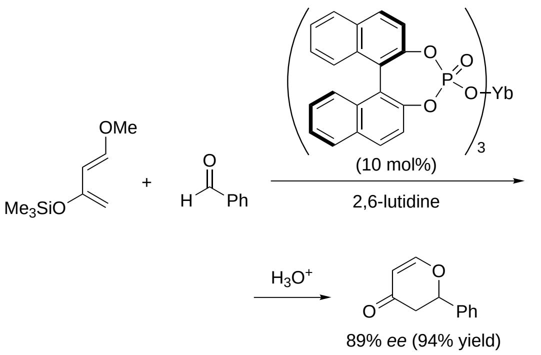
We found that the lanthanide triflate/binaphthol complex which was generated by treatment with KH or NaH only led to a low enantioselectivity. However, the use of lanthanide triflate, bis(triflyl)amide, or chiral bis(triflyl)amide complexes generated with KH or NaH provides a higher level of enantioselecivity [Eq. (27)].[55] We found that the use of KOH instead of KH provides a similarly high level of enantioselectivity, which indicates the stability of the lanthanide triflate/bis(triflyl)amide complex in the presence of water. Consequently, the addition of water to the hetero-Diels – Alder reaction conditions led to the highest enantioselectivity.



(27)

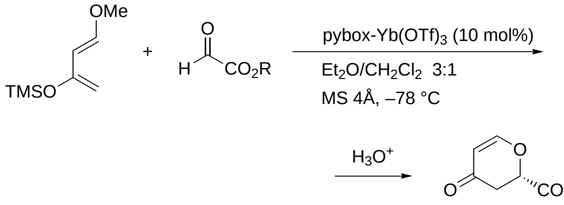
Inanaga and co-workers reported the use of chiral binaphthol-derived phosphate complexes for the hetero-Diels – Alder reaction with the Danishefsky diene [Eq. (28)].[56] This complex is insoluble in dichloromethane but becomes soluble upon addition of a tertiary amine to the solution. They also observed a significant, positive nonlinear effect.

Qian and Wang performed asymmetric hetero-Diels – Alder reactions catalyzed by various chiral bis(oxazoline) –



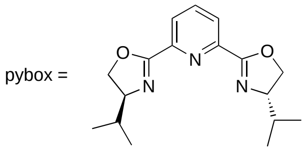
(28)

lanthanide complexes.[57] From these studies, the ytterbium triflate/*i*Pr-pybox complex was the best catalyst in this reaction [Eq. (29); pybox = bis(oxazolinyl)pyridine].[58] It is interesting that higher enantioselectivity was obtained using the sterically less-demanding methyl glyoxylate and by slow addition of Danishefskys diene.



(29)

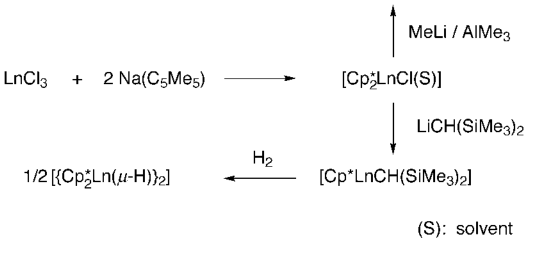
R =		
Me	73% yield	77% *ee*
Et	41% yield	72% *ee*
*n*Bu	73% yield	71% *ee*



2.6. Hydrogenation

2.6.1. Lanthanide Metallocene Catalysts

Much attention has been focused on lanthanide metallocene complexes since the discovery of their high catalytic activity for polymerization of cyclopentadienyllanthanide complexes [Eq. (30)].[59] Marks has developed the enantioselective hydrogenation of 2-phenyl-1-butene [Eq. (31)].[59a, 60] Incorporation of a chiral menthyl group in the 3-position of an *ansa*-bis(cyclopentadienyl)ligand leads to two diastereomeric complexes of samarium (Figure 10). These complexes are active catalysts for the hydrogenation of 2-phenyl-1-butene under mild conditions (25 °C, $p(H_2)$ 760 mmHg, 5 min). Even with a 70:30 diastereomeric mixture of the menthyl-substituted samarium-metallocene complex, good [64% *ee* (*R*)] to excellent [96% *ee* (*S*)] enantioselectivities were obtained at 25 and –80 °C, respectively.



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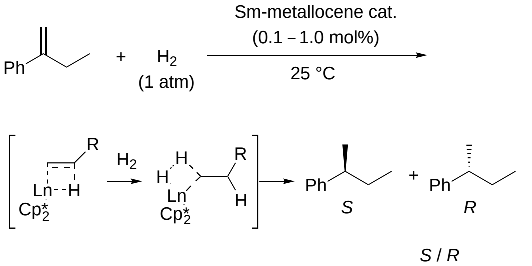


(31)

	S / *R*
(*R*)-(+)-neomenthyl-SmCH(SiMe3)2	13 : 87
(*S*)-(+)-neomenthyl-SmCH(SiMe3)2	59 : 41
(*R*)-(–)-menthyl-SmCH(SiMe3)2	42 : 58
70:30 (*S*/*R*)-(–)-menthyl-SmCH(SiMe3)2	90 : 10
70:30 (*S*/*R*)-(–)-menthyl-SmCH(SiMe3)2	98 : 2*

* At –80 °C.

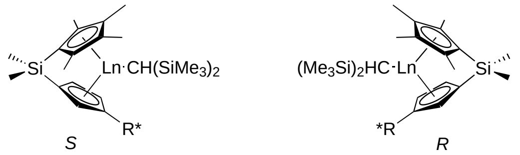


Figure 10. Chiral lanthanide-containing metallocene complexes. Ln = La, Nd, Sm, Y, Lu; R* = (+)-neomenthyl, (–)-menthyl, (–)-phenylmenthyl.

3. Asymmetric Reactions with Ln^{II} Catalysts

3.1 Reagents and Reactions

Kagan reported the use of a THF solution of SmI_2 as a one-electron reducing reagent in organic synthesis.[3a, 12] Then, Inanaga found that the addition of hexamethyl phosphoramide (HMPA)[61] causes a remarkable increase in the reducing ability of SmI_2; SmI_2 with 4 equiv of HMPA has the highest reducing ability with an oxidation potential of –2.05 V.[62] The resultant Sm^{III} species may be used in situ as a Lewis acid catalyst. In turn, the Sm^{III} species can be reduced to an Sm^{II} species to complete the catalytic process and regeneration of not only SmI_2 but also of the chiral ligands coordinated to the $Sm^{II/III}$ center (Figure 11).

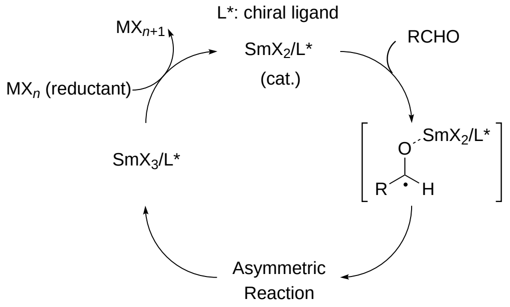
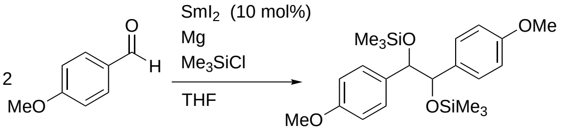


Figure 11. Catalytic cycle of asymmetric $Sm^{II/III}$-mediated reactions.

3.2. Pinacol Coupling

Pinacol coupling[63] has long been known using titanium[64] and zinc reagents.[65] Lanthanides such as Ce^{II},[66] Sm^{II},[67] and Yb^{II}[68] were also shown to be effective.

Endo and co-workers reported that a catalytic quantity of SmI_2 is good enough for the reductive coupling reaction of aliphatic and aromatic aldehydes and ketones in the presence of Mg/Me_3SiCl [Eq. (32)].[69] On the basis that reactions with both catalytic and stoichiometric SmI_2 exhibit the same level of diastereoselectivity, the samarium-catalyzed coupling reaction has been concluded to proceed prior to silylation of the alkoxide (Figure 12). In the presence of only Mg/Me_3SiCl, the coupling reaction of benzaldehyde does not occur. In the absence of Me_3SiCl, a complex mixture of products is formed, presumably because of inefficient turnover of the Sm^{II} catalyst. Using an inexpensive alloy of the light lanthanides, acetophenone can be reductively coupled in 70% yield without Me_3SiCl.[70] However, no reaction takes place in the absence of SmI_2.



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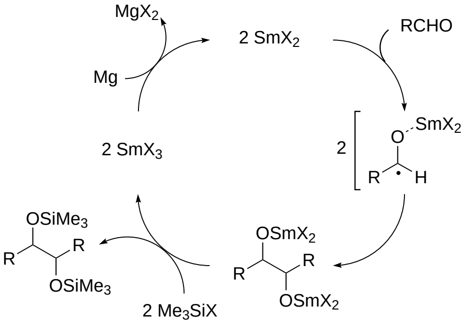
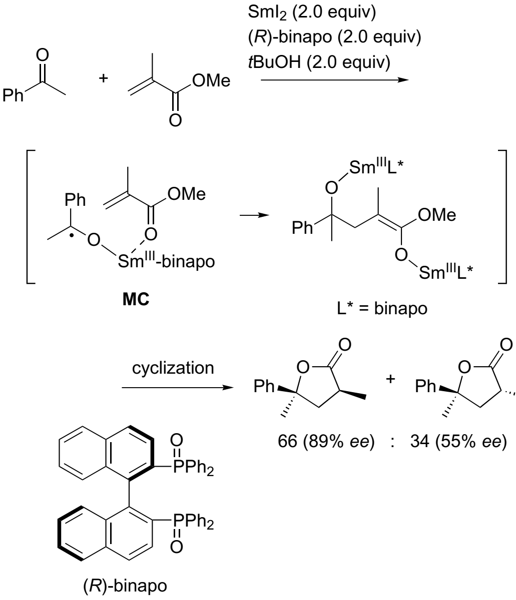


Figure 12. Proposed mechanism for the samarium-catalyzed pinacol coupling reaction.

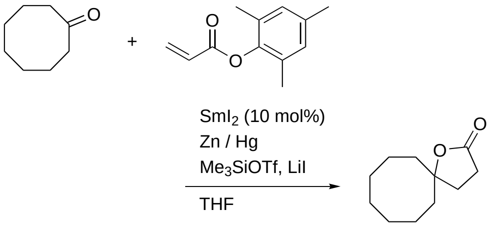
3.3. Radical Addition Reactions

Inanaga et al. reported on Sm^{II}-mediated radical addition reactions to α,β-unsaturated esters.[71] We have recently reported the first successful Sm^{II}-mediated, asymmetric, radical addition reaction [Eq. (33)].[72, 73] The ligand binapo is the best chiral ligand to date in this type of asymmetric radical addition reaction. The ketyl samarium intermediate can be trapped by α,β-unsaturated esters through formation of a medium ring chelate species (**MC**)[73] to form new carbon–carbon bonds. One equivalent of binapo to SmI_2 is necessary to give a high level of enantioselectivity. Unfortunately, upon mixing SmI_2 and binapo in a 1:2 ratio, a precipitate was formed. Asymmetric protonation of the resultant samarium enolate takes place to control the second stereogenic center of the α-substituted γ-butyrolactone with the assistance of binapo ligands on the samarium enolate.



(33)

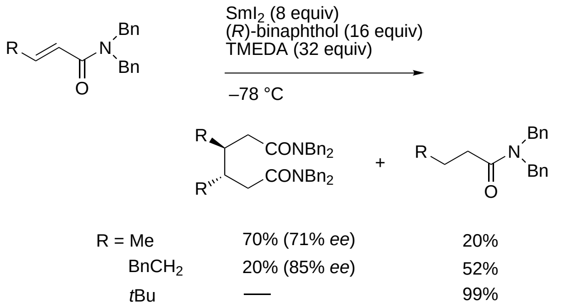
This asymmetric radical addition reaction might be established as a catalytic process by the catalytic use of not only SmI_2 but also chiral ligands coordinated to the samarium center. This expectation is based on the elegant study by Corey on a catalytic process for the radical addition reaction by the use of 10 mol% of SmI_2 with Zn–Hg, Me_3SiOTf, and LiI [Eq. (34)].[74]



(34)

3.4. Radical Homocoupling Reaction of β-Monosubstituted Acrylic Acid Amides

The stereocontrol of radical reactions, especially intermolecular ones, remains one of the most difficult problems in modern organic synthesis. However, unlike free radicals, conjugated ketyl radicals have anionic character. Therefore, it should be possible to differentiate the enantiotopic face of the ketyl radicals kinetically for the subsequent reaction, by coordinating their countercations with the appropriate chiral ligand. According to this idea, Inanaga and co-workers performed the ligand-controlled enantioselective hydrodimerization of acrylamide derivatives, which proceeded through the formation of conjugated ketyl radicals.[75] The reaction was carried out using SmI_2 (8 equiv), (*R*)-binol (16 equiv), and tmeda (tmeda = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine; 32 equiv) in THF at −78 °C for 4 h [Eq. (35)]. High enantioselectivities (up to 85 % *ee*) were obtained when primary alkyl-substituted acrylic amides were used as substrates. As the β-substituent becomes bulkier, the yield of the coupling product decreases (when R = *t*Bu, the only product was the monoamide). The postulated transition state is a nine-membered chelate structure (Figure 13). In the transition state, the conjugated ketyl radical and the ligated crotonamide are in a *cis*-arrangement in the chiral coordination sphere of the samarium center.



(35)

R =		
Me	70% (71% *ee*)	20%
$BnCH_2$	20% (85% *ee*)	52%
*t*Bu	—	99%

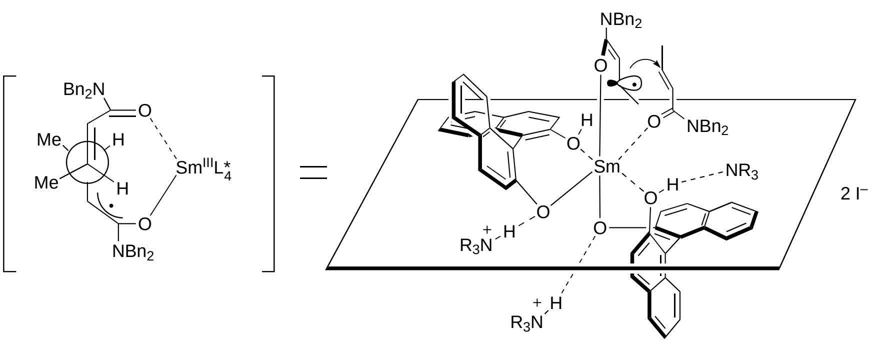
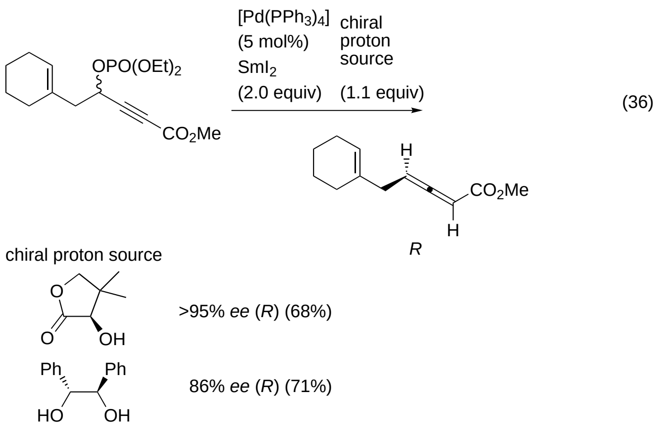


Figure 13. A possible transition state for asymmetric hydrodimerization of crotonamide.

3.5. Dynamic Kinetic Protonation of the Samarium Carbanion

We have reported that the reduction of secondary propargylic phosphates provided allenes with higher regioselectivity than did the propargylic acetates, through SmI_2-mediated reduction followed by protonation in the presence of a palladium(0) catalyst.[76] We further reported that SmI_2-mediated reduction of secondary propargyl phosphates gives allenic esters with high regio- and enantioselectivity through dynamic kinetic protonation, without a chirality-transfer process [Eq. (36)].[77]



(36)

The starting propargylic phosphate can be prepared by asymmetric carbonyl-ene reaction with an alkynyl analogue of glyoxylate catalyzed by a binaphthol–titanium complex, followed by phosphorylation.[78] The cationic allenylpalladium(II) species are converted into carbanionic organosamarium(III) species by sequential one-electron reductions with two equiv of SmI_2 (Figure 14). This carbanionic Sm^{III} species racemizes readily. This result suggests the possibility of dynamic kinetic resolution[79] using chiral proton sources,[80] even when starting from racemic phosphates; namely a deracemization process of a racemic allenylsamarium(III) species. The organosamarium(III) species, formed by reduction of phosphates with Sm^{II}, are strongly oxophilic and Lewis acidic. Thus, chiral diols and hydroxycarbonyl compounds can be effective as proton sources, since the chelation of such chiral alcohols with Sm^{III} constructs a favorable asymmetric environment.

The sense of asymmetric protonation to provide (*R*)-allenic ester using (*R*)-hydrobenzoin and (*R*)-pantolactone can be well explained by the transition state model (Figure 15), in which there is severe steric repulsion between alkyl

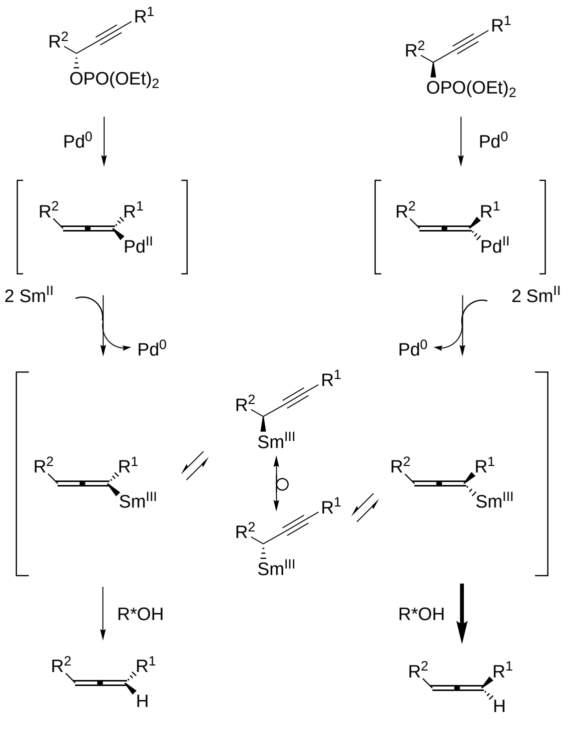


Figure 14. Dynamic kinetic resolution of racemic allenylsamarium(III) species by asymmetric protonation.

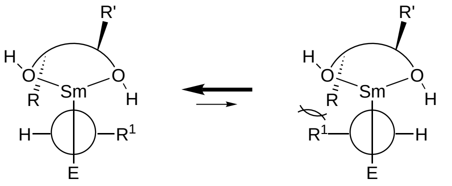


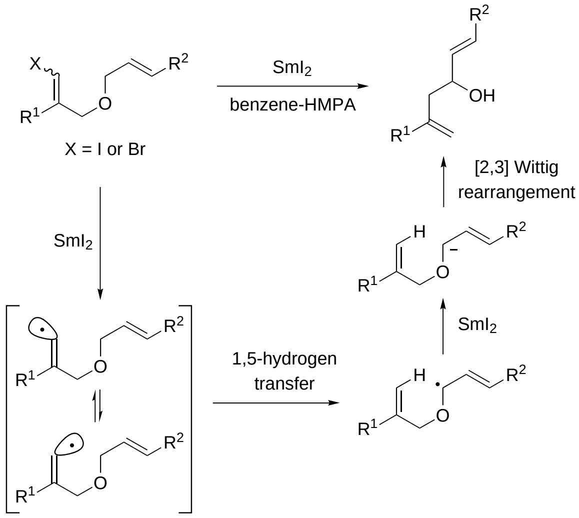
Figure 15. Chiral allene formation by asymmetric protonation.

groups in the right-hand-side (see Figure 15) diastereomer. Thus, protonation proceeds through the favorable diastereomer on the left-hand side, to give highly enantioenriched allenic ester.

3.6. Wittig Carbanion Rearrangement

In the very important field of carbanion chemistry, the [2,3] Wittig rearrangement has a wide application in asymmetric syntheses of natural products such as steroids;[81] an enantioselective version of the Wittig rearrangement has therefore been a true challenge. The regioselectivity of the [2,3] and [1,2] Wittig rearrangement of bisallylic and allyl propargyl ethers has been reported;[82] deprotonation at the α- and γ-position of less substituted allylic ethers or of γ-substituted propargylic ether moieties gives a [2,3] Wittig rearrangement product. However, γ-unsubstituted propargylic ether derivatives are metalated at the terminal acetylenic position and, in turn, the allylic carbanion is generated to give the [1,2] Wittig rather than [2,3] Wittig rearrangement products.[82d]

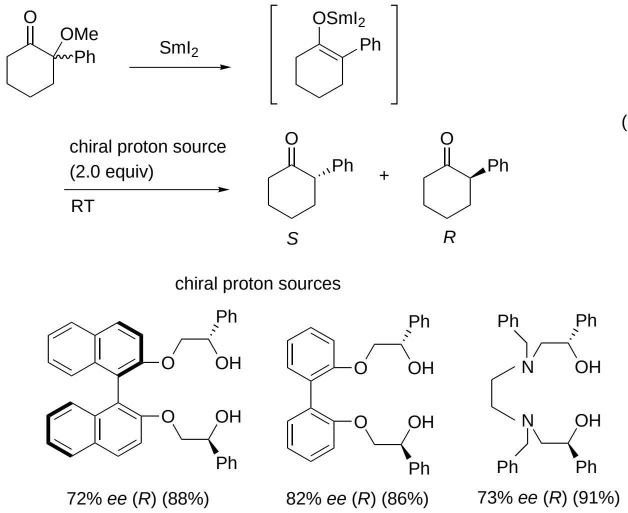
Kunishima and Tani reported highly regiocontrolled [2,3] Wittig rearrangement by the judicious choice of benzene – HMPA as the solvent, in which a radical species can be generated; this is otherwise difficult, particularly in THF solution [Eq. (37)].[83] This method facilitates the synthesis of the less favorable regioisomer under the standard conditions.[82] In a similar manner, enantioselective carbanion rearrangement might be demonstrated by the proper choice of a chiral coordinating ligand to samarium to make this process catalytic and asymmetric.



(37)

3.7. Samarium Enolate Reaction

In a similar manner, the enantioselective protonation of enolates is an effective method for preparing chiral carbonyl compounds [Eq. (38)]. Therefore, a catalytic process for the enantioselective protonation of enolates has become an important target in synthetic chemistry. In 1986, Molander reported that a wide range of α-substituted carbonyl compounds are rapidly reduced under mild conditions by SmI_2 in the presence of a proton source such as methanol and proposed a reaction mechanism in which reductive cleavage of the carbon – heteroatom bond takes place with two equiv of SmI_2 to give the samarium enolate.[84] A transition-state model of the protonation has already been proposed, in which a chiral proton source coordinates to the Sm^{III} ion as a tetradentate ligand.[85] This model clearly explains the enantioselectivities. In the transition state (**TS$_1$**, Figure 16), the substituent in the C2 position of the enolates is far from the benzene ring and has no repulsive interaction with it. Consequently, protonation at the top side, namely from the *si* face of the enolate, gives the *R* product. The biphenyl auxiliary is easily adjustable to the favorable conformation **TS$_3$**.



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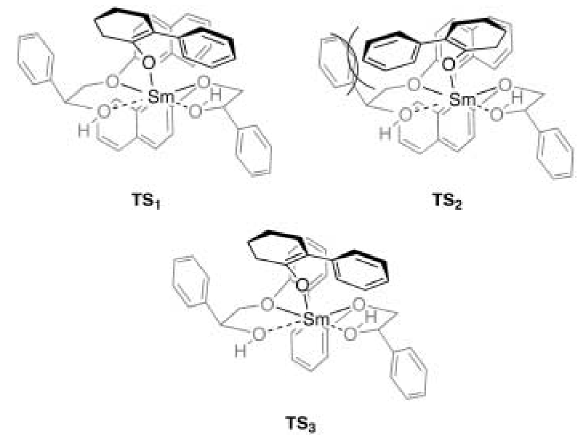
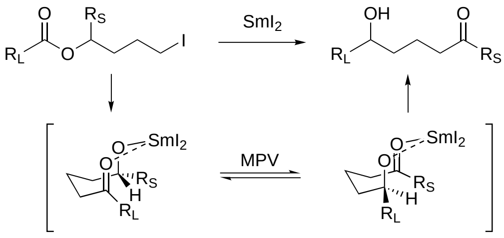


Figure 16. Transition states for asymmetric protonation of samarium enolates.

4. Sequential Sm^{II} to Sm^{III} Catalysis

4.1. Meerwein–Ponndorf–Verley (Tiščenko) Reactions

In 1977, Kagan and co-workers suggested that the catalytic activity of Sm^{III} complexes in Meerwein–Ponndorf–Verley (MPV) reactions is a consequence of the (intramolecular) pseudo-Barbier reaction initiated by SmI_2 [Eq. (39)].[86] Evans et al. reported that Sm^{III} alkoxide complexes exhibit a higher catalytic activity for MPV reactions than Al complexes [Eq. (40)].[87] A samarium(III) complex with an enantiopure chiral tridentate ligand gave a high level of enantioselectivity [Eq. (41)]. The order of the catalytic activity and the level of enantioselectivity are as follows: $Sm, Tb > Nd > Y \gg Lu \gg Sc$. As expected from the high coordination number and oligomeric nature of the samarium complexes, a high level of positive nonlinear phenomena (asymmetric amplification) was observed: thus, a Sm complex of 80% *ee* purity provides the reduced alcohol in 95% *ee*, an equally high level of enantioselectivity to that obtained with an enantiopure samarium complex.



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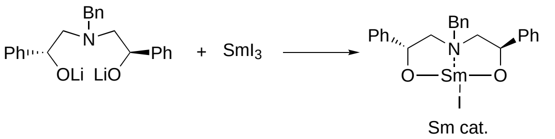

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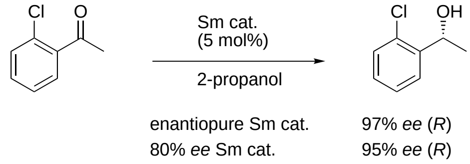

(41)

5. Perspectives

Asymmetric catalysis of organic reactions has been greatly advanced by the creation of lanthanide complexes with chiral ligands, which maximize the characteristic features of the central lanthanide cations. For further development of asymmetric lanthanide catalysis, the recyclable use of lanthanide complexes is important in "green chemistry".[88] It is possible to reclaim and reuse triflate, bis(sulfonyl)amide, and tris(sulfonyl)methide salts of lanthanides. However, the lanthanide catalysts recovered from the aqueous phase have the serious disadvantage that water must be removed prior to reuse. For easy recyclable use, the preparation of polymer-bound lanthanide catalysts[89] is promising. As an alternative, lanthanide complexes with perfluorinated ligands ("fluorous ponytail") can also be immobilized, but in a fluorous fluid phase (biphasic fluid) rather than in the solid phase[52, 90].

High stereoselectivities have been reached by the use of samarium(II) complexes, which exploit the strong oxophilicity of the samarium ion. It is important that the catalytic use of SmI_2 with or without chiral ligands has been established. To minimize the number of resultant samarium(III) species, including chiral species in some cases, a reducing metal (for example, magnesium) is employed. However, the reported methods are limited in the range of applicable reactions or by their excessive use of reducing metals. If these problems were overcome and recyclable use were to be established, nontoxic and nonharmful lanthanide complexes would certainly play a greater role in green (asymmetric) catalysis.

We are grateful to Prof. Takeshi Nakai, who retired from the Tokyo Institute of Technology and is now at Niigata University. We also thank Prof. Junji Inanaga of Kyushu University, Prof. Seji Takeuchi and Dr. Yutaka Nakamura of Niigata College of Pharmacy, and our past and present students listed in the references, particularly Dr. Yukihiro Motoyama, now in Toyohashi University of Technology & Science, Dr. Akihiro Yoshida of Noguchi University, and Makoto Yamaoka, of Sankyo Pharmaceutical Co. Ltd., for their contribution to the lanthanide-catalysis research project.

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