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Asymmetric Cyanation with the Chiral Ru–Li Combined Catalysts

Takeshi Ohkuma,* Nobuhito Kurono

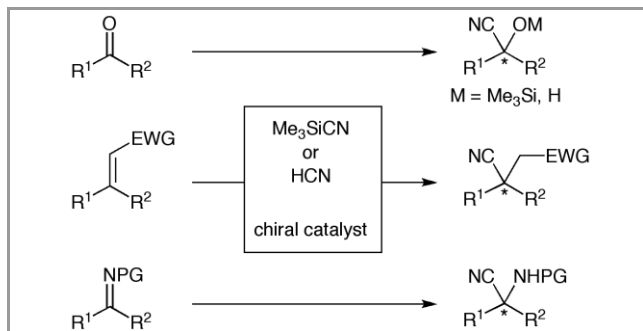
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Abstract: The combined systems of phenylglycinate/BINAP/Ru(II) complex and Li compounds have been found to act as highly reactive and enantioselective catalysts for cyanosilylation and hydrocyanation of aldehydes, α -keto esters, α,β -unsaturated ketones, and *N*-protected aldimines. In this account, we describe the concept of catalyst design, the catalytic efficiency of the novel combined systems in the asymmetric cyanation, and the proposed reaction pathway based on the spectral analysis data.

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Key words: aldehydes, asymmetric catalysis, cyanosilylation, hydrocyanation, imines, lithium, ruthenium, α,β -unsaturated ketones



Scheme 1 Enantioselective nucleophilic cyanation with chiral catalyst by using TMSCN or HCN

Various chiral organometallic catalysts and organocatalysts have been developed for these important transformations.¹ Three major indices for judgment of the catalyst efficiency are as follows: 1) catalytic activity (reflecting the amount of catalyst loading), 2) enantioselective ability, and 3) range of application for substrates. Regarding the first item, the substrate-to-catalyst molar ratio (S/C) and turnover number (TON) of the catalyst are generally used as indicators. Regarding the second item, the ability is estimated by the degree of enantiomeric excess (ee) of the cyanated products. Several well-designed chiral catalysts have achieved very high ee of >95% in recent years. Finally, in the case of the third index, the catalyst with wider application ability is obviously preferable.

This account describes our studies on the asymmetric cyanosilylation and hydrocyanation of aldehydes, α -keto esters, α,β -unsaturated ketones, and *N*-protected aldimines catalyzed by unique chiral Ru(II) complex–Li compound combined systems for achieving high catalytic activity, enantioselectivity, and a wide range of substrates.

2 Cyanosilylation of Aldehydes and Ketones Catalyzed by LiCl

We first focused our attention on finding a catalyst that exhibits high activity in the cyanosilylation of aldehydes. When we started this research, many catalyst systems for this reaction were already known.¹ Among them, Lewis acids mainly activate aldehydes by the reversible coordination at the carbonyl oxygen of the substrates.³ Lewis basic catalysts interact with the silicon moiety of TMSCN, thereby improving the nucleophilicity of

1 Introduction

Enantioselective nucleophilic cyanation of prochiral unsaturated compounds affording the optically active nitrile products is among the most useful and versatile methods in the area of synthetic organic chemistry.¹ As shown in Scheme 1, aldehydes, ketones, alkenes activated by an electron-withdrawing group (EWG), and imines are cyanated with high enantioselectivity under appropriate conditions. Many bioactive chiral compounds, including α -hydroxy carboxylic acids, β -amino alcohols, and α -amino acids, are readily prepared from these cyanated compounds.¹ The cyanation reagents can be selected according to one's synthetic purpose. For example, the cyanation with TMSCN (cyanosilylation) provides silyl-protected compounds, which are sometimes suitable for further transformations. The use of the simplest cyanation reagent HCN (hydrocyanation), affording unprotected chiral nitriles, is appropriate for the practical synthesis.²

Table 1 Cyanosilylation of Benzaldehyde (**1a**)^a

Entry	Catalyst	Method ^b	S/C ^c	Solvent ^d	Yield ^e (%)
1	LiCl	A	10,000	neat	100
2	LiCl	B	10,000	neat	100
3	LiCl	A	50,000	neat	56
4	LiCl	A	50,000	CH ₂ Cl ₂ ^f	<0.3
5	LiCl	A	50,000	THF ^f	7
6	LiCl	A	10,000	toluene ^f	7
7	NaCl	B	20	neat	1
8	KCl	B	20	neat	0.3
9	CsCl	B	20	neat	22
10	LiF	A	10,000	neat	<0.3
11	LiBr	A	10,000	neat	86
12	LiI	A	10,000	neat	98
13	LiClO ₄	A	10,000	neat	2.5
14	– ^g	–	–	neat	<0.3

^a Unless otherwise described, reactions were carried out using **1a** and 1 equiv of TMSCN with catalyst at 20–25 °C for 1 h.

^b A: Catalyst was added as a 29.5 mM solution of THF. B: Catalyst was added as a solid.

^c Substrate/catalyst molar ratio.

^d Neat: The reaction was conducted under solvent-free conditions.

^e Determined by GC or ¹H NMR analysis.

^f The initial concentration of **1a** was 1.0 M.

^g Reaction without catalyst.

this reagent.⁴ The Lewis acid–Lewis base bifunctional catalysts activate both the substrate and the reagent cooperatively.^{1f,i} Metal halides, such as AlCl₃,^{3b,4a} BiBr₃,^{3l} BF₃,^{3f} InX₃ (X = Br,^{3o} F^{3m}), LnCl₃ (Ln = La, Ce, Sm),^{3e} MgBr₂,^{3f} SnCl₄,^{3f} R₂SnCl₂ (R = *n*-C₄H₉, C₆H₅),^{3j} TiCl₄,^{3f} and ZnI₂,^{3a} have been reported as typical Lewis acidic catalysts. However, the catalytic behavior of LiCl, which is one of the simplest metal halides, has not been investigated for this reaction.⁵ Thus, we decided to examine the catalytic efficiency of LiCl in the cyanosilylation of aldehydes in detail.

Benzaldehyde (**1a**), an aromatic aldehyde, was selected as the standard substrate. As shown in Table 1, LiCl showed significantly high catalytic activity under solvent-free conditions at ambient temperature.⁶ The aldehyde **1a** was quantitatively converted with 1 equiv of TMSCN at an S/C of 10,000 in 1 h to afford the silylated cyanohydrin **2a** (entries 1 and 2). LiCl could be used as either a solid or a THF solution. The reaction with an S/C of 50,000 proceeded to 56% even in 1 h (entry 3). Interestingly, the reaction rate notably decreased in solution ([**1a**]₀ = 1.0 M) (entries 4–6). Other alkaline metal chlorides, NaCl, KCl, and CsCl, as well as LiF were far less active under the same conditions (entries 7–10).^{7,8} The catalytic efficiency of LiBr and LiI was comparable (entries 11 and 12). LiClO₄, which has been reported to promote the cyanation of aldehydes and ketones,⁹ did not

exhibit sufficient catalytic activity under the regular conditions (entry 13). These results indicated that exceptionally high reactivity is achieved by using LiX (X = Cl, Br, I) as a catalyst under solvent-free conditions.

The cyanosilylation catalyzed by LiCl was applied to a range of aldehydes **1** (Table 2).⁶ The cyanated products, **2** and **3**, were isolated with >98% purity just by distillation of the reaction mixture. The reaction of **1a** and TMSCN with an S/C of 100,000 for 48 h afforded **2a** in 99% yield (entry 2). A bulky reagent *t*-BuMe₂SiCN could be used with a slightly lower reaction rate (entries 3, 6, 12, and 17). The benzaldehydes with an electron-donating group (EDG) at the C4 position, **1b** and **1e**, showed relatively low reactivity (entries 4 and 8). On the other hand, the reaction of the electron-withdrawing Cl- or CF₃-substituted aldehydes at the C2 or C4 position, **1c**, **1d**, and **1f**, with an S/C of 10,000 was completed within 40 min (entries 5, 7, and 9). 2-Naphthaldehyde (**1g**) also showed high reactivity (entry 10). The cyanation of α,β-unsaturated aldehydes, **1h** and **1i**, proceeded in a 1,2-fashion (entries 11–13). Formation of the 1,4-cyanated products was not observed at all. The reactivity of

Table 2 Cyanosilylation of Aldehydes **1** Catalyzed by LiCl^a

^a R ¹ = Ph ^b R ¹ = 4-MeC ₆ H ₄ ^c R ¹ = 2-ClC ₆ H ₄ ^d R ¹ = 4-ClC ₆ H ₄ ^e R ¹ = 4-MeOC ₆ H ₄ ^f R ¹ = 4-CF ₃ C ₆ H ₄ ^g R ¹ = 2-naphthyl ^h R ¹ = (E)-PhCH=CH ⁱ R ¹ = (E)- <i>n</i> -C ₅ H ₁₁ CH=CH ^j R ¹ = <i>n</i> -C ₇ H ₁₅ ^k R ¹ = <i>cyclo</i> -C ₆ H ₁₁ ^l R ¹ = <i>t</i> -Bu					
Entry	1	R ₃ Si	S/C	Time (h)	Yield ^b (%)
1	1a	TMS	10,000	1	100 (94)
2	1a	TMS	100,000	48	99 (c)
3	1a	<i>t</i> -Bu(Me) ₂ Si	10,000	5	100 (96)
4	1b	TMS	5000	5	100 (98)
5	1c	TMS	10,000	0.5	100 (93)
6	1c	<i>t</i> -Bu(Me) ₂ Si	10,000	1	100 (93)
7	1d	TMS	10,000	0.6	100 (97)
8	1e	TMS	5000	6	100 (97)
9	1f	TMS	10,000	0.5	100 (98)
10	1g	TMS	10,000	0.4	100 (96)
11	1h	TMS	10,000	3	97 (88)
12	1h	<i>t</i> -Bu(Me) ₂ Si	10,000	8	100 (93)
13	1i	TMS	10,000	22	99 (98)
14	1j	TMS	10,000	0.5	100 (95)
15	1k	TMS	10,000	0.5	100 (94)
16	1l	TMS	10,000	0.2	100 (98)
17	1l	<i>t</i> -Bu(Me) ₂ Si	10,000	2	100 (90)

^a Unless otherwise described, reactions were carried out using **1** and 1–1.3 equiv of R₃SiCN with LiCl (24–310 mM in THF) at 20–25 °C under solvent-free conditions.

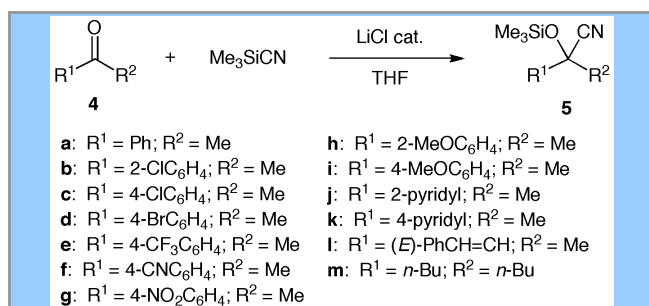
^b Yield of **2** or **3** determined by GC or ¹H NMR analysis. The isolated yield is indicated in parenthesis.

^c Not isolated.

aliphatic aldehydes, **1j–1l**, was found to be notably high (entries 14–17). The bulky aldehyde **1l** quantitatively reacted with TMSCN in only 10 min under the typical conditions.

We next examined the cyanosilylation of ketones **4** catalyzed by LiCl. These results are listed in Table 3.^{6,10} As we expected, the reactivity of acetophenone (**4a**), a simple aromatic ketone, was found to be much lower than that of aromatic aldehyde **1a** (entry 1 and Table 2, entry 1). The reaction with an S/C of 100 was completed in 3 h. Although the 2'- and 4'-chloroacetophenones, **4b** and **4c**, showed the same level of reactivity, the 4'-bromo ketone **4d** (S/C = 1000) was quantitatively converted into the cyanohydrin derivative **5d** in 6 h (entries 2–4). Furthermore, acetophenones with strong EWGs of CF₃ (**4e**), CN (**4f**), and NO₂ (**4g**) exhibited even higher reactivity (entries 5–7). The reactivity of methoxyacetophenones, **4h** and **4i**, was low, but the cyanation with an S/C of 100 was completed within 8 h (entries 8 and 9). Acetylpyridines, **4j** and **4k**, showed remarkably high reactivity (entries 10 and 11). The cyanation of 2-acetylpyridine (**4j**) with an S/C of 20,000 was completed in 45 min. The reactivity of the vinylic and aliphatic ketones, **4l** and **4m**, was similar to that of the aromatic ketone **4a** (entries 1, 12, and 13). The 1,2-adduct **5l** was the only detectable

Table 3 Cyanosilylation of Simple Ketones **4** Catalyzed by LiCl^a



Entry	4	S/C	Time (h)	Yield (%) ^b
1	4a	100	3	100 (96)
2	4b	100	2	99.8 (97)
3	4c	100	2.5	99.1 (98)
4	4d	1000	6	99.8 (97)
5	4e	1000	1.5	100 (98)
6	4f	1000	1	100 (99)
7	4g	1000	1	100 (98)
8	4h	100	5	99.6 (96)
9	4i	100	8	99.7 (98)
10	4j	20,000 ^c	0.75	100 (80)
11	4k	1000	0.5	99.6 (96)
12	4l	100	3	100 (98)
13	4m	100	2.5	100 (94)

^a Unless otherwise described, reactions were carried out using 5 mmol of **4** and 1–1.3 equiv of TMSCN with LiCl (200–220 mM in THF) at 20–25 °C. The total volume of THF was 0.24–0.76 mL (reaction with an S/C = 100), 0.52–1.03 mL (reaction with an S/C = 1000), or 0.01 mL (reaction with an S/C = 20,000).

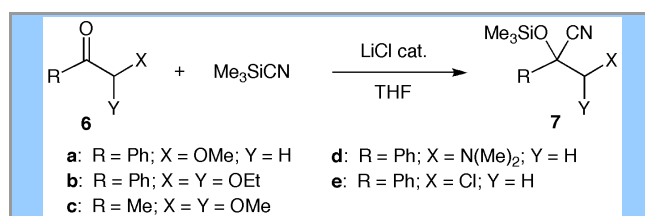
^b Yield of **5** determined by GC or ¹H NMR analysis. The isolated yield is indicated in parenthesis.

^c 25 mM of LiCl in THF was used.

product in the reaction of **4l**.

We found that exceptionally high catalytic activity of LiCl was achieved in the reaction of α-hetero-substituted ketones **6** and TMSCN (Table 4).^{3d,n,o,4d,g,11} Thus, the reaction of 2-methoxyacetophenone (**6a**) with an S/C of 5000 was completed in 30 min (entry 1).¹⁰ Phenylglyoxal diethylacetal (**6b**) and methylglyoxal dimethylacetal (**6c**), which are aromatic and aliphatic α,α-dialkoxyketones, quantitatively reacted with TMSCN at an S/C of 100,000 in 1 h and 15 min, respectively (entries 2 and 3). The acceleration effect of the α-alkoxy groups of ketones can be clearly seen by comparing the reactivity of **6a,b** and **4a** (see Table 3, entry 1). The α-dimethylamino- and α-chloroacetophenones, **6d** and **6e**, were also quantitatively cyanated with a tiny amount of LiCl (entries 4 and 5).

Table 4 Cyanosilylation of α-Hetero-substituted Ketones **6** Catalyzed by LiCl^a



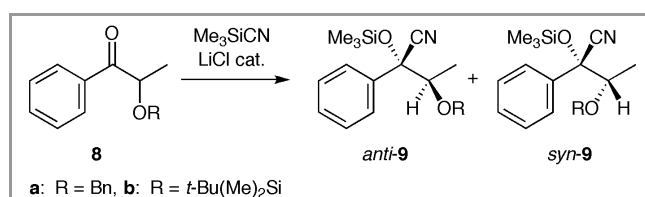
Entry	6	S/C	Time (h)	Yield (%) ^b
1	6a	5000	0.5	100 (97)
2	6b	100,000	1	99.9 (96)
3	6c	100,000	0.25	100 (95)
4	6d	5000	3	100 (97)
5 ^c	6e	10,000	1	100 (98)

^a Unless otherwise described, reactions were carried out using 5 mmol of **6** and 1.3 equiv of TMSCN with LiCl at 20–25 °C. The total volume of THF was 0.01 mL.

^b Yield of **5** determined by GC or ¹H NMR analysis. The isolated yield is indicated in parenthesis.

^c The total volume of THF was 0.51 mL.

The Lewis acidic character of LiCl was expected to control the diastereoselectivity in the cyanosilylation of 2-alkoxypropiophenones **8** (Scheme 2).¹² When the 2-benzyloxy ketone **8a** (1.0 mmol) and 1.3 equiv of TMSCN were reacted in the presence of LiCl (S/C = 5000) in CH₂Cl₂ (0.5 mL) at 27 °C for 1.5 h, *anti*- and *syn*-**9a** were quantitatively obtained in a 14:1



Scheme 2 Diastereoselective cyanosilylation of ketones **8** catalyzed by LiCl

ratio.¹⁰ The *anti/syn* ratio decreased to 6:1 in polar THF (0.1 mL) solution. These observations suggested that the cyanation proceeded through a chelation intermediate consisting of the Li cation and **8a** (see Section 5.1 for details).¹² Interestingly, the reaction of **8b** with a bulky *tert*-Bu(Me)₂SiO group in CH₂Cl₂ also gave *anti*-**9b** as a major isomer (*anti/syn* = 3:1).¹³

3 Asymmetric Cyanosilylation of Aldehydes and α -Keto Esters

3.1 Design of Chiral Ru–Li Combined Catalyst Systems

The notably high catalytic activity of LiCl in the cyanosilylation of aldehydes and ketones prompted us to design chiral Li catalysts for development of the enantioselective reaction. Kagan¹⁴ and Ishihara¹⁵ have reported elegant asymmetric cyanosilylation of aldehydes with chiral Li catalysts derived from BINOL and SALEN compounds. Our concept for the design of catalysts was very much different from others. As shown in Figure 1, we expected that the Li cation could be coordinated by a chiral metal complex to form a chiral metal–Li combined catalyst. Metal complexes have an advantage for the formation of a variety of chiral structures from chiral ligands and the center metals with coordination bonds. Here, the metal complexes are recognized as “chiral templates,” which are readily modified just by changing the chiral ligands.

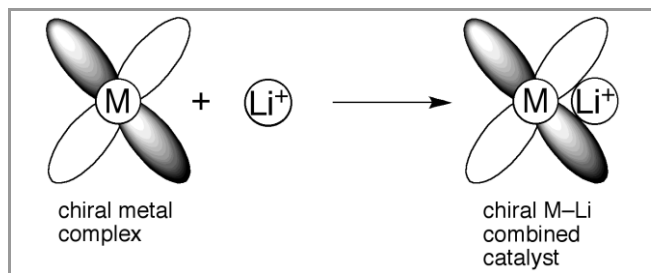


Figure 1 Working hypothesis for the design of the catalyst

Since 1995, we have studied asymmetric hydrogenation of ketones catalyzed by Ru(II) complexes bearing both chiral diphosphine and diamine ligands.¹⁶ The typical structure of the catalyst precursor is shown in the upper part of Figure 2.¹⁷ The chiral structure of the Ru(II) complex varies as the combination of these two chiral ligands is changed. A wide variety of ketones have been hydrogenated with high enantioselectivity by using appropriately tuned chiral diphosphine/diamine–Ru(II) complexes. Based on the positive results from the asymmetric hydrogenation, we planned to utilize chiral Ru(II) complexes as the chiral templates for achieving high enantioselectivity in cyanation reactions. After screening of Ru(II) complexes with two chiral ligands,

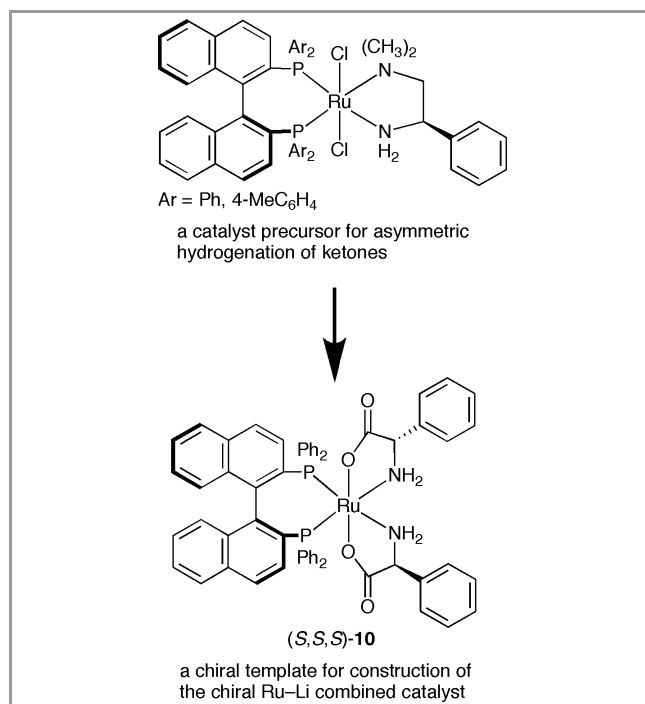
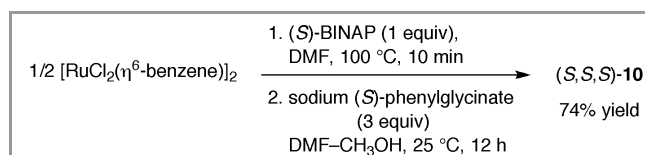


Figure 2 Design of a chiral template for construction of the chiral Ru–Li combined catalyst

the chiral amino acid/diphosphine–Ru(II) complexes were found to have sufficient stability for use as the chiral templates. The structure of Ru[(*S*)-phgly]₂[(*S,S,S*)-BINAP] ((*S,S,S*)-**10**: PhGly = phenylglycinate, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) is shown as a typical example in the lower part of Figure 2.^{18,19} The Ru(II) complex (*S,S,S*)-**10** was readily prepared from commercial [RuCl₂(η^6 -benzene)]₂ in two steps, and purified with a silica-gel preparative TLC in the open air (74% isolated yield: Scheme 3).



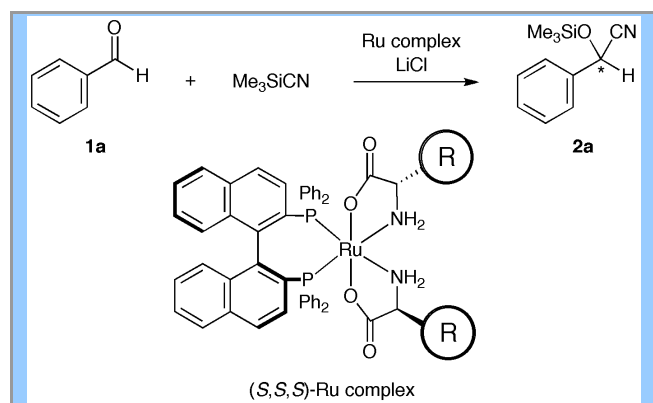
Scheme 3 Preparation of (*S,S,S*)-**10**

3.2 Cyanosilylation of Aldehydes

The reaction of benzaldehyde (**1a**) and a 1.2 equiv of TMSCN in *tert*-BuOMe was selected for screening of the amino acid/BINAP–Ru(II) complexes (Table 5).^{14,15,20} The catalytic species was prepared in situ from the complex and LiCl in a 1:1 ratio. The S/C was set at 10,000:1. When the reaction was conducted with the (*S*)-PhGly/(*S,S,S*)-BINAP complex (R = Ph) at 0 °C, the *R* cyanated product (*R*)-**2a** in 73% ee was quantitatively obtained in 1 h (entry 1).¹⁸ The higher enantioselectivity was obtained at the lower reaction temperature (entries 2–4). Thus, the excellent ee value of 94% was observed at –78 °C, but the reaction rate was significantly decreased (18% in 18 h). Many

(*S*)-arylglycinate/(*S*)-BINAP complexes (*R* = aryl group) were applied to this reaction (entries 5–11). The electronic and steric modifications on the aromatic moiety did not improve the enantioselectivity. The use of the 2'-anisylglycinate complex almost lost the stereoselectivity, which may have been due to the inhibitory effect of the 2'-methoxy moiety interacting appropriately with LiCl (entry 7). Less satisfactory results were obtained by using the Ru(II) complexes with glycinate and anions of alkyl-substituted α -amino acids (entries 12–16). The reaction with the diastereomeric (*R*)-PhGly/(*S*)-BINAP complex resulted in the (*S*)-**2a** in only 2% ee, indicating that the appropriate combination of stereochemistry of the two chiral ligands is crucial to obtain high enantioselectivity (entry 17; see also entry 1).

Table 5 Asymmetric Cyanosilylation of Benzaldehyde (**1a**) with Ru Complex–LiCl Catalyst Systems^a



Entry	R	Temp (°C)	Time (h)	Yield (%) ^b	Ee (%) ^b
1	Ph	0	1	>99	73 (<i>R</i>)
2	Ph	–20	1	>99	83 (<i>R</i>)
3	Ph	–40	18	>99	87 (<i>R</i>)
4	Ph	–78	18	18	94 (<i>R</i>)
5	2-Tol	0	1	>99	47 (<i>R</i>)
6	3,5-Xyl	0	1	>99	61 (<i>R</i>)
7	2-Anisyl	0	1	92	1 (<i>R</i>)
8	4-Anisyl	0	1	99	70 (<i>R</i>)
9	4-CF ₃ Ph	0	1	>99	65 (<i>R</i>)
10	1-Naph	0	1	>99	43 (<i>R</i>)
11	2-Naph	0	1	>99	60 (<i>R</i>)
12	H	0	1	59	8 (<i>S</i>)
13	Me	0	1	64	17 (<i>R</i>)
14	<i>i</i> -Pr	0	1	90	1 (<i>S</i>)
15	<i>s</i> -Bu	0	1	97	37 (<i>R</i>)
16	<i>t</i> -Bu	0	1	90	13 (<i>R</i>)
17	Ph (<i>R</i>) ^c	0	1	85	2 (<i>S</i>)

^a Unless otherwise stated, reactions were carried out using **1a** (10.0 mmol) and TMSCN (12.0 mmol) in *t*-BuOMe (10 mL) with an (*S,S,S*)-Ru complex (20 mM in THF) and LiCl (50 mM in THF). **1a**:Ru:Li = 10,000:1:1.

^b Data for **2a** were determined by chiral GC analysis.

^c Ru[(*R*)-phgly]₂[(*S*)-binap] was used.

The catalytic activity of (*S,S,S*)-**10**–LiCl was not sufficient for the reaction of **1a** and TMSCN at –78 °C, although the enantioselectivity was high (Table 5, entry 4). We therefore used the basic salt Li₂CO₃²¹

instead of neutral LiCl, because the LiCO₃ anion was expected to strongly activate TMSCN as a nucleophile. The results are summarized in Table 6. The cyanation of **1a** with the (*S,S,S*)-**10**–Li₂CO₃ catalyst system at a **1a**/**10**/Li₂CO₃ ratio of 10,000:1:1 in ether at –78 °C was completed in 12 h to afford (*R*)-**2a** in 97% ee (entry 1). The 1:2 **10**–Li₂CO₃ system showed slightly lower enantioselectivity (entry 2). The reaction rate slowed with decrease of the Li₂CO₃ proportion in the catalyst system (entries 3 and 4). No conversion was observed in the absence of the Li salt (entry 5). Li₂CO₃ alone exhibited moderate activity, suggesting that the complexation of **10** and Li₂CO₃ forms the more reactive chiral catalyst (entry 6). The enantioselectivity of the reaction in *tert*-BuOMe was slightly lower (entry 7). Interestingly, both the reactivity and the stereoselectivity were significantly decreased in THF (entry 8). A moderate catalyst efficiency was observed in the less polar solvents (entries 9 and 10).

Table 6 Asymmetric Cyanosilylation of Benzaldehyde (**1a**)^a

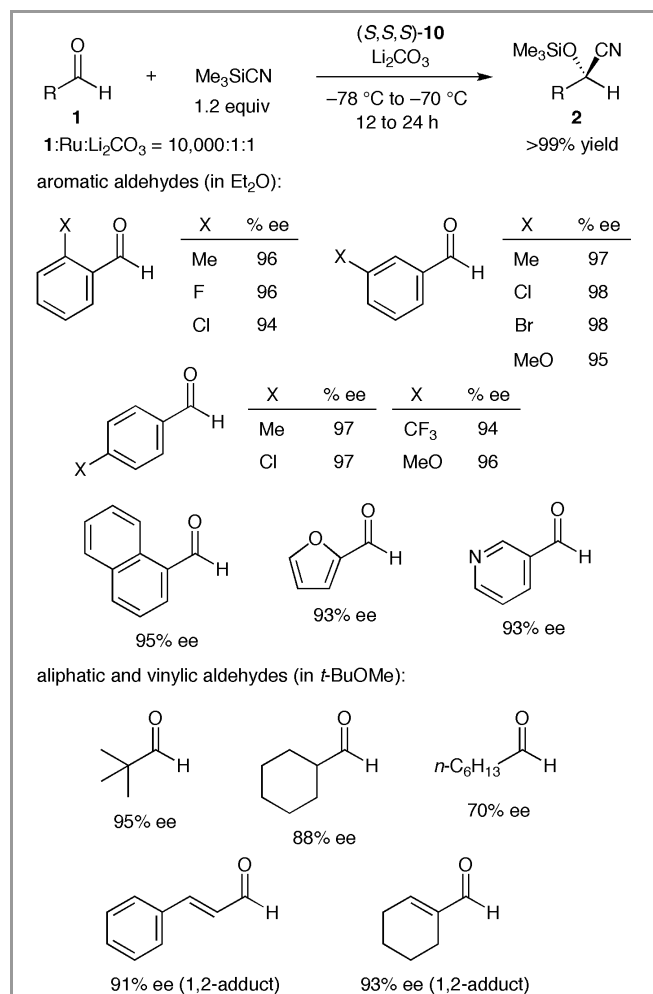
Entry	1a / 10 /Li ₂ CO ₃	Solvent	Yield (%) ^b	Ee (%) ^b
1	10,000:1:1	Et ₂ O	>99	97
2	10,000:1:2	Et ₂ O	>99	95
3	10,000:1:0.5	Et ₂ O	98	97
4	10,000:1:0.2	Et ₂ O	9	98
5	10,000:1:0	Et ₂ O	<1	n.d. ^c
6	10,000:0:1	Et ₂ O	47	–
7	10,000:1:1	<i>t</i> -BuOMe	>99	94
8	10,000:1:1	THF	38	39
9	10,000:1:1	PhMe	84	88
10	10,000:1:1	CH ₂ Cl ₂	84	88

^a Unless otherwise stated, reactions were carried out using **1a** (9.9–10.0 mmol) and TMSCN (12.0 mmol) in solvent (10 mL) with (*S,S,S*)-**10** (20 mM in THF) and aqueous Li₂CO₃ (0.1 M) at –78 °C for 12 h.

^b Data for (*R*)-**2a** were determined by chiral GC analysis.

^c Not determined.

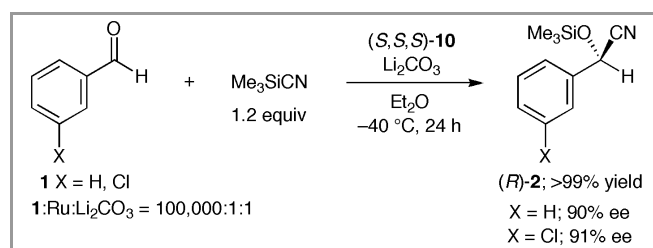
The (*S,S,S*)-**10**–Li₂CO₃ catalyst system was applied to the cyanation of a series of aldehydes **1** (Scheme 4).¹⁸ All reactions with an S/C of 10,000 at –78 °C to –70 °C were completed in 12 to 24 h. Benzaldehydes with an EWG or EDG at the 2', 3', or 4' position were cyanated with excellent enantioselectivity. Among them, the 3'-chloro and 3'-bromo aldehydes were converted to the silylated cyanohydrins in the highest 98% ee. 1-Naphthaldehyde and heteroaromatic aldehydes were also selectively cyanated under the regular conditions. For the cyanation of aliphatic and α,β -unsaturated aldehydes, a slightly higher enantioselectivity was obtained in *tert*-BuOMe than in ether. The primary and secondary alkyl



Scheme 4 Asymmetric cyanosilylation of aldehydes **1**

aldehydes reacted with high enantioselectivity. A medium ee value of the product was observed in the reaction of a primary alkyl aldehyde.²² Only 1,2-adducts in $\geq 91\%$ ee were obtained in the cyanation of the α,β -unsaturated aldehydes.

The excellent catalytic activity of the (*S,S,S*)-**10**–Li₂CO₃ system led to complete conversion in the cyanosilylation with an S/C of 100,000 at $-40\text{ }^{\circ}\text{C}$ for 24 h (Scheme 5).²³ The silylated cyanohydrins derived from benzaldehyde and the 3'-chloro ketone were obtained in 90% ee and 91% ee, respectively.



Scheme 5 Asymmetric cyanosilylation with an S/C of 100,000

3.3 Cyanosilylation of α -Keto Esters

Asymmetric reaction of prochiral ketones and TMS-CN is one of the most reliable method to synthesize optically enriched tertiary cyanohydrin derivatives.^{1,24–28} In particular, the reaction of α -keto esters, a class of functionalized ketones, affords chiral multi-functionalized cyanated products, which are difficult to make by other methods (see the equation in Table 7).²⁹

Table 7 Asymmetric Cyanosilylation of Methyl Benzoylformate (**11a**) with the **10**–PhOLi System^a

Entry	[11a] ₀ (M) ^b	S/C	Temp ($^{\circ}\text{C}$)	Time (h)	Yield (%) ^c	Ee (%) ^c
1	0.1	1000	-40	3	>99	97
2	0.1	1000	-60	18	>99	99
3	0.3	1000	-60	18	>99	98
4	0.8	1000	-60	18	99	97
5	0.1	10,000	-40	36	>99	97
6	0.3	10,000	-40	18	>99	97
7	0.3	10,000	-50	18	>99	98
8	0.3	10,000	-60	18	69	98
9	0.8	10,000	-50	18	>99	96

^a Unless otherwise stated, reactions were conducted using **11a** (5–10 mmol) and 2 equiv of TMS-CN in *tert*-BuOMe with (*S,S,S*)-**10** (1–5 μmol) and PhOLi. **10**:PhOLi = 1:1.

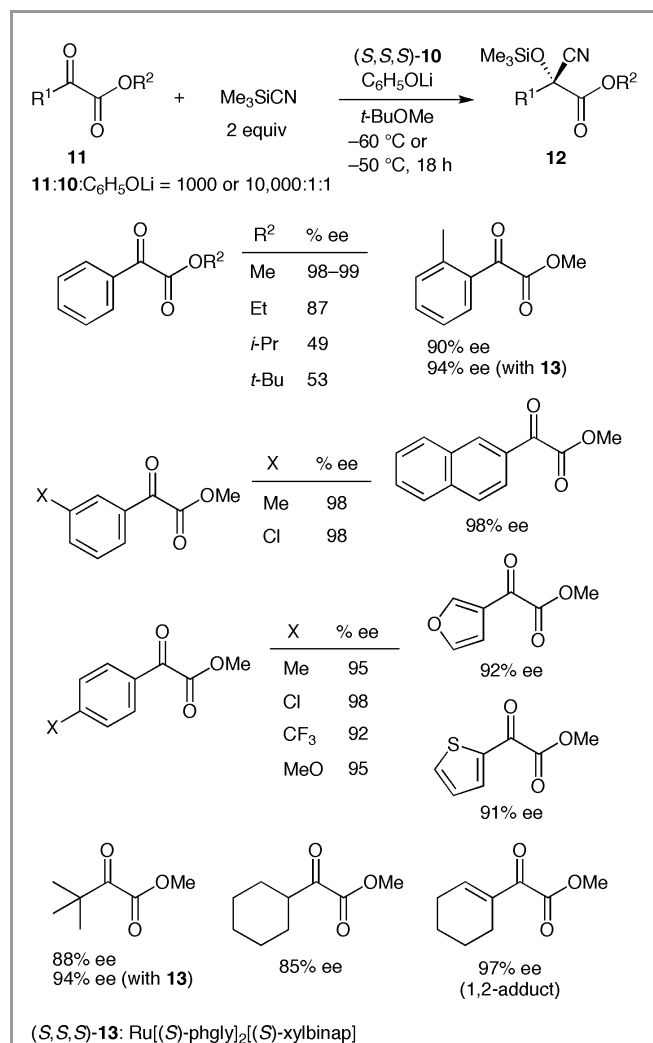
^b Initial concentration of **11a**.

^c Data for (*R*)-**12a** were determined by chiral GC analysis.

The (*S,S,S*)-**10**–C₆H₅OLi system exhibited an excellent catalyst performance in the reaction of methyl benzoylformate (**11a**), a standard aromatic α -keto ester, and 2 equiv of TMS-CN in *tert*-BuOMe (Table 7).³⁰ PhOLi is a preferable nucleophilic Li compound, the amount of which is easily determined in solution.³¹ The cyanation of **11a** (0.1 M) with an S/C of 1000 at $-40\text{ }^{\circ}\text{C}$ was completed in 3 h to afford the *R* silylated cyanohydrin (*R*)-**12a** in 97% ee (entry 1). An excellent ee value of 99% was achieved in the reaction at $-60\text{ }^{\circ}\text{C}$, although the reaction rate was slowed (entry 2). To our knowledge, this is the first example of the asymmetric cyanosilylation of α -keto esters.³² The enantioselectivity tended to decrease slightly with an increase of substrate concentration (entries 2–4). The reaction of **11a** (0.1 M) with an S/C of 10,000 at $-40\text{ }^{\circ}\text{C}$ required 36 h for completion (entry 5). The reaction rate increased under a higher substrate concentration of 0.3 M without loss of enantioselectivity (entry 6). The optimized conditions with an S/C of 10,000 were determined to be 0.3 M of **11a** at $-50\text{ }^{\circ}\text{C}$, affording **12a** in 98% ee quantitatively in 18 h (entry 7). The lower temperature and the higher substrate concentration conditions decreased

the reaction rate and the enantioselectivity, respectively (entries 8 and 9).

The cyanation catalyzed by the **10**-C₆H₅OLi system under the optimized conditions (S/C = 1000, -60 °C; S/C = 10,000, -50 °C) was applied to a series of α -keto esters (Scheme 6).³⁰ The enantioselectivity was highly dependent on the size of the ester moiety (OR²). The smallest methyl ester resulted in the highest selectivity. Several methyl benzoylformates with a substituent at the 2', 3', or 4' position were smoothly cyanated to give the desired products in 90%–98% ee. The naphthyl, furyl, and thienyl ketones were also converted with high selectivity. The *tert*-butyl and cyclohexyl ketones reacted with the same sense of enantioselection as that of benzoylformate. The cyanosilylation of the 1-cyclohexenyl ketone predominantly occurred in a 1,2-fashion to afford the allylic cyanohydrin derivative in 97% ee. For the cyanation of sterically hindered 2'-methylphenyl and *tert*-butyl ketones, the use of Ru[(*S,S,S*)-**13**; XylBINAP = 2,2'-bis(di-3,5-xylylphosphino)-1,1'-binaphthyl) instead of the BINAP complex **10** showed even higher



Scheme 6 Asymmetric cyanosilylation of α -keto esters **11**

enantioselectivity, yielding both cyanohydrin products in 94% ee. The sterically more demanding structure of XylBINAP seemed to be appropriate for these substrates.

Comparing the enantioselectivity in the cyanosilylation of phenyl (99%), cyclohexyl (85%), and 1-cyclohexenyl ketones (97%) suggested that the **10**-PhOLi catalyst preferably differentiated aryl and alkenyl groups (Csp² groups) to alkyl groups (Csp³ groups) from the CO₂Me group (Csp² group), although the mode of enantioselection is not clear yet.

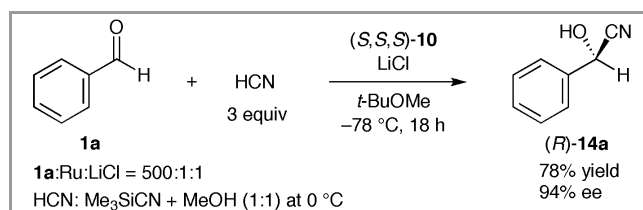
4 Asymmetric Hydrocyanation of Aldehydes, α,β -Unsaturated Ketones, and Aldimines

4.1 Hydrocyanation of Aldehydes

Asymmetric reaction of aldehydes and HCN (hydrocyanation) is the simplest and most direct method to produce optically active cyanohydrins.^{1,33} HCN is a highly toxic and volatile (bp. 25.6 °C) compound, so that it should be used in a well-ventilated fume hood with the utmost care in a laboratory. However, HCN is produced in the SOHIO acrylonitrile process as a byproduct (about 150 kg per 1000 kg of acrylonitrile),³⁴ and it is utilized for the production of methyl methacrylate in industrial processes (on a million-ton scale worldwide).³⁵ Therefore, HCN is a useful material especially from a practical viewpoint.²

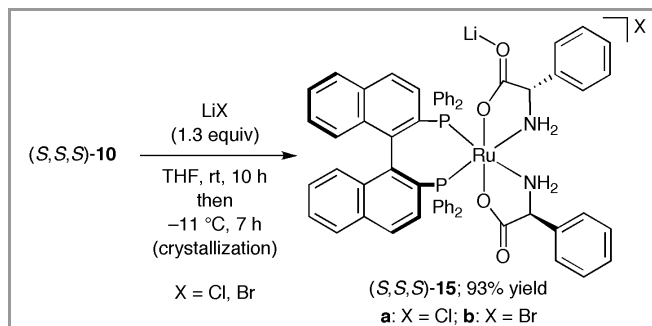
Asymmetric hydrocyanation of aldehydes catalyzed by oxynitrilase is a well-known procedure.^{2,36,37} However, studies on this asymmetric transformation with artificial catalysts have been quite limited. Pioneering works using the cyclic dipeptide *cyclo*[(*S*)-phenylalanyl-(*S*)-histidyl]^{38–40} and a Ti(IV) complex with a modified dipeptide ligand⁴¹ have reported high enantioselectivity, although these catalytic activity (S/C < 50) and the substrate applicability have room for improvement. Thus, we examined the asymmetric reaction catalyzed by our original chiral Ru–Li combined systems.

Benzaldehyde (**1a**) was selected as a standard substrate (Scheme 7).⁴² HCN was conveniently



Scheme 7 Asymmetric hydrocyanation of benzaldehyde (**1a**) with the **10**-LiCl system

prepared in situ by mixing TMSCN and MeOH in a 1:1 ratio at 0 °C. First, we use the neutral Ru[(*S,S,S*)-phgly]₂[(*S,S,S*)-binap] ((*S,S,S*)-**10**)–LiCl catalyst system to avoid the base-catalyzed achiral cyanation. The reaction of **1a** and HCN (3 equiv) with an S/C of 500 at –78 °C for 18 h afforded the *R* cyanohydrin (*R*)-**14a** in 94% ee and in 78% yield. This result prompted us to prepare the chiral bimetallic complexes [Li{Ru[(*S,S,S*)-phgly]₂[(*S,S,S*)-binap]}]X ((*S,S,S*)-**15**: **a**: X = Cl; **b**: X = Br; Scheme 8), which were the expected active species, and to utilize them as pre-formed catalysts to achieve high reactivity.



Scheme 8 Preparation of Ru•Li combined complexes **15**

The desired complex (*S,S,S*)-**15a** (yellow crystal) was readily prepared just by mixing (*S,S,S*)-**10** and a 1.3 equiv of LiCl in THF at room temperature and then placing the mixture in a freezer at –11 °C (Scheme 8). The Br complex **15b** was obtained as a needle-like crystal with the same procedure. As shown in Figure 3, single-crystal X-ray measurement revealed that **15b** has a Ru center with a distorted octahedral structure in which two carboxylate oxygens bind at the apical positions ($\angle\text{O}(1)\text{--Ru--O}(2) = 163^\circ$). The Li cation is placed close to a carbonyl oxygen ($\text{O}(2)\text{--Li} = 1.92 \text{ \AA}$),

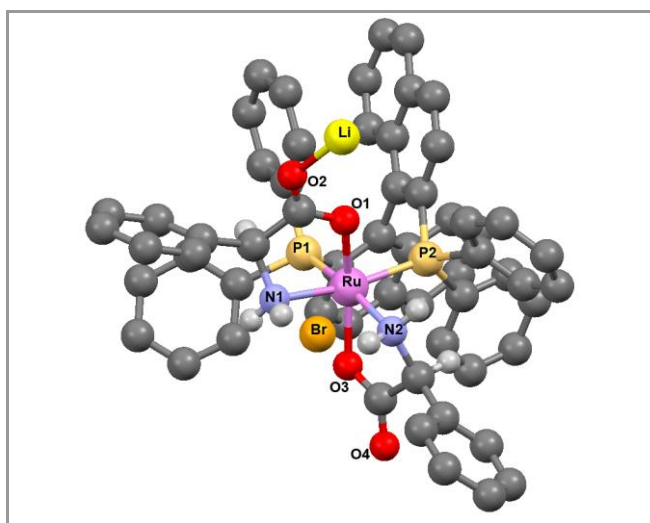
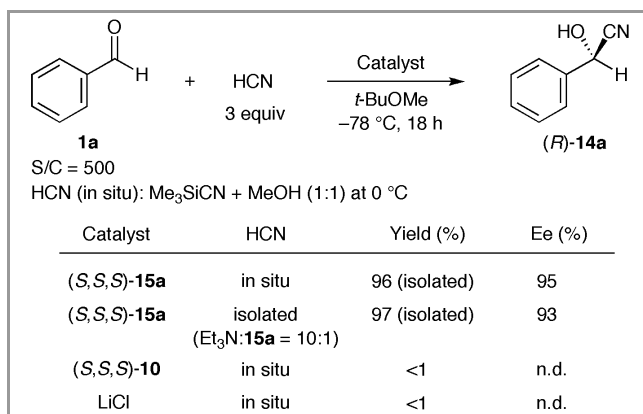


Figure 3 ORTEP drawing of (*S,S,S*)-**15b**. Selected distances (Å) and bond angles (deg): Ru–O1 2.108(4), Ru–O3 2.110(4), Ru–N1 2.209(4), Ru–N2 2.117(5), Ru–P1 2.283(1), Ru–P2 2.271(2), Li–O2 1.940(1); O1–Ru–O3 162.6(1), N1–Ru–N2 89.3(1), P1–Ru–P2 89.0(5). Only amino and methyne protons of PhGly are shown for clarity.

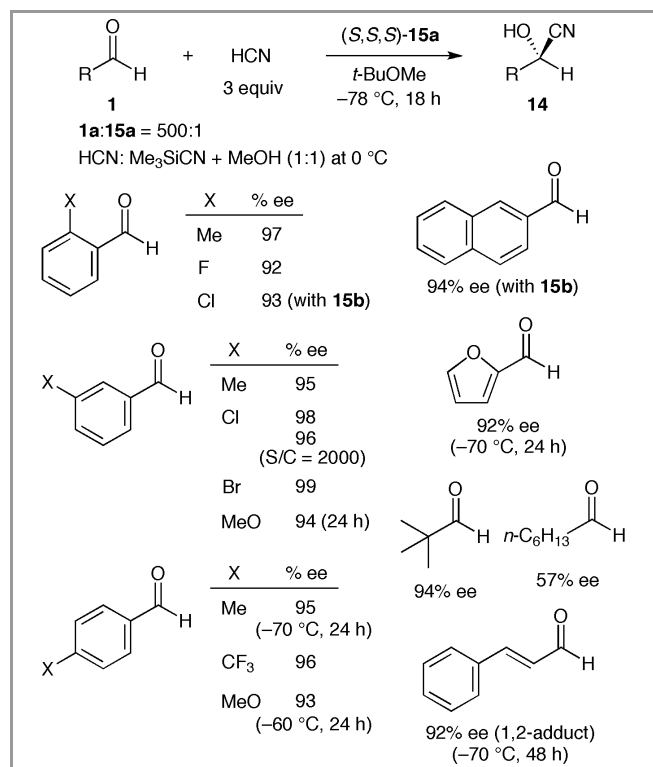
and the Br anion locates between two nitrogen atoms. The NMR analyses suggested that this structure of **15** is maintained in the solution phase.

The catalytic efficiency of the bimetallic complex (*S,S,S*)-**15a** was examined in the hydrocyanation of **1a** (Scheme 9). The reaction with an in-situ prepared HCN at an S/C of 500 was completed in 18 h to afford (*R*)-**14a** in 95% ee. The highest level of catalytic activity and enantioselectivity was achieved. The reaction with isolated HCN prepared and purified as described in the literature⁴³ gave a comparable result in the presence of a small amount of triethylamine (**1a**:amine = 50:1). The amine appeared to catalytically promote the deprotonation from HCN. These results suggest that the reaction is the net hydrocyanation without substantial assistance from silicon compounds when the in-situ prepared HCN is used. The Ru complex **10** or LiCl alone feebly catalyzed the reaction under the regular conditions.



Scheme 9 Asymmetric hydrocyanation of benzaldehyde (**1a**)

A range of aldehydes was cyanated with the bimetallic catalyst (*S,S,S*)-**15a** to yield the cyanohydrins in high ee.⁴² The results are summarized in Scheme 10. In many cases the reaction with an S/C of 500 at –78 °C was completed in 18 h to give the cyanohydrins in >92% ee. The excellent ee value of 99% was observed in the cyanation of 3'-bromobenzaldehyde. The reaction of the 3'-chloro aldehyde with an S/C of 2000 was completed with maintenance of a high level of selectivity. The reaction rate of benzaldehydes with an EDG and 2-furancarbaldehyde was slow, but the complete conversion was achieved in the reaction at higher temperature. A few substrates were cyanated with higher enantioselectivity in the presence of the Br complex **15b** than in the presence of the Cl complex **15a**. Cinnamaldehyde was exclusively converted to the 1,2-adduct in 92% ee. The degree of enantioselectivity and the 1,2/1,4 selectivity were basically the same as those in the cyanosilylation of aldehydes with the (*S,S,S*)-**10**–Li₂CO₃ catalyst system, suggesting that the reaction mechanisms of both cyanations are closely related with each other, while the cyanide sources are different.



Scheme 10 Asymmetric hydrocyanation of aldehydes **1** with Ru•Li combined complexes **15**

4.2 Conjugate Cyanation of α,β -Unsaturated Ketones

As shown in Scheme 10, the 1,2-adduct was the only detectable product in the hydrocyanation of the α,β -unsaturated aldehyde.^{44–47} The regioselectivity was completely reversed in the reaction of α,β -unsaturated ketones. When 1-phenyl-2-buten-1-one (**16a**) and 1.5 equiv of HCN (formed in situ) were reacted with the (S,S,S)-**10**–PhOLi catalyst system at an S/C of 500 at 25 °C for 1 h, the *R* β -cyano ketone (*R*)-**17a** was produced in 89% ee quantitatively (Table 8, entry 1).⁴⁸ No 1,2-adduct was observed. The 1:1 **10**/PhOLi ratio of the catalyst system showed the best efficiency in terms of reactivity and enantioselectivity (entries 1–5). The reactions at 0 °C (5 h) and –20 °C (18 h) achieved higher product ee values of 93% and 97%, respectively (entries 6 and 10). The use of isolated HCN gave the same result (entry 7).⁴⁹ The catalyst system of Ru(phgly)₂(tolbinap) (**18**: TolBINAP = 2,2'-bis(di-4-tolylphosphino)-1,1'-binaphthyl) and PhOLi exhibited a similar efficiency (entry 8). The cyanation with the (S,S,S)-**10**–C₆H₅OLi system at an S/C of 1000 was also completed in 5 h with high enantioselectivity (entry 9).

The (S,S,S)-**10**–PhOLi catalyst system was broadly applied to the asymmetric 1,4-cyanation of α,β -

Table 8 Asymmetric Hydrocyanation of 1-Phenyl-2-buten-1-one (**16a**) with the **10**–PhOLi System^a

Entry	16a/10/ C ₆ H ₅ OLi	Temp (°C)	Time (h)	Yield (%) ^b	Ee (%) ^b
1	500;1;1	25	1	89	89
2	500;0:1	25	1	35	–
3	500:1:0	25	1	<1	n.d.
4	500:1:0.5	25	1	53	90
5	500:1:2	25	1	>99	82
6	500:1:1	0	5	99	93
7 ^c	500:1:1	0	5	99	93
8 ^d	500:1:1	0	5	98	90
9	1000:1:1	0	5	98	90
10	500:1:1	–20	18	96	97

^a Unless otherwise stated, reactions were conducted using **16a** (1.0 mmol) and HCN (1.5 mmol) in *t*-BuOMe (6 mL) with (S,S,S)-**10** (20 mM in THF) and PhOLi (20 mM in THF). HCN was prepared in situ from TMSCN and MeOH in a 1:1 ratio.

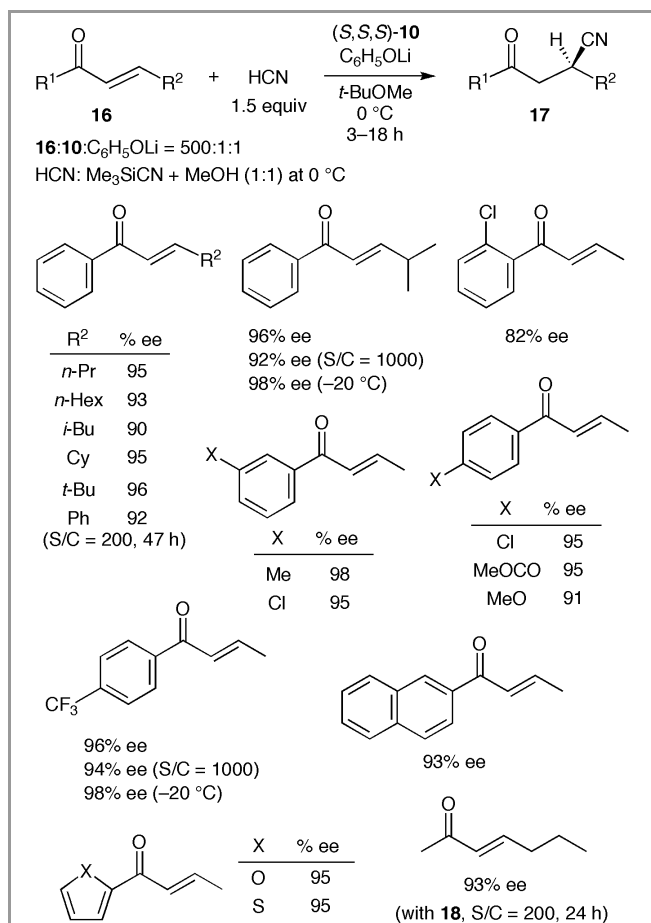
^b Data for (S)-**17a** were determined by chiral GC analysis.

^c Isolated HCN was used.

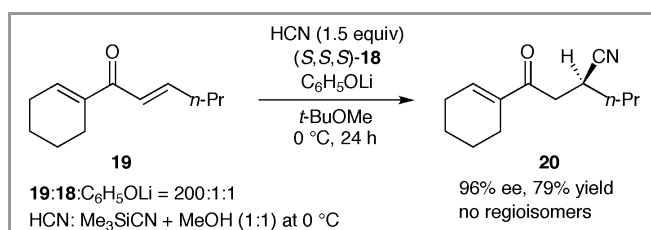
^d Ru[(S)-phgly]₂[(S)-tolbinap] [(S,S,S)-**18**] was used instead of **10**.

unsaturated ketones.⁴⁸ The results are shown in Scheme 11. The phenyl vinyl ketones (R¹ = Ph) with a β -alkyl substituent (R² = alkyl) were quantitatively cyanated (S/C = 500, 0 °C) to give the keto nitriles in 90–96% ee. The size of R² had a minor influence on the reactivity and enantioselectivity. Thus, the reaction of the β -isopropyl ketone with an S/C of 1000 at 0 °C and with an S/C of 500 at –20 °C was completed to afford the product in 92% ee and 98% ee, respectively. The reactivity of chalcone, a β -phenyl ketone, was somewhat lower, but the stereoselectivity was still high.⁵⁰ The phenyl vinyl ketones with an EDG or EWG on the phenyl ring were cyanated with high enantioselectivity of >90%, except in the case of the 2'-chlorophenyl ketone. The 4'-CF₃-substituted ketone reacted with the highest reaction rate. The cyanation of 2'-naphthyl, furyl, and thienyl ketones showed the same level of reactivity and selectivity. The reactivity of 3-hepten-2-one, an aliphatic substrate, was relatively low, but complete conversion was achieved by using the **18**–PhOLi system with an S/C of 200 to give the β -keto nitrile in 93% ee. The sense of enantioselectivity was the same as that of the phenyl ketone **16a**.

When the **18**–PhOLi catalyst system was applied to the hydrocyanation of dialkenyl ketone **19** (S/C = 200, 0 °C), the mono-cyano ketone **20** was obtained in 96% ee (Scheme 12). Neither a regioisomer nor a di-cyano ketone was observed. This selectivity was expected to be useful for the synthesis of multi-functionalized chiral ketones.



Scheme 11 Asymmetric hydrocyanation of α,β -unsaturated ketones **16** into β -cyano ketones **17**



Scheme 12 Regioselective cyanation of dienone **19**

The robustness of the Ru complex **10** enabled us to recover it with silica-gel column chromatography after the reaction.⁴⁸ The recovered **10** with an addition of PhOLi showed catalytic efficiency comparable to that of the fresh catalyst. Thus, the complex **10** could be used five times in the cyanation with an initial S/C of 500, as shown in Table 9. Five different unsaturated ketones were converted successfully by using the same Ru complex (total TON = 2500).

4.3 Strecker-type Reaction

Asymmetric hydrocyanation of imines (Strecker-type reaction) producing optically active α -amino nitriles, which are direct precursors of α -amino acids, is the indispensable synthetic procedure.^{1,51,52} The wide substrate-applicability is required for the synthesis of

Table 9 Recycled Use of **10** in the Hydrocyanation of **16**^a

Run number ^b	Ar	Time (h)	Yield (%) ^c	Ee (%) ^d
1	4-CH ₃ OCOC ₆ H ₄	3	96	93
2	2-NaPh	12	96	90
3	3-ClC ₆ H ₄	5	98	96
4	4-ClC ₆ H ₄	3	95	95
5 ^e	3-CH ₃ OC ₆ H ₄	12	99	96

^a Reactions were conducted using **16** (8.2 mmol) and HCN (11.8 mmol) in *t*-BuOMe (48 mL) at 0 °C with a solid (S,S,S)-**10** and PhOLi (50 mM in THF). **16**/**10**/PhOLi = 1:1:1 (initial). HCN was prepared in situ from TMSiCN and MeOH in a 1:1 ratio.

^b Number of times the catalyst was used.

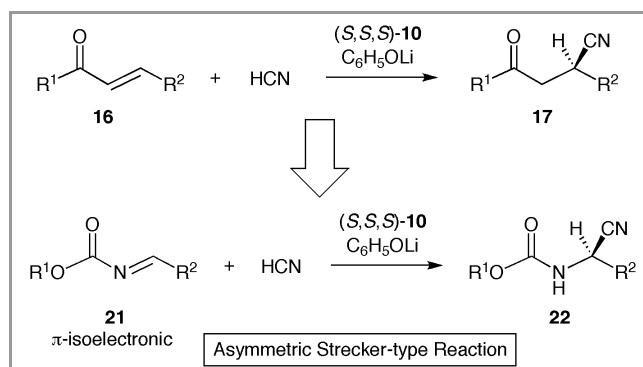
^c Isolated yield.

^d Determined by chiral GC or HPLC analysis.

^e Reaction using **16** (3.2 mmol) and HCN (4.8 mmol) in *t*-BuOMe (19 mL).

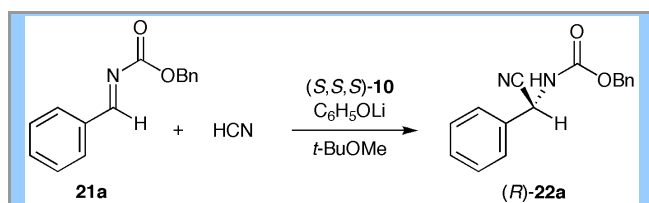
a variety of the proteinogenic and the non-proteinogenic amino acids. When two enantiomers of the catalysts are available, the natural type and the unnatural type of amino acids can be selectively synthesized.

We have revealed that the **10**–PhOLi system efficiently catalyzed asymmetric conjugate addition of HCN to α,β -unsaturated ketones **16** under mild temperature conditions of –20 °C to 0 °C. We therefore expected that the π -isoelectronic *N*-alkoxycarbonyl aldimines **21** could be cyanated with high reactivity and enantioselectivity by using the same catalyst system under the mild conditions (Scheme 13).



Scheme 13 Asymmetric hydrocyanation of α,β -unsaturated ketones and *N*-protected imines

The cyanation of *N*-benzyloxycarbonyl (Cbz) imine **21a** derived from benzaldehyde according to the reported method⁵³ was selected as the typical reaction to optimize the reaction conditions (Table 10). The aldimine **21a** and a 3 equiv of HCN (in situ) smoothly

Table 10 Asymmetric Hydrocyanation of *N*-Cbz Aldimine **21a** with the **10**-PhOLi System^a

Entry	S/C	Temp (°C)	Time (h)	Yield (%) ^b	Ee (%) ^c
1	500	0	0.5	99	97
2	500	-20	0.5	98	98
3	500	25	0.5	98	89
4 ^d	500	0	0.5	98	96
5 ^e	5000	0	2	95	96

^a Unless otherwise stated, reactions were conducted using **21a** (1.0 mmol, 0.15 M) and HCN (3.0 mmol) in *t*-BuOMe with a solid **(S,S,S)-10** and PhOLi (100 mM in THF). **10**:PhOLi = 1:1. HCN was prepared in situ from TMSCN and MeOH in a 1:1 ratio.

^b Isolated yield of **22a**.

^c Determined by chiral HPLC analysis.

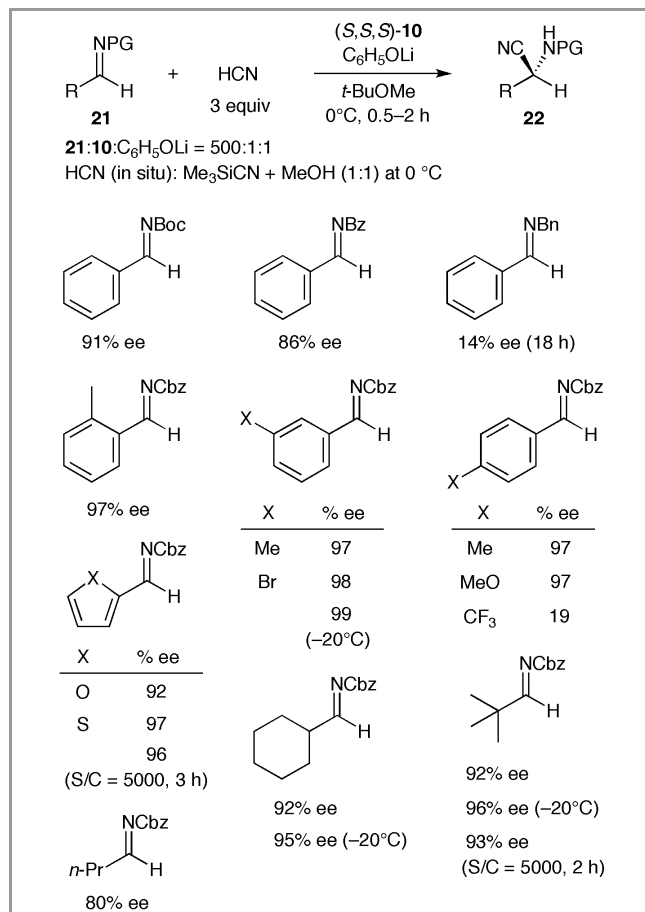
^d Isolated HCN was used.

^e Reaction using 10 mmol of **21a**.

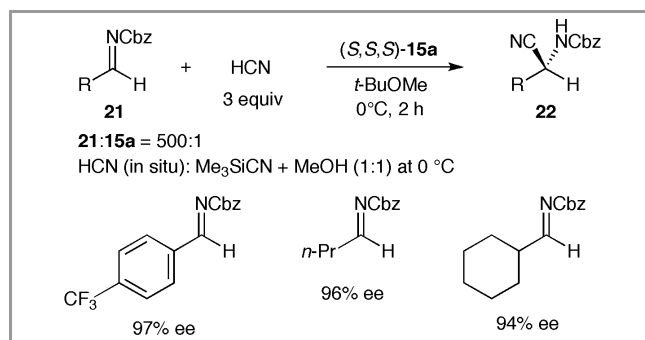
reacted in the presence of the **(S,S,S)-10**-PhOLi catalyst system with an S/C of 500 at 0 °C to afford the *R* amino nitrile **(R)-22a** in 97% ee quantitatively in 30 min (entry 1).⁵⁴ The reaction at -20 °C also completed in 30 min to give **22a** in 98% ee (entry 2). The high ee value of 89% was obtained even at 25 °C (entry 3). The use of isolated HCN gave a comparable result to that with the in situ-formed HCN (entry 4). The high catalytic efficiency of the **10**-PhOLi system achieved complete conversion in the cyanation with an S/C of 5000 at 0 °C in 2 h to yield **22a** in 96% ee (entry 5).

The Strecker-type reaction with the **10**-PhOLi catalyst system was applied to a variety of *N*-protected aldimines (Scheme 14).⁵⁴ As we expected, *N*-tert-butoxycarbonyl (Boc) and *N*-benzoyl (Bz) imines were cyanated with a high level of enantioselectivity. The reactivity and selectivity were significantly decreased in the reaction of the *N*-benzyl (Bn) imine. Various aromatic, heteroaromatic, and aliphatic *N*-Cbz aldimines were cyanated with high reactivity and enantioselectivity. An excellent ee value of 99% was obtained in the reaction of 3'-bromo imine at -20 °C. The reaction of the sterically hindered *tert*-butyl imine with an S/C of 5000 at 0 °C was completed in 2 h. The 4'-CF₃-phenyl imine and *n*-propyl imine were reacted with low to moderate enantioselectivity, possibly due to the competitive base-catalyzed achiral cyanation.

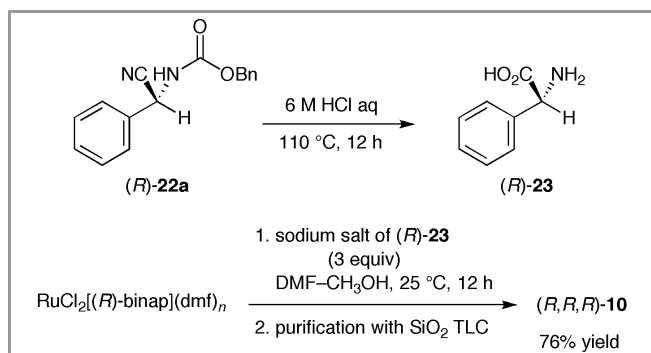
This problem was solved by the use of the less basic Ru•Li bimetallic catalyst **15a** (Scheme 15). The ee values of the products were significantly increased: for 4'-CF₃-phenyl imine, from 19% to 97%; for *n*-propyl imine, from 80% to 96%; and for cyclohexyl

**Scheme 14** Asymmetric hydrocyanation of *N*-protected aldimines **21** with the **10**-PhOLi system

imine; from 92% to 94%. In particular, the excellent enantioselectivity in the reaction of *n*-alkyl imine was noteworthy.⁵⁵

**Scheme 15** Asymmetric hydrocyanation of *N*-Cbz aldimines **21** with the Ru•Li combined complex **15a**

The cyanated product **(R)-22a** in 97% ee was hydrolyzed under the acidic conditions at 110 °C to give *(R)*-phenylglycine (**(R)-23**) in 96% ee and 94% yield (Scheme 16). The *R* product in 96% ee was applied for the synthesis of Ru[(*R*)-phgly]₂[(*R*)-binap] (**(R,R,R)-10**). The diastereomeric byproducts were easily removed with a silica-gel preparative TLC to afford pure **(R,R,R)-10**.

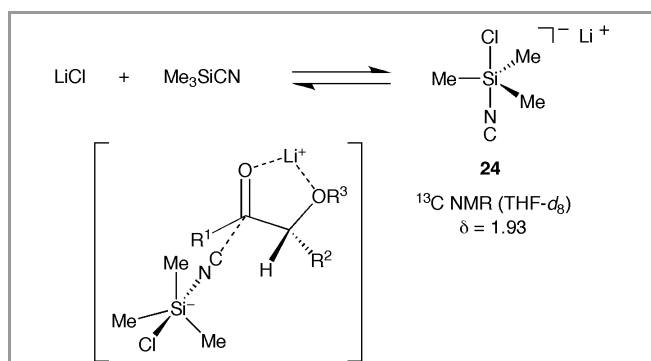


Scheme 16 Preparation of (R)-phenylglycine ((R)-23) and the application to formation of (R,R,R)-10

5 Mechanistic Considerations for Cyanosilylation of Aldehydes and Ketones

5.1 Achiral Reaction Catalyzed by LiCl

The reaction of carbonyl compounds and TMSCN was efficiently catalyzed by LiCl as discussed in Section 2. LiCl is an inorganic salt, but it is soluble in several organic polar solvents and acts as a Cl anion source.⁵⁶ Therefore, LiCl probably acts as a nucleophilic (Lewis basic) catalyst to activate the reagent TMSCN. The ¹³C NMR (THF-*d*₈) measurement suggested that LiCl reacted with TMSCN (CH₃; $\delta = -2.07$) to form Li[Me₃SiCl(NC)] (**24**) showing a CH₃ signal at δ 1.93 (Scheme 17).⁶ This NMR behavior was consistent with the observation in the measurement of a mixture of 18-crown-6, KCN, and TMSCN, indicating the CH₃ signal at δ 1.91, which corresponded to the pentavalent [Me₃Si(NC)₂][−] reported in the literature.⁵⁷ No CH₃ signal of TMSCl at δ 3.20 was detected. The nucleophilic property of the reactive species was confirmed by Hammett experiments⁵⁸ for the cyanosilylation of 4'-substituted benzaldehydes catalyzed by LiCl. Thus, the relative rates toward the reaction of benzaldehyde were plotted against the σ_p constant, showing a linear relationship with a ρ value of +1.24.



Scheme 17 Plausible active species **24** and the reaction pathway in the cyanosilylation of α -alkoxy ketones catalyzed by LiCl

The high *anti*-selectivity in the cyanation of 2-benzyloxypropiphenone (**8a**) described in Scheme 2 of Section 2 was interpreted by using a chelation intermediate as shown in Scheme 17.^{12,13} This observation strongly suggested that LiCl also behaved as a source of Lewis acidic Li cation to activate the carbonyl moiety of substrates.

5.2 Asymmetric Reaction with the Chiral Ru–Li Combined Catalyst

The combined system of Ru(phgly)₂(binap) (**10**) and PhOLi showed high catalytic activity and enantioselectivity in the cyanation of α -keto esters, as mentioned in Section 3.3. The Ru complex **10** alone exhibited feeble catalytic activity. ESI mass-spectroscopic analysis of a mixture of **10** (*m/z* 1024), PhOLi, and TMSCN in a 1:1:10 ratio showed prominent signals centered at *m/z* 1031, which correspond to the Ru–Li combined species [10•Li]⁺.³⁰ The same signals were detected in the measurement of the **10**–Li₂CO₃ system.¹⁸ ¹H and ¹³C NMR measurements of this 1:1:10 mixture suggested that PhO[−] quantitatively reacted with TMSCN to give TMSOPh and CN[−] (Figure 4, (1)-(a) and (2)-(a)). The pentacoordinate Si species [Me₃Si(NC)₂][−] was not observed, while an excess

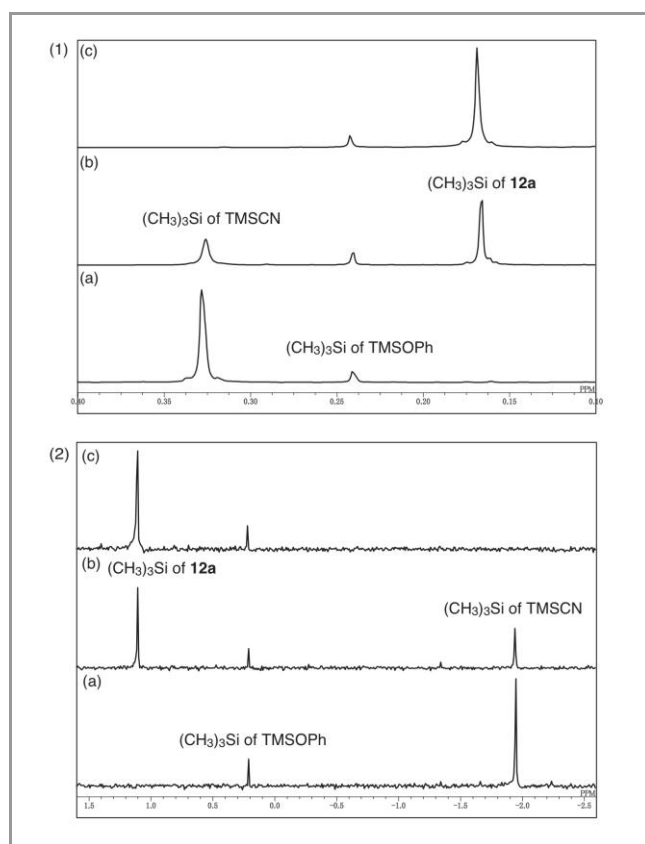
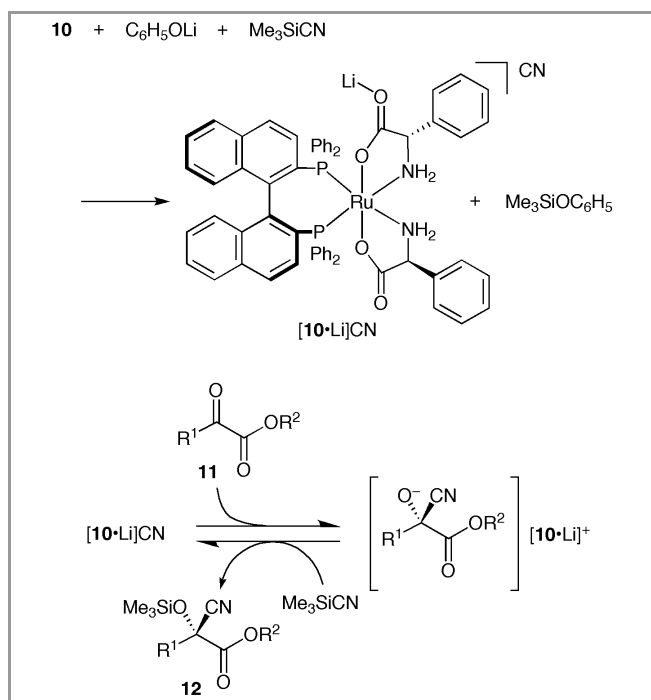


Figure 4 ¹H NMR (1) and ¹³C NMR (2) spectra: (a) a 1:1:10 mixture of (S,S,S)-10, PhOLi, and TMSCN; (b) a 1:1:10:3 mixture of (S,S,S)-10, PhOLi, TMSCN, and 11a; (c) a 1:1:10:10 mixture of (S,S,S)-10, PhOLi, TMSCN, and 11a

amount of TMSCN existed in this mixture. An α -keto ester **11a** smoothly reacted in this system to give the silylated cyanohydrin **12a** (Figure 4, (1)-(b) and (2)-(b)). When a sufficient amount of **11a** was added to this mixture, the signal of TMSCN disappeared with the increase of the cyanated product **12a** (Figure 4, (1)-(c) and (2)-(c)). The peak of TMSOPh remained intact during this procedure.

Scheme 18 illustrates the plausible reaction pathway for the cyanosilylation of α -keto esters **11** catalyzed by the Ru complex **10**–PhOLi system, according to the above-mentioned experimental data. Nonproductive and minor pathways are not considered here. The complex **10**, PhOLi, and TMSCN afford the bimetallic complex $[\mathbf{10}\cdot\text{Li}]\text{CN}$ accompanied by TMSOPh. The structure of $[\mathbf{10}\cdot\text{Li}]^+$ is thought to be the same as that of $[\text{Li}\{\text{Ru}(\text{phgly})_2(\text{binap})\}]\text{Br}$ (**15b**; see Figure 3).⁴² When LiCl is used instead of PhOLi, $[\text{Me}_3\text{SiCl}(\text{NC})]^-$ is a possible counter anion. The keto ester **11** smoothly reacts with $[\mathbf{10}\cdot\text{Li}]\text{CN}$, in which $[\mathbf{10}\cdot\text{Li}]^+$ effectively acts as a chiral Lewis acid, affording the cyanated anion with $[\mathbf{10}\cdot\text{Li}]^+$. The cyanated anion spontaneously reacts with TMSCN to give the silylated cyanohydrin **12** with the regeneration of the active species $[\mathbf{10}\cdot\text{Li}]\text{CN}$. This proposed pathway is consistent with the result that the **10**–Li compound system catalyzes the hydrocyanation with high reactivity and enantioselectivity as described in Section 4.



Scheme 18 Plausible mechanism for cyanosilylation of α -keto esters **11**

6 Conclusion

LiCl, a simple Li salt, shows exceptionally high catalytic activity in the cyanosilylation of aldehydes and functionalized ketones with hetero-atom groups. The reaction with a substrate-to-catalyst molar ratio (S/C) of 100,000 at about 25 °C completes within 48 h in the best cases. The reactivity of unfunctionalized acetophenone is relatively low, but the cyanation with an S/C of 100 quantitatively affords the desired product in 3 h.

The combined catalyst systems consisting of $\text{Ru}[(S)\text{-phgly}]_2[(S,S,S)\text{-10}]$ and Li compounds exhibit excellent reactivity and enantioselectivity in the cyanosilylation and hydrocyanation of aldehydes, α -keto esters, α,β -unsaturated ketones, and *N*-protected aldimines. The Ru complex **10** is considered to act as the “chiral template” for modification of Li cation. The chiral structure of the catalyst system is easily constructed by complexation of the PhGly and BINAP ligands on the Ru center.

The reaction of aldehydes and TMSCN (cyanosilylation) is catalyzed by the **10**– Li_2CO_3 system in ether solvents to afford the silylated cyanohydrins in up to 98% ee. The cyanosilylations of benzaldehyde (**1a**) with an S/C of 10,000 at –78 °C and 100,000 at –40 °C are completed in 12 h (97% ee) and 24 h (90% ee), respectively. The high catalytic activity of this system is notable, although the low reaction temperature is a disadvantage from a practical viewpoint. When the **10**–PhOLi catalyst system is utilized at –60 °C (S/C = 1000), a series of α -keto esters is cyanated to produce the tertiary cyanohydrin derivatives with multi functionalities in up to 99% ee quantitatively. The transformation with an S/C of 10,000 at –50 °C also completes with high enantioselectivity. This is the first example of the highly enantioselective cyanosilylation of α -keto esters to our knowledge.

HCN is a toxic compound, but it is known to be a useful and practical synthetic material. Asymmetric reaction of aldehydes and HCN (hydrocyanation) is achieved by using the preformed catalyst $[\text{Li}\{\text{Ru}[(S)\text{-phgly}]_2[(S,S,S)\text{-15a}]\}\text{Cl}]$ ((*S,S,S*)-**15a**) with an S/C as high as 2000 at –78 °C to afford the cyanohydrins in up to 99% ee. The degree and sense of enantioselectivity are the same as those in the cyanosilylation of aldehydes. The wide scope of substrates for this hydrocyanation is noteworthy, although the low reaction temperature is a drawback to be improved.

Enantioselective conjugate cyanation of α,β -unsaturated ketones into the β -cyano ketones is also catalyzed by the **10**–PhOLi system. The reaction is conducted with an S/C of 200 to 1000 at –20 °C to 0 °C to yield the chiral nitriles in 82% ee to 98% ee.

Significantly low reaction temperature is not required in this reaction. No 1,2-addition products are observed under the regular reaction conditions. The Ru complex **10** is so robust that it can be recovered by column chromatography. Therefore, it is reusable for this reaction, achieving a total turnover number of 2500 (S/C = 500, 5 times).

The catalyst system **10**–PhOLi and **15a** are effective for the asymmetric hydrocyanation of *N*-benzyloxycarbonyl aldimines (Strecker-type reaction). The reaction is carried out with an S/C of 500 to 5000 at –20 °C to 0 °C, resulting in the amino nitriles in 92% ee and 99% ee quantitatively. This transformation is widely applied to the primary, secondary, and tertiary alkyl imines as well as the aryl and heteroaryl substrates. Therefore, this system is among the best catalysts for the hydrocyanation of imines in terms of reactivity, enantioselectivity, and the substrate scope to our knowledge.

A reaction pathway of the cyanosilylation of α -keto esters is proposed based on the spectral analysis data. The nature of active species could depend on the Lewis basicity (or nucleophilicity) of the Li compound. Thus, TMSiCl and LiCl form the pentavalent Si species $\text{Li}[\text{Me}_3\text{SiCl}(\text{NC})]$, while the reaction of TMSiCl and PhOLi affords TMSOPh and LiCN. The cyanosilylation with the **10**–PhOLi system is proposed to proceed with the Ru–Li combined complex $[\text{Li}\{\text{Ru}(\text{phgly})_2(\text{binap})\}]\text{CN}$ as the active catalytic species.

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Biographical Sketches

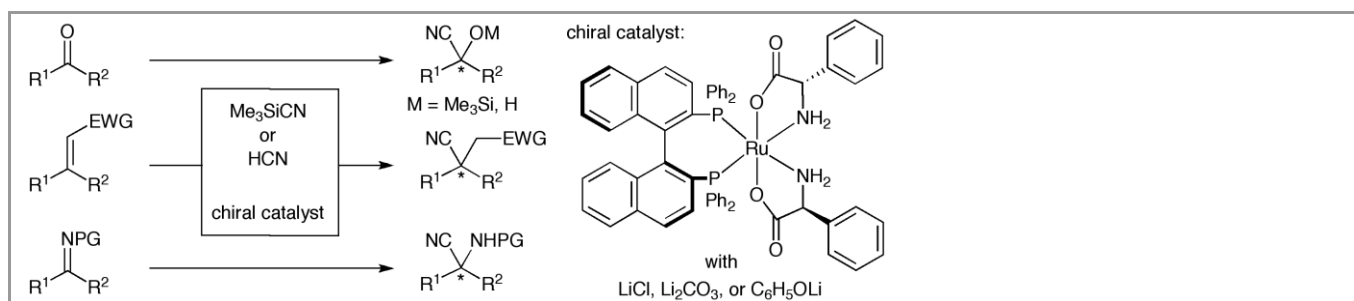


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Graphical Abstract