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Recent progress in asymmetric two-center catalysis

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Recent progress using two types of enantioselective two-center catalysts, Lewis acid–Brönsted base and Lewis acid–Lewis base bifunctional complexes, is described. The first part of this review discusses improvements in the *syn*-selective direct catalytic enantioselective aldol reaction and 1,4-addition reaction of a 2-hydroxyacetophenone derivative using a Zn-linked-BINOL complex. In the second part, we describe the development of catalysts displaying Lewis acidity and Lewis basicity in a catalytic enantioselective cyanosilylation of aldehydes and the logical extension to a tetrasubstituted carbon synthesis through a Reissert-type reaction and a cyanosilylation of ketones.

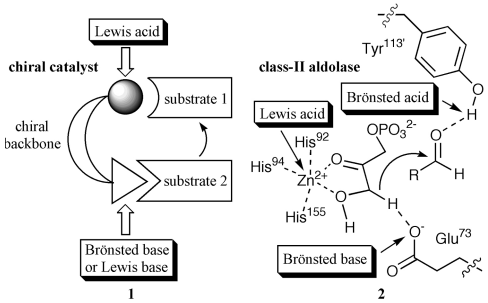

Fig. 1 General concept of two-center catalysis and mechanism of natural two-center catalysis by enzyme (class-II aldolase).

Introduction

Catalytic enantioselective reactions are extremely powerful methods for organic synthesis. The development of new enantioselective catalysts continues to be an important topic in the field of organic chemistry. A number of chiral catalysts have been reported, some of which exhibit a much higher catalytic efficiency than do natural catalysts, enzymes.[1] Most of the synthetic asymmetric catalysts, however, are limited in terms of enantioselectivity or substrate generality. The major difference between synthetic asymmetric catalysts and enzymes is that the former activates, in general, only one side of the substrate in an intermolecular reaction, whereas the latter activates both sides and can also control the orientation of the substrates (Fig. 1). If this type of synergistic cooperation can be realized with artificial asymmetric catalysts, a new field in asymmetric synthesis can be developed, resulting in a wide range of applications. Thus, we are developing asymmetric catalysts based on the concept of a two-center catalysis. The present review discusses recent advances[2,3] in two types of asymmetric two-center catalyses promoted by complexes with Lewis acidity and Brönsted basicity and/or Lewis acidity and Lewis basicity.

Direct catalytic enantio- and diastereoselective aldol reaction promoted by a Lewis acid–Brönsted base two-center catalyst

The aldol reaction is generally regarded as one of the most powerful and efficient carbon–carbon bond-forming reactions. Many efforts have been directed towards the development of catalytic asymmetric aldol reactions,[4] but almost all of these reactions require preconversion of the ketone or ester moiety into a more reactive species such as an enol silyl ether or a ketene silyl acetal using no less than stoichiometric amounts of

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Motomu Kanai was born in 1967 in Tokyo, Japan, and received his PhD from Osaka University in 1995 under the direction of Professor Kiyoshi Tomioka before doing postdoctoral studies with Professor Laura L. Kiessling at the University of Wisconsin. In 1997 he returned to Japan and joined Professor Shibasaki's group in the University of Tokyo as an assistant professor. He is currently a lecturer in Shibasaki's group, and a PREST (Precursory Research for Embryonic Science and Technology) member of JST (Japan Science and Technology Corporation). He has received the Pharmaceutical Society of Japan Award for Young Scientists (2001).

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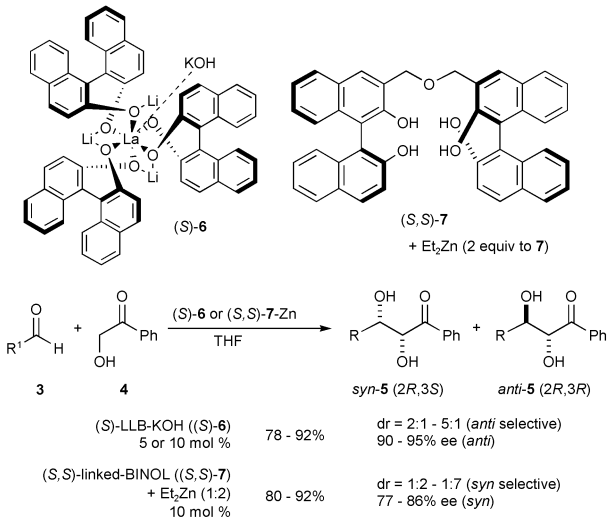
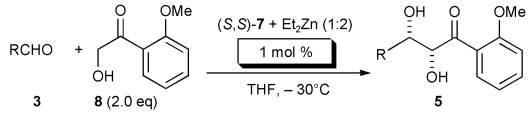
reagents. Since we successfully performed direct catalytic asymmetric aldol reactions using unmodified ketones such as acetophenone and acetone,[5] this potentially advantageous strategy has attracted much interest in terms of atom economy.[6] List *et al.*[7] and Trost *et al.*[8] reported direct asymmetric aldol reactions using L-proline or a chiral semi-crown Zn complex as catalysts.[9] Moreover, several groups recently reported enantio- and diastereoselective direct aldol reactions with α-hydroxyketones using biological-type catalysts[10] or small molecular catalysts,[11,12] which has considerably widened the scope of the field. We also reported an enantio- and diastereoselective direct aldol reaction with 2-hydroxyacetophenone (**4**), which provided either *anti*- or *syn*-α,β-dihydroxyketones using two Lewis acid-Brönsted base two-center catalysts, a $LaLi_3$tris(binaphthoxide)·KOH (LLB·KOH) complex (**6**: *anti* selective) or a Zn-linked-BINOL (**7**) complex (*syn* selective) (Scheme 1).[13] Our ongoing investigations to further improve the efficiency of these reactions with respect to catalyst amount, diastereomeric ratio, enantiomeric excess, reaction rate, and yield led to the development of a practical atom-economical direct aldol reaction promoted by Zn-linked-BINOL complex.[14]

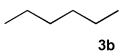
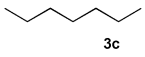
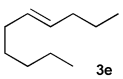
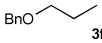
Previous results suggested that substituents on the aromatic ring of the acetophenones affected both diastereoselectivity and enantioselectivity. We chose methoxy substituted acetophenones, because the additional coordination of the methoxy group to the metal more predominantly defines the specific orientation of the intermediate zinc enolate in the catalyst and because conversions such as a Baeyer-Villiger oxidation of the product are more facile. The reaction rate, yield, diastereomeric ratio, and enantiomeric excess of the aldol reaction improved when 2-hydroxy-2′-methoxyacetophenone (**8**) was used.[15] The aldol reaction of **8** proceeded smoothly, even when the catalyst amount was reduced to 1 mol%. Table 1 shows the scope and limitations of the reaction. In all cases, 1 mol% of the Zn-**7** complex was sufficient to complete the reaction within 24 h.[16] Both normal (entries 1–3 and 5–7) and branched (entry 4) primary (α-unsubstituted) aldehydes gave the corresponding aldol adducts in good to excellent yield and enantiomeric excess without forming any self-condensation products. The results indicate high chemoselectivity of the present catalysis. In the case of *trans*-4-decenal (**3e**, entry 5), synthesis of the corresponding diol **5e** *via* Sharpless asymmetric dihydroxylation (AD)[17] is difficult due to the problems with chemoselectivity. Aldehydes with oxygen functionalities such as **3f** (entry 6) and **3g** (entry 7), which lead to useful intermediates for the synthesis of polyoxygenated compounds, were also converted into diols in excellent enantiomeric excess. Remarkably, secondary (α-monosubstituted) aldehydes (entries 8–10) showed good yield, excellent diastereomeric ratio, and enantiomeric excess. In all cases in which the absolute configurations of the product were



Scheme 1 Direct catalytic enantio- and diastereoselective aldol reaction.

Table 1 Direct aldol reaction of various aldehydes with 2-hydroxy-2′-methoxyacetophenone (**8**)[a]

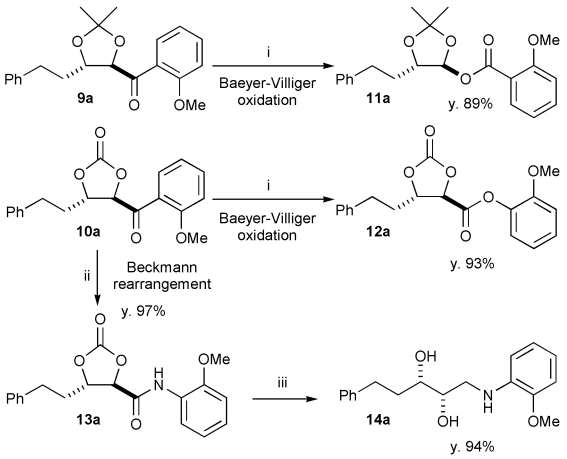


Entry	R	Product	Time (h)	Yield[b] (%)	dr[c] (*syn*/ *anti*)	ee[d](*syn*/ *anti*)
1	 3a	**5a**	20	94	89/11	92/89
2	 3b	**5b**	18	88	88/12	95/91
3	 3c	**5c**	18	84	87/13	96/87
4	 3d	**5d**	18	84	84/16	93/87
5	 3e	**5e**	24	94	86/14	87/92
6	 3f	**5f**	18	81	86/14	95/90
7	 3g	**5g**	16	84	72/28	96/93
8	 3h	**5h**	24	83	97/3	98/—
9	 3i	**5i**	16	92	96/4	99/—
10	 3j	**5j**	18	95	97/3	98/—

[a] All reactions were run on 1.0 mmol scale at 0.2 M in aldehyde. [b] Isolated yield after conversion to acetonides. [c] Determined by ^{1}H-NMR of crude mixture. [d] Determined by chiral HPLC analysis of diols.

determined, both the *syn*- and *anti*-products contained the (*R*)-configuration at the α-carbons, indicating that the chiral catalyst shields the *Si*-face of the enolate generated from the ketone **8**. To the best of our knowledge, in terms of catalyst loading, this is the most effective small molecular catalyst for direct asymmetric aldol reactions. The reaction proceeded smoothly without any problems on a gram scale. Combined with the simple protocol, the present reaction is practical and useful. The reaction was performed by just mixing commercially available Et_2Zn in hexanes and easily available linked-BINOL in THF, followed by the addition of ketone **8** and aldehyde.

The utility of the aldol adducts becomes even higher using the 2-methoxyphenyl moiety as a placeholder for further conversions. As shown in Scheme 2, the Baeyer-Villiger oxidation



Scheme 2 Transformations of aldol adducts *via* regioselective rearrangement. Reagents and conditions: (i) *m*CPBA, NaH_2PO_4, $ClCH_2CH_2Cl$, 50 °C, 2 h; (ii) *O*-mesitylenesulfonylhydroxylamine, CH_2Cl_2, rt, 4 h; (iii) DIBAL, CH_2Cl_2, −78 °C to rt, 2 h.

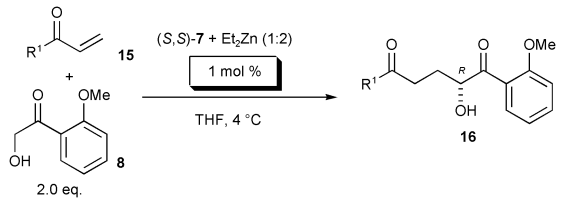
proceeded smoothly by treating the acetonide-protected ketone **9a** and the cyclic carbonate-protected ketone **10a** with *m*CPBA, probably with the aid of neighboring oxygen atoms. Benzoate **11a** was obtained in 89% yield from **9a**, and phenyl ester **12a** was obtained in 93% yield from **10a** under the same conditions. No regioisomers were observed in either case. Furthermore, **10a** afforded amide **13a** exclusively in 97% yield in one step *via* a Beckmann rearrangement with *O*-mesitylenesulfonylhydroxylamine (MSH).[18] The amide **13a** was readily transformed into **14a** by reduction with DIBAL. **14a** can be converted into an amino-diol after oxidative removal of the 2-methoxyphenyl group.[19]

Although the detailed mechanism of the above mentioned direct catalytic asymmetric aldol reaction is currently under investigation, it is reasonable to assume a two-center mechanism in which a zinc naphthoxide functions as a Brönsted base to generate a Zn-enolate from the ketone and another zinc functions as a Lewis acid to activate the aldehyde.[20]

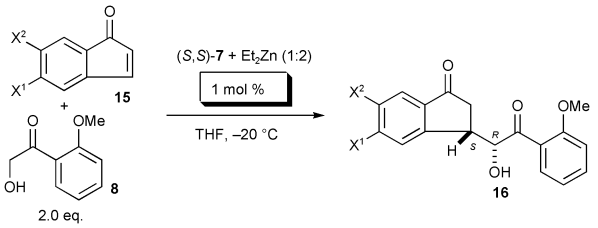
Catalytic asymmetric 1,4-addition of unmodified ketone promoted by Zn-linked-BINOL complex

The Zn-linked-BINOL complex is very effective for shielding one enantioface of enolate generated from **8**, therefore we investigated the direct catalytic asymmetric 1,4-addition of the ketone to various vinyl ketones **15**[21] that usually tend to polymerize under harsh reaction conditions (Table 2). Because of the mild basicity of the Zn-linked-BINOL complex, 1,4-addition of **8** proceeded smoothly using 1 mol% of catalyst with only a small amount of polymerization. Aryl vinyl ketones with and without substituents on the aromatic ring (entries 1–4) and alkyl vinyl ketones (entries 5, 6) were successfully converted to the corresponding 1,4-adducts in good chemical yield and enantiomeric excess. With indenone **15g**–**15i**, an

Table 2 Catalytic asymmetric 1,4-addition of unmodified ketone[a]

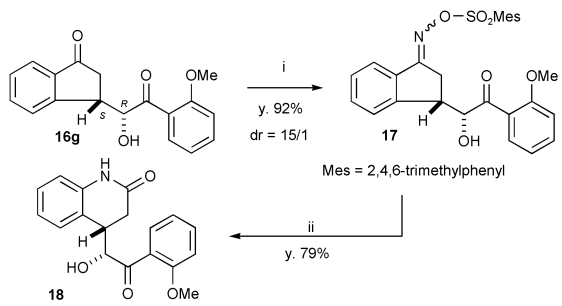


Entry	R^1	Vinyl ketone	Time (h)	Yield[b] (%)	Ee[c] (%)
1	*p*-$MeOC_6H_4$	**15a**	8	83	95
2	C_6H_5	**15b**	4	86[d]	93
3	*o*-$MeOC_6H_4$	**15c**	12	90	94
4	*p*-ClC_6H_4	**15d**	12	84[d]	92
5	CH_3	**15e**	4	86	93
6	CH_3CH_2	**15f**	4	82	91



Entry	X^1	X^2	Enone	Time (h)	Yield[b]	dr[e]	Ee[c] (%)
7	H	H	**15g**	4	74	98/2	99
8	Br	H	**15h**	4	74	98/2	99
9	H	MeO	**15i**	4	65	97/3	97

[a] Reactions were run on 1.0 mmol scale (entries 1–7, 9) or 0.5 mmol scale (entry 8) at 0.4 M (entries 1–6) or 0.25 M (entries 7–9) in **15**. [b] Isolated yield unless otherwise noted. [c] Determined by chiral HPLC analysis. [d] Determined by ^{1}H-NMR analysis with hexamethyldisiloxiane as an internal standard. [e] Determined by ^{1}H-NMR analysis of crude mixture.



Scheme 3 Transformation of **16g** into lactam **18**. Reagents and conditions: (i) *O*-mesitylenesulfonylhydroxylamine, CH_3CN, rt, 1 h; (ii) $AlCl_3$, CH_2Cl_2, rt, 30 min.

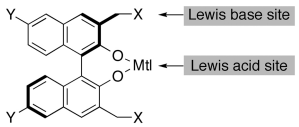
excellent diastereomeric ratio was achieved when the reaction was run at −20 °C. Products were converted to the corresponding esters or amines *via* regioselective Baeyer-Villiger oxidation or a Beckmann rearrangement. One example is shown in Scheme 3.

Catalytic asymmetric cyanosilylation of aldehydes promoted by Lewis acid–Lewis base two-center catalysts

The success of the Lewis acid–Brönsted base catalysts led us to design a new bifunctional asymmetric catalyst consisting of Lewis acid and Lewis base moieties, which simultaneously activate both electrophiles and nucleophiles at defined positions. This type of asymmetric catalysis is rarely observed.[22]

We selected TMSCN as a nucleophile, because TMSCN is activated by a Lewis base, forming hypervalent silicate.[23] Thus, we first examined the catalytic enantioselective cyanosilylation of aldehydes.[24]

BINOL was selected as the chiral backbone for arranging the Lewis acid (Mtl) and Lewis base (X) moieties, as shown in Fig. 2. When the Lewis acid metal is connected to the two



19: X = $P(O)Ph_2$, Y = H
20: X = $CH_2P(O)Ph_2$, Y = H
21: X = $CHPh_2$, Y = H
22: X = $P(O)(C_6H_4N(CH_3)_2\text{-}p)_2$, Y = H
23: X = $P(O)(o\text{-tol})_2$, Y = H
24: X = $P(O)Ph_2$, Y = F
25: X = $P(O)Ph_2$, Y = Cl
26: X = $P(O)Ph_2$, Y = Br
27: X = $P(O)Ph_2$, Y = I
28: X = $P(O)Ph_2$, Y = CF_3

Fig. 2 Lewis acid-Lewis base two-center catalysts.

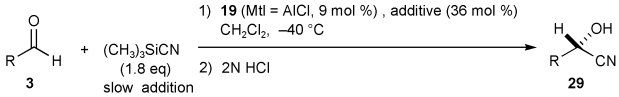
naphthoxides, the Lewis base moieties should be connected to the 3,3′-positions of BINOL to promote the reaction efficiently *via* a dual activation pathway. The following two points are important for constructing a successful bifunctional catalyst: (1) The activation ability of the Lewis acid and Lewis base moieties toward an aldehyde and TMSCN should be balanced to promote the reaction *via* a dual activation pathway. (2) Internal coordination of the Lewis base to the Lewis acid should be avoided. The design shown in Fig. 2 is very flexible for optimizing these points by altering the metal, the Lewis base, and the linker length connecting the Lewis base and BINOL as needed. For example, the importance of point (2) was demonstrated by the results of catalyst **20** containing an ethylene linker: **20** did not promote the reaction efficiently probably because internal coordination of the Lewis base to the Lewis acid metal diminished catalyst activity.

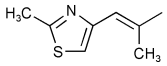
Intensive optimization revealed that catalyst **19**, which contains an aluminium as the Lewis acid and a phosphine oxide as the Lewis base, is the best catalyst.[25] The optimized conditions are 9 mol% of **19** (Mtl = AlCl) and the additive phosphine oxide[26] ($Bu_3P(O)$ or $Ph_2MeP(O)$; probably for a balance of the Lewis acidity and the Lewis basicity of the catalyst by coordination with Al) with the slow addition of TMSCN at −40 °C in CH_2Cl_2. Thus, **19** produced generally excellent enantioselectivity from a wide range of aldehydes (Table 3). Moreover, the practicality of **19** was clearly demonstrated by its application to a catalytic enantioselective total synthesis of important anti-cancer natural products, such as epothilones.[27] The following experimental results support the two-center catalysis mechanism of **19**. (1) A control catalyst **21** (Mtl = AlCl), which contains only a steric bulkiness (diphenylmethyl group), but not a Lewis base, at the 3,3′-position of BINOL produced cyanohydrins in lower yield and enantioselectivity with the opposite configuration compared to those obtained by **19**. In the case of **21**, it is reasonable to assume that TMSCN attacks the activated aldehyde, coordinating to the aluminium from the less hindered side (opposite to the diphenylmethyl group). In the case of **19**, TMSCN appears to attack the aldehyde from the side of the phosphine oxide. This can be explained if we assume that TMSCN, which is activated by the phosphine oxide, reacts with the aldehyde. (2) The initial reaction rate using **22** (10 mol%) was 1.2 times faster than that using **19** (10 mol%) ($k_{\mathbf{22}}/k_{\mathbf{19}}$ = 1.2), reflecting the higher Lewis basicity of the phosphine oxide in the reaction of hydrocinnamaldehyde in the presence of $Bu_3P(O)$ (40 mol%). Furthermore, with the one-portion addition of TMSCN, catalyst **22** (10 mol%) gave a higher yield and enantioselectivity than **19** in the presence of $Bu_3P(O)$ (40 mol%). The increased reaction rate and enantioselectivity by **22** is consistent with the dual activation mechanism of these catalysts. A more electron-rich phosphine oxide activates TMSCN more efficiently, thus facilitating the desired dual activation pathway. These mechanism studies led us to propose a working model for the transition state of the cyanosilylation of aldehydes by catalyst **19** or **22** (Fig. 3).

A H^+ source for this reaction is very important. Thus, when this catalytic asymmetric cyanosilylation was applied to a larger scale reaction (5 g scale of aldehyde **3n**), the addition of a catalytic amount of proton source (5 mol% of MeOH) was necessary to reproduce the results of smaller scale reactions. Although the role of the proton source is not clear at present, we think that the proton source facilitates the catalytic cycle by protonating the intermediate generated by a cyanide attack. The free cyanohydrin **29n** was silylated immediately under the reaction conditions. For a discussion of the role of the proton source in facilitating the catalytic cycle, see ref. 33.

Although ^1H, ^{13}C, and ^{31}P NMR did not indicate any interaction between TMSCN and the phosphine oxide, we recently observed infrared (IR) spectroscopic evidence for the interaction (Fig. 4). Belokon' *et al.* utilized the IR spectra (CN stretching frequency) to determine the generation of titanium cyanide in their catalytic system.[28] In the Belokon' system, the weakly coordinating cyanide to titanium produced a band at 2070 cm^{-1}. In our experiments, the absorption band derived from C≡N of TMSCN in CH_2Cl_2 was observed at 2192 cm^{-1}. Upon addition of TMSCN to catalyst **19**, this band disappeared and a new band appeared at 2057 cm^{-1} (Fig. 4, A). A similar change was observed in the case of the TMSCN + $Bu_3P(O)$ (Fig. 4, B), however no change occurred in the case of TMSCN +

Table 3 Catalytic asymmetric cyanosilylation of various aldehydes under the optimized conditions



Entry	R	Aldehyde	Product	Additive	Time (h)	Yield (%)	Ee (%)	*S/R*
1	$Ph(CH_2)_2$	**3a**	**29a**	$Bu_3P(O)$	37	97	97	*S*
2	$CH_3(CH_2)_5$	**3b**	**29b**	$Bu_3P(O)$	58	100	98	*S*
3	$(CH_3)_2CH$	**3h**	**29h**	$Bu_3P(O)$	45	96	90	*S*
4	$(CH_3CH_2)_2CH$	**3i**	**29i**	$Bu_3P(O)$	60	98	83	*S*
5	*trans*-$CH_3(CH_2)_3CH{=}CH_2$	**3k**	**29k**	$Bu_3P(O)$	58	94	97	—
6	PhCH=CH	**3l**	**29i**	$Bu_3P(O)$	40	99	98	*S*
7[a]		**3m**	**29m**	$Bu_3P(O)$	50	97	99	*S*
8[b]	Ph	**3n**	**29n**	$CH_3P(O)Ph_2$	96	98	96	*S*
9	*p*-$CH_3C_6H_4$	**3o**	**39o**	$CH_3P(O)Ph_2$	79	87	90	*S*
10[c]		**3p**	**29p**	$CH_3P(O)Ph_2$	70	86	95	*R*

[a] 5 mol% of **19** (Mtl = AlCl) was used. [b] TMSCN was added over 1 min. [c] 18 mol% of **19** (Mtl = AlCl) and 72 mol% of additive were added.

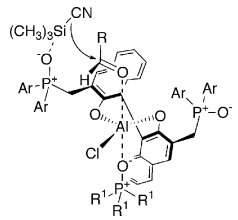


Fig. 3 Proposed transition state of the cyanosilylation of aldehydes.

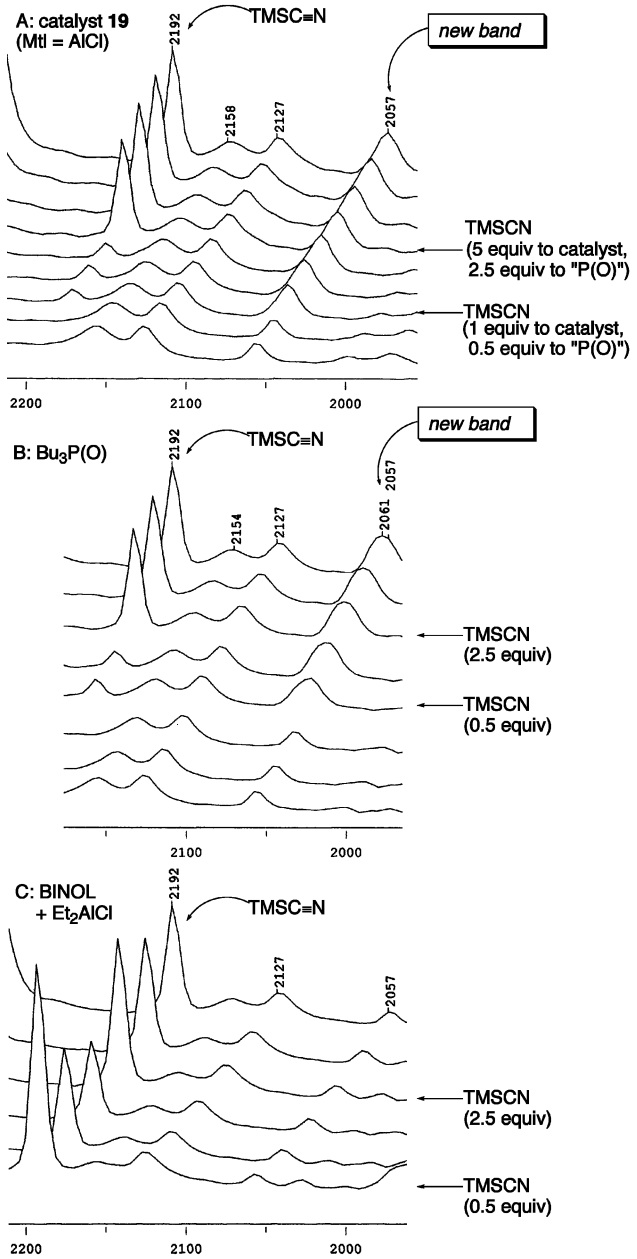


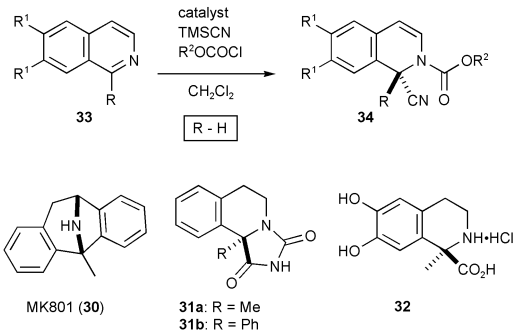
Fig. 4 IR spectra of mixtures of TMSCN and catalyst **19** (MtI = AlCl) (A), TMSCN and $Bu_3P(O)$ (B), TMSCN and BINOL–Al complex (C).

BINOL–Al complex (Fig. 4, C). These data indicated that the IR absorption change was derived from the interaction between TMSCN and the phosphine oxide.[29] Because the absorption of silyl isonitriles was reported to be around 2100 cm^{-1},[30] the observed absorption at 2057 cm^{-1} might indicate the generation of a *dissociated* cyanide ion.[31,32] This dissociated cyanide nucleophile is more reactive than TMSCN alone. As expected, $Bu_3P(O)$ (40 mol%) catalyzed the cyanosilylation of hydrocinnamaldehyde at an ambient temperature to give the corresponding cyanohydrin in 81% yield (7.5 h). The same conditions in the absence of $Bu_3P(O)$ gave the product in only 12% yield.

Catalyst **19** and modified **23** were useful in a Strecker-type reaction[33] and Reissert-type reaction of quinolines.[34] Furthermore, immobilization of these catalysts to resin (Janda*J*EL) produced recyclable catalysts.[34b,35] Because these topics were recently reviewed,[2] we have restricted our discussion to recent progress on the construction of tetrasubstituted carbons through a Reissert-type reaction.

Catalytic asymmetric construction of chiral tetrasubstituted carbons through Reissert-type reaction

A Reissert-type reaction is an acyl-cyanation of heteroaromatics such as quinolines and isoquinolines *via* acyl (iso)quinolinium intermediates.[36] The reaction is widely used as a key step for the synthesis of various heterocyclic compounds, especially for the synthesis of biologically important alkaloids. In 2000, we reported the first example of a catalytic enantioselective Reissert-type reaction promoted by a two-center catalyst **23**. We planned to extend the reaction scope to a chiral tetrasubstituted carbon synthesis,[37] because there are many biologically active natural products and pharmaceuticals that contain chiral tetrasubstituted centers (Scheme 4).



Scheme 4 Catalytic enantioselective Reissert-type reaction: chiral tetrasubstituted center construction.

Catalytic construction of chiral tetrasubstituted stereocenters is also very important, but challenging. Difficulties in the construction of chiral tetrasubstituted carbons through an addition of nucleophiles to carbonyl derivatives, such as ketones, ketoimines, and their equivalents, are due mainly to the lack of the hydrogen on the *pro*-chiral carbon (Fig. 5). In tetrasubstituted carbon synthesis (Fig. 5, B), the transition state

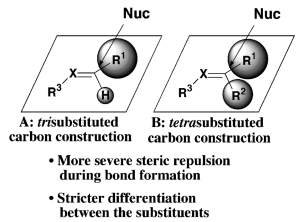
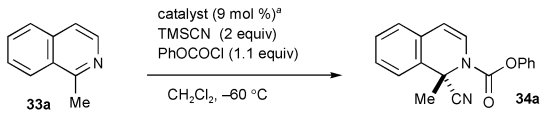


Fig. 5 Conceivable difficulties in chiral tetrasubstituted carbon construction.

energy is higher than that of the trisubstituted carbon synthesis (Fig. 5, A) due to a more severe steric repulsion between the reacting nucleophile and the substrate. Furthermore, differentiation of the two substituents (R^1 and R^2) is required for high enantio-induction. The differentiation, however, is difficult due to the small steric difference. To overcome these difficulties and achieve an efficient catalytic construction of chiral tetrasubstituted carbons, the asymmetric catalyst needs to be more active and enantioselective. We anticipated that the concept of the two-center catalysis would be advantageous for this purpose

When the optimized reaction conditions previously reported[34] (9 mol% of catalyst **19**, 1.1 equiv of 2-furoyl chloride as an acylating reagent, and 2 equiv of TMSCN) were applied using 2-methylquinoline as a substrate, the tetrasubstituted carbon-constructing reaction did not proceed. On the other hand, the more reactive substrate, 1-methylisoquinoline (**33a**), gave the corresponding Reissert product in 60% yield with 38% ee at −40 °C for 48 h. Preliminary screening of the acylating reagents revealed that chloroformates produced better chemical yield and enantioselectivity than did acid chlorides. Thus, PhOCOCl gave the corresponding product from **33a** in 72% yield with 56% ee at −60 °C (Table 4, entry 1).

Table 4 Ligand effect on catalytic enantioselective Reissert-type reaction[a]



Entry	Catalyst	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**19** (Y = H)	48	72	56
2	**24** (Y = F)	48	74	71
3	**25** (Y = Cl)	48	88	81
4	**26** (Y = Br)	48	91	84
5[d]	**26** (Y = Br)	48	93	88
6	**27** (Y = I)	60	85	81
7	**28** (Y = CF_3)	60	68	48

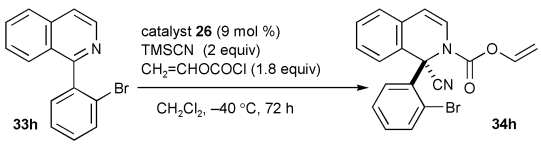
[a] Mtl = AlCl. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Vinyl chloroformate (1.2 equiv) was used instead of phenyl chloroformate.

The two-center catalyst was then electronically tuned to further improve its efficiency. The Lewis acidity and/or Lewis basicity were increased by substitutions on the naphthyl or phenyl groups. Although the catalyst containing a more electron-rich di-*p*-methoxyphenylphosphine oxide gave poorer results, the strategy to increase the Lewis acidity by introducing an electron withdrawing group at the 6,6′-positions of the BINOL (Y, Fig. 2) was successful. Thus, as shown in Table 4, entries 2–4 and 6, catalysts derived from the 6,6′-dihalogen-substituted BINOL had improved activity and enantioselectivity.[38] Among them, the 6,6′-dibromo substituted catalyst **26** (Mtl = AlCl) had the best results and the product was obtained in 91% yield with 84% ee (entry 4). Use of vinyl chloroformate improved the yield (93%) and enantiomeric excess (88%) (entry 5).

These initial promising results led us to apply this reaction to a catalytic enantioselective synthesis of a pharmaceutically important agent, MK801 (**30**).[39] MK801 is a very potent noncompetitive antagonist of the *N*-methyl-D-aspartate (NMDA) subclass of receptors for the excitatory amino acid L-glutamate in brain tissue, and might therefore be clinically useful as an anticonvulsant and neuroprotective drug. The (5*S*,10*R*)-(+) isomer is seven times more potent than the (5*R*,10*S*)-(−) isomer, however there are no reports of an enantioselective synthesis.[40] We expected that Reissert compound **34h** would be directly converted to the 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine core structure of MK801 by regioselective radical cyclization.

Thus, we attempted a Reissert-type reaction of 1-*o*-bromophenylisoquinoline (**33h**) at −40 °C in the presence of 9 mol% of **26** (Mtl = AlCl), and **34h** was obtained in 53% yield with 73% ee (Table 5, entry 1). To improve the yield and enantioselectivity, we further increased the Lewis acidity of the catalyst by tuning the counterion of the aluminium.[41] As shown in Table 5, when an aluminium triflate (Mtl = AlOTf) was used as the Lewis acid, product **34h** was obtained in higher yield (63%) with 98% ee (entry 3). These improvements were not due to the formation of an aluminium cyanide (Mtl = AlCN) by anion exchange, because the aluminium cyanide catalyst gave

Table 5 Counterion effect on catalytic enantioselective Reissert-type reaction



Entry	Catalyst	Yield (%)[a]	Ee (%)[b]
1	**26** (Mtl = AlCl)	53	73
2	**26** (Mtl = AlCN)	73	65
3	**26** (Mtl = AlOTf)	63	98
4	**26** (Mtl = $AlNTf_2$)	55	88
5	**26** (Mtl = $AlBF_4$)	58	31

[a] Isolated yield. [b] Determined by HPLC analysis.

significantly lower enantiomeric excess (entry 2), albeit in higher yield. On the other hand, when more electron-withdrawing counterions (NTf_2[42] or BF_4) than triflate were used (entries 4, 5), enantioselectivity decreased. These results indicated that there was almost no anion exchange on the aluminium when weakly coordinating triflate was used as the counterion.

The substrate scope was investigated once the reaction conditions were optimized. As shown in Table 6, using 2.5 mol% of **26** (Mtl = AlOTf), the Reissert-type reaction proceeded with a broad range of 1-substituted isoquinolines to give the products in excellent yield and enantioselectivity. The reaction is not very sensitive to the steric bulkiness of the substituent at the 1-position (R). In some cases, catalyst loading could be reduced to 1 mol% (entries 8 and 10).

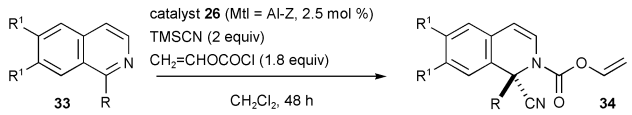
The utility of this reaction was clearly demonstrated by an efficient catalytic enantioselective synthesis of several biologically significant compounds. First, MK801 (**30**) was synthesized in six steps from the Reissert product *ent*-**34h**, using radical cyclization as a key step (Scheme 5). Second, anticonvulsant phenytoin analogs[43] **31a** and **31b** were synthesized in high yield from *ent*-**34a** or *ent*-**34g**. To our knowledge, this is the first example of an asymmetric synthesis of these three compounds. Similarly, an enantioselective synthesis of **32**, a biosynthetic intermediate of a dopamine-derived alkaloid salsolinol,[44] was achieved in three steps from *ent*-**34i**.

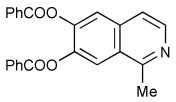
Although the complete reaction mechanism is not clear at present, the absolute configuration of the products and results using control catalyst **21** supports the idea that the reaction proceeds *via* dual activation of the acyl isoquinolinium and TMSCN by the Lewis acid and the Lewis base of the catalyst, as depicted in Fig. 6. Thus, using 2.5 mol% of **21** (Mtl = AlCl), (*R*)-**34a** (the opposite configuration) was obtained in 36% yield with 12% ee. Similarly, **21** (Mtl = AlOTf) gave (*R*)-**34g** in 95% yield with 4% ee. These control experiments indicated that in the case of bifunctional catalyst **21** the cyanide attacked the activated acyl isoquinolinium from the side of the phosphine oxide.

Catalytic asymmetric cyanosilylation of ketones promoted by lanthanide catalyst

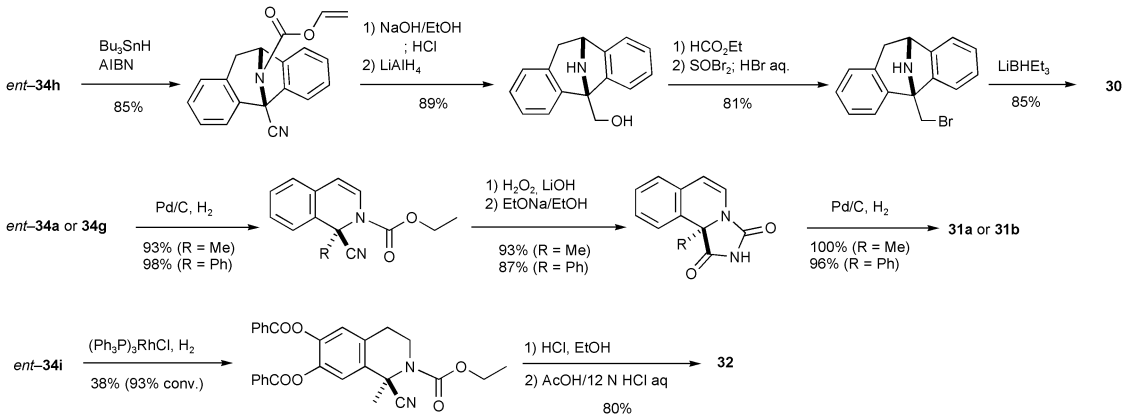
We reported the first example of catalytic enantioselective cyanosilylation of ketones with broad substrate generality using a titanium catalyst generated from D-glucose-derived ligands **35** and **36** (Fig. 7).[45,46] (*R*)-Tertiary cyanohydrins are obtained from both aromatic and aliphatic ketones with high enantioselectivity using 1–10 mol% of **35** or **36**. Using catalyst **19**, which gives excellent results in the cyanosilylation of aldehydes or in the Reissert-type reaction, did not promote this reaction. The mechanism studies indicate that **35** works as a two-center catalyst with the titanium and the phosphine oxide activating the substrate ketone and TMSCN as a Lewis acid and a Lewis base, respectively. In collaboration with Curran's group at the

Table 6 Catalytic enantioselective tetrasubstituted stereocenter-forming Reissert-type reaction



Entry		33 (R)	Catalyst 26 Z	Temp. (°C)	Yield (%)	Ee (%)
1		**33a** (Me)	OTf	−60	88	89
2		**33b** (Et)	OTf	−60	98	88
3		**33c** (CH_2Ph)	OTf	−60	95	92
4		**33d** (CH_2OCH_3)	OTf	−60	84	73
5		**33e** ($CH{=}CH_2$)	OTf	−60	80	84
6		**33f** ((*E*)-$CH{=}CHCH_3$)	OTf	−60	88	87
7		**33g** (Ph)	OTf	−40	95	95
8[a]		**33g** (Ph)	OTf	−50	88	95
9[b]		**33h** (*o*-Br-C_6H_4)	OTf	−40	62	95
10[ab]		**33h** (*o*-Br-C_6H_4)	OTf	−40	59	93
11		**33i**	Cl	−60	94	94

[a] 1 mol% of catalyst **26** was used. [b] The reaction time was 72 h.



Scheme 5 Application of the catalytic enantioselective Reissert-type reaction to synthesis of biologically active compounds.

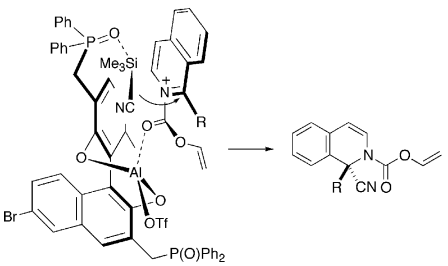


Fig. 6 Proposed transition state of the Reissert-type reaction.

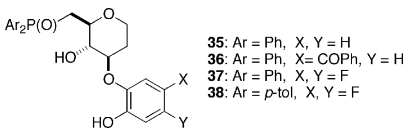
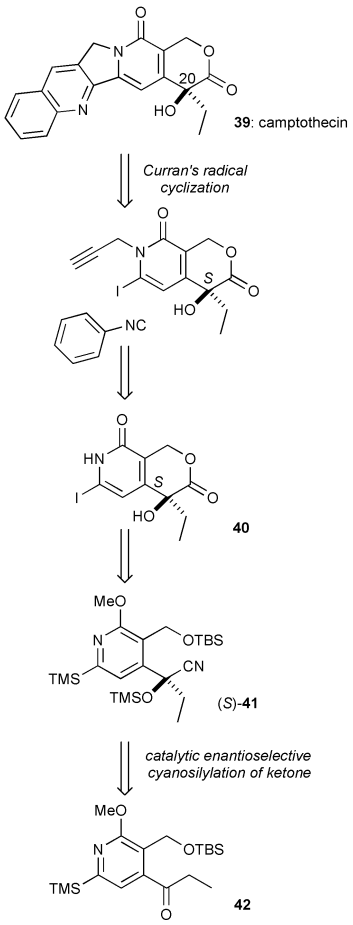


Fig. 7 D-Glucose derived ligands for catalytic asymmetric cyanosilylation of ketones.

University of Pittsburgh, we applied this reaction to the catalytic enantioselective synthesis of (20*S*)-camptothecin **39** and its analogs, which are among the most effective agents for the treatment of solid tumors.[47] For this purpose, however, the more expensive L-glucose was needed as the chiral source.[48] The synthetic utility of the reaction is highly improved if both of the product enantiomers can be similarly accessible using a readily available chiral source.

Based on Curran's established synthetic route, α-hydroxy lactone **40** offers a general synthetic intermediate for the synthesis of the camptothecin family. Therefore, we selected ethyl ketone **42** as a substrate for the catalytic enantioselective cyanosilylation (Scheme 6). Although the Ti-**35** complex (20 mol%) produced the undesired (*R*)-**41** in low yield with low enantioselectivity, a samarium catalyst (5 mol%) prepared from $Sm(O^iPr)_3$[49] and **35** in a ratio of 1 : 1.8 gave the desired (*S*)-**41** in 92% yield with 72% ee at −40 °C for 24 h (THF). When propionitrile was used as a solvent, both the reactivity and enantioselectivity were improved and **41** was obtained in 98% yield with 84% ee for 18 h.[50]

Although the initial results were promising, neither enantioselectivity nor catalyst loading were satisfactory for the application to plant synthesis of camptothecin analogs. Therefore, we continued to attempt to improve the catalyst. To do so required a more flexible synthetic route of the chiral ligand, which allows a rapid synthesis of an array of various ligands. The ligand was previously synthesized through an aromatic substitution of an arene–chromium complex. Use of a stoichiometric amount of chromium, however, is environmentally problematic, especially in a large-scale synthesis. Furthermore, tuning the catechol moiety of **35** was very difficult using this synthetic route, because arene–chromium complexes containing electron-deficient aromatic groups are generally difficult to prepare. Introducing an electron-withdrawing group on the catechol moiety is an attractive approach for improving the catalyst efficiency, because it increases the Lewis acidity of the metal. Thus, we developed a new synthetic route *via* cyclic

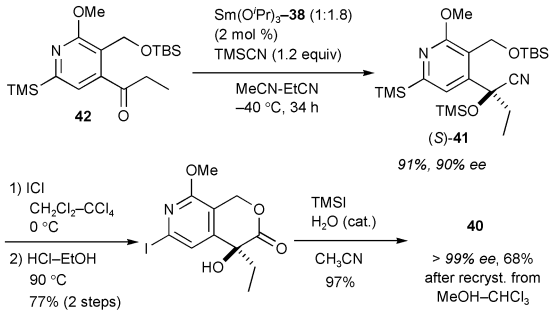


Scheme 6 Synthetic plan of camptothecin.

sulfate **43** (Scheme 7).[51] Facile synthesis of a wide range of chiral ligands containing a variety of catechol groups and phosphine oxides was possible using this new route.

We expected to improve the catalyst by increasing the Lewis acidity of the metal and Lewis basicity of the phosphine oxide, by introducing electron-withdrawing groups on the catechol moiety and electron-donating groups on the phosphine oxide, respectively. Among many ligands synthesized through the new route, ligand **38** containing difluorocatechol and di-*p*-tolylphosphine oxide produced significantly improved results. Thus, 2 mol% of the catalyst derived from **38** gave **41** in 95% yield with 89% ee in 19 h. Under similar conditions, the original catalyst **35** gave the product in 100% yield with 82% ee in 44 h. Using a mixed solvent of acetonitrile and propionitrile (1:1), the enantiomeric excess was further improved to 90%, using **38**.[52] This reaction was performed on a 10 gram scale without any difficulties. Further catalyst improvement is currently in progress.

Key intermediate **40** for the synthesis of the camptothecin family was synthesized in three steps from (*S*)-cyanohydrin **41** (Scheme 8). Enantiomerically pure **40** was obtained by recrystallization from MeOH–$CHCl_3$ (8:1).



Scheme 8 Catalytic enantioselective synthesis of key intermediate **40**.

Next, to demonstrate the generality of this catalytic (*S*)-selective cyanosilylation, we used acetophenone (**44a**) as a substrate using ligand **35**. The new catalyst derived from **38** gave comparable results for **44a**. Thus, in the presence of 5 mol% of Sm-**35** complex (1:1.8), the reaction in THF was completed at −40 °C in 2 h, giving (*S*)-cyanohydrin **45a** in 85% yield with 82% ee. When Gd was used instead of Sm, the enantiomeric excess further improved to 89%. The optimal ratio of Gd to **35** was 1:2 (92% ee), as shown in Fig. 8, although the

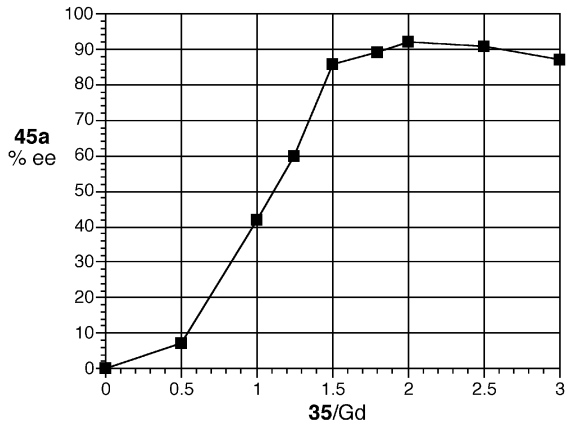
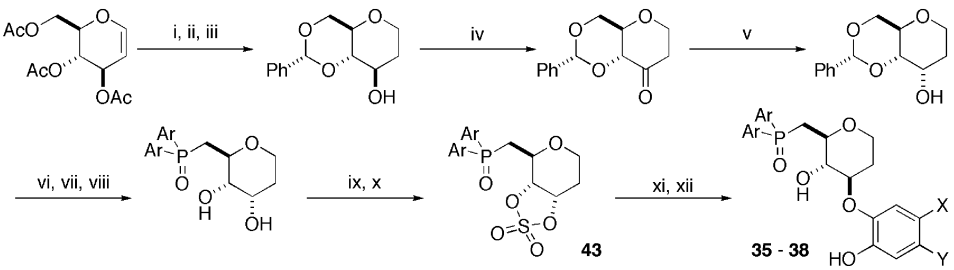


Fig. 8 Relationship between ee and **35**/Gd ratio.

enantiomeric excess reached a plateau at a **35**/Gd = 1.5:1 ratio. Under the optimized conditions in propionitrile, **45a** was obtained in 89% yield with 95% ee (Table 7, entry 1). The results of using Ti-**35** (or **36**) complex with other ketones are



Scheme 7 The practical synthetic route to chiral ligands for catalytic asymmetric cyanosilylation of ketones. *Reagents and conditions*: (i) Pd/C, H_2, MeOH, rt; (ii) NaOMe (0.25 equiv), MeOH, rt; (iii) $PhCH(OMe)_2$ (1.2 equiv), *p*-TsOH·H_2O (0.3 equiv), toluene, reflux, 57% (3 steps); (iv) DMSO (2.5 equiv), $(COCl)_2$ (1.3 equiv), Et_3N (5 equiv), CH_2Cl_2, −78 °C to rt; (v) L-Selectride (1.03 equiv), THF, −78 °C, 93% (2 steps); (vi) Pd/C, H_2, MeOH–AcOH (1:1), rt, 92%; (vii) TsCl (1.1 equiv), pyridine, 78%; (viii) Ph_2PK (2.5 equiv), THF, 0 °C; H_2O_2, 94% (Ar = Ph), [Ar = *p*-$CH_3C_6H_4$: MOMCl (2.5 equiv), $^iPr_2NEt$ (3 equiv), CH_2Cl_2, reflux, 72%; Ar_2PLi (2 equiv), THF, 0 °C; H_2O_2; cat. HCl aq.-MeOH, reflux, 85% (3 steps)]; (ix) $SOCl_2$ (1.2 equiv), CH_2Cl_2; (x) $RuCl_3·3H_2O$ (1 mol%), $NaIO_4$ (1.5 equiv), CCl_4–CH_3CN–H_2O, 90% (Ar = Ph), 98% (Ar = *p*-$CH_3C_6H_4$) (2 steps); (xi) catechol monomethyl ether derivatives (1.3 equiv), K_2CO_3 (2 equiv), DMF; 20% H_2SO_4 aq, Et_2O–$CHCl_3$, 65 ~ 86% (2 steps); (xii) EtSH, $AlCl_3$, CH_2Cl_2, 82 ~ 100% (2 steps).

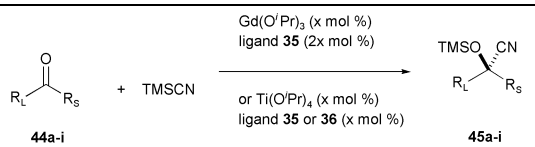
summarized in Table 7. The reaction gave good to excellent enantioselectivity when aromatic ketones or enones were used as substrates (entries 1–11). Enones gave cyanohydrins with complete regioselectivity. Although aliphatic ketones gave less satisfactory results (entries 15 and 17), these products could be easily synthesized by hydrogenation of the cyanohydrins from enones in quantitative yield without loss of the enantiomeric purity. Therefore, the present reaction affords a broad range of (*S*)-ketone cyanohydrins using readily available D-glucose as a chiral source. Combined with the previous Ti-**35** or **36** catalyzed reaction, both of the enantiomers can be synthesized by the catalysts derived from one chiral source.

A preliminary catalyst structure and the reaction mechanism are postulated in Scheme 9 based on the following experiments performed in THF. When $Pr(O^iPr)_3$ and **35** were mixed in a 1 : 2 ratio,[53] a complete ligand exchange was observed by ^{1}H NMR analysis, indicating the generation of presumed complex **46** and free **35**. After evaporating ^{i}PrOH, excess TMSCN (> 4 mol equiv) was added at −40 °C. Then, peaks corresponding to mono-silylated **35** (0.34 ppm, derived from **47**) and di-silylated **35** (0.38, 0.50 ppm) were observed in *ca*. 90% yield from **46** and free **35**, respectively. These observations indicated that **46** was converted to praseodymium cyanide **47** by mono-silylation of **35** and free **35** was di-silylated. Furthermore, the molecular formula of complex **47** (Ln = Gd) was confirmed by ESI-MS.[54] The relationship between the enantiomeric excess of the product and **35**/Gd ratio (Fig. 8) was also consistent with these results. Therefore, the active catalyst was determined to be 2:3 complex **47**.

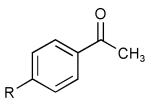
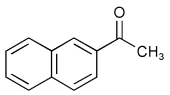
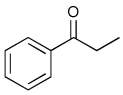
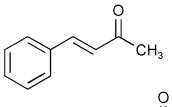
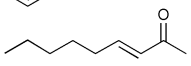
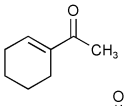
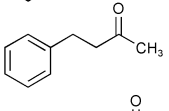
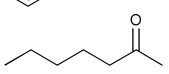
The higher activity of the lanthanide-**35** catalyst compared to Ti-**35**, as well as the structure of catalyst **47** suggests that the active nucleophile is the lanthanide metal cyanide, not TMSCN. This was confirmed by the following results. First, there was a facile CN-scrambling between the gadolinium cyanide of the catalyst and TMSCN. Thus, after complex **47** (1 equiv) containing ^{13}CN was prepared from TMS^{13}CN, acetophenone (**44a**) (1 equiv) and a variable amount of TMS^{12}CN (1, 2, or 3 equiv) were added. ^{13}C NMR analysis of the product cyanohydrin indicated that the incorporation of ^{13}CN was dependent on the ratio of added TMS^{13}CN and TMS^{12}CN. Moreover, only one signal corresponding to a cyanide (117 ppm) was observed on ^{13}C NMR analysis of **47** (Ln = Pr) labeled by ^{13}CN in the presence of a variable amount of TMS^{13}CN (0 or 2 equiv) at −60 °C. With confirmation of the *pre*-equilibrium, kinetic studies were performed and the order with regard to TMSCN was determined to be 0. In contrast, the Ti-**35** catalyzed reaction, in which TMSCN activated by the phosphine oxide acts as the active nucleophile, had an order dependency of 0.7 with regard to TMSCN. Therefore, in the reaction catalyzed by Ln-**35**, the lanthanide metal cyanide acted as the active nucleophile.

These findings suggest a bimetallic transition state **48** in Scheme 9 as a working model. The Ln^1 cyanide is more electron-rich, and therefore more active as a nucleophile, because Ln^1 is bound to two alkoxides and coordinated by the phosphine oxide of the linker ligand. On the other hand, Ln^2 is more Lewis acidic. The intramolecular cyanide transfer from the nucleophilic Ln^1 cyanide to a ketone activated by the more

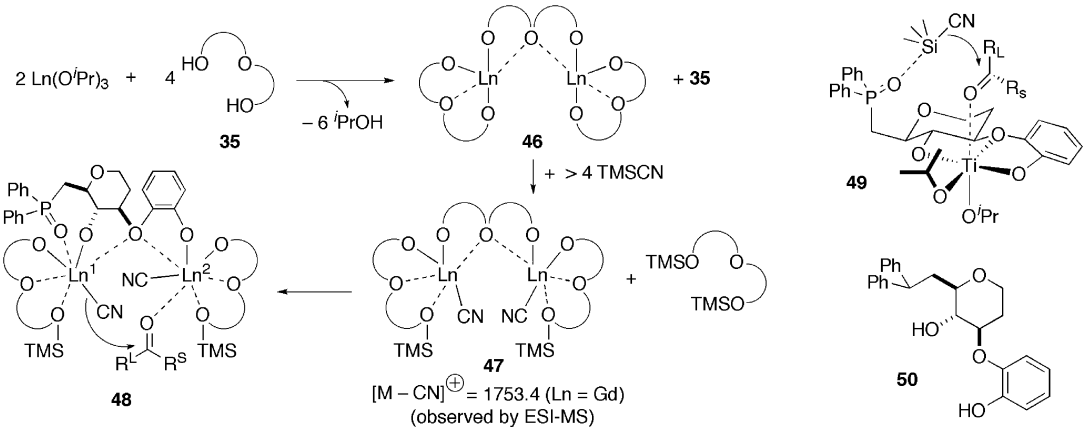
Table 7 Catalytic asymmetric cyanosilylation of ketones[a]



44a-i **45a-i**

Entry	Ketone		Lewis acid	Ligand	Loading (× mol%)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	Ee[c] (%)	Absolute configuration
1		**44a**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−40	2	89	95	(*S*)[d]
2		**44a**	Gd(O^{i}Pr)$_3$	**35**	1	EtCN	−40	16	93	91	(*S*)[d]
3		**44a**	Ti(O^{i}Pr)$_4$	**36**	1	THF	−20	88	92	94	(*R*)[d]
4		**44b**	Gd(O^{i}Pr)$_3$	**35**	5	THF	−60	55	89	89	(*S*)
5		**44b**	Ti(O^{i}Pr)$_4$	**36**	1	THF	−25	92	72	90	(*R*)
6		**44c**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	18	93	96	(*S*)
7		**44c**	Ti(O^{i}Pr)$_4$	**35**	10	THF	−40	80	82	95	(*R*)
8		**44d**	Gd(O^{i}Pr)$_3$	**35**	5	THF	−60	14	93	97	(*S*)
9		**44d**	Ti(O^{i}Pr)$_4$	**36**	1	THF	−10	92	90	92	(*R*)
10		**44e**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	6.5	94	87	(*S*)
11		**44e**	Ti(O^{i}Pr)$_4$	**35**	10	THF	−50	88	72	91	(*R*)
12		**44f**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	19	96	76	(*S*)
13		**44f**	TiO^{i}Pr)$_4$	**36**	2.5	THF	−30	92	72	90	(*R*)
14		**44g**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	9	92	94	(*S*)
15		**44h**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	1	97	66	(*S*)
16		**44h**	Ti(O^{i}Pr)$_4$	**35**	10	THF	−50	36	92	85	(*R*)
17		**44i**	Gd(O^{i}Pr)$_3$	**35**	5	EtCN	−60	0.5	79	47	(*S*)
18		**44l**	Ti(O^{i}Pr)$_4$	**36**	2.5	THF	−45	92	80	82	(*R*)

[a] The method for preparation of the catalysts and the general procedure of the reaction, see ref. 45 and 50. [b] Isolated yield. [c] Determined by chiral HPLC or GC analysis. [d] The absolute configurations were determined by comparison with the reported value of optical rotation. Others were assigned tentatively.



Scheme 9 Working model of catalyst structure and reaction mechanism for Ln-**35** system (left). Postulated transition state for Ti-**35** system (top right, **49**) and the control ligand **50** (bottom right).

Lewis acidic Ln^2 should control the direction of the cyanide entry, giving products with high enantioselectivity. Consistent with this model, the order dependency of the reaction rate with regard to the catalyst was determined to be 0.8. The reversal of the enantioselectivity using either the Ti-complex or the Ln-complex is due to the different catalyst structure and the reaction mechanism. In the case of the Ti-catalyst, TMSCN activated by the phosphine oxide works as the nucleophile, suggested by the mechanistic studies as shown in Scheme 9, **49**. The essential contribution of the Lewis basic phosphine oxide in the reaction of the Ln-catalyst was also highlighted from the results by the catalyst prepared from control ligand **50**. Thus, Gd-**50** (1 : 2) promoted the reactions of **44a** and **44h** much more slowly in THF, giving **45a** and **45h** with only 7% ee (98% yield at −40 °C for 10 h) and 2% ee (97% yield at −40 °C for 18 h), respectively. NMR studies revealed that less TMSCN was consumed during the catalyst formation of Pr-**50** (1 : 2) than that of Pr-**35**, which indicated the formation of less lanthanide metal cyanide in the case of the Pr-**50** catalyst compared with the Pr-**35** catalyst. There were no ESI-MS peaks corresponding to the Gd-**50** complex under any conditions, which suggests a lack of defined structure in this case. Therefore, the phosphine oxide facilitates the lanthanide metal cyanide formation and stabilizes the active 2:3 complex **47**, together with activating the lanthanide metal cyanide. Complete structure determinations of the active catalyst through X-ray analysis, improvement of the enantioselectivity, especially for aliphatic ketones, and application for synthesis of natural products are now being investigated.

Conclusion

The present review clearly demonstrates the power of asymmetric two-center catalysis. These studies, however, are just the first step for truly efficient organic synthesis with respect to atom economy, energy cost, and environmental friendliness. The development of catalytic enantioselective carbon–carbon bond formation reactions is a major future target in synthetic organic chemistry.

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