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Enantioselective Cyanosilylation of Ketones with Amino Acid/BINAP/Ruthenium(II)-Lithium Phenoxide Catalyst Systems

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Abstract: Enantioselective reactions of simple ketones, α,α- and β,β-dialkoxy ketones, and α-alkoxy ketones with trimethylsilyl cyanide catalyzed by the bimetallic systems of amino acid/BINAP/ruthenium(II) complexes and lithium phenoxide have been studied [BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]. The $Ru(PhGly)_2$(BINAP)-lithium phenoxide system showed high enantioselectivity for the reaction of acetophenone derivatives to afford the cyanated products in up to 90% *ee* [PhGly = phenylglycinate]. For the cyanosilylation of dialkoxy ketones and α-alkoxy ketones, the $Ru(t\text{-Leu})_2$(BINAP)-lithium phenoxide system exhibited the best catalyst performance to produce the cyanohydrin derivatives in up to 99% *ee* and 98% *ee*, respectively [*t*-Leu = *tert*-leucinate]. The excellent catalytic activity resulted in complete conversion in the reaction with a substrate-to-catalyst molar ratio (S/C) of 10,000 in the best cases.

Keywords: asymmetric catalysis; bimetallic catalysts; cyanosilylation; enantioselectivity; ketones; lithium; ruthenium

Introduction

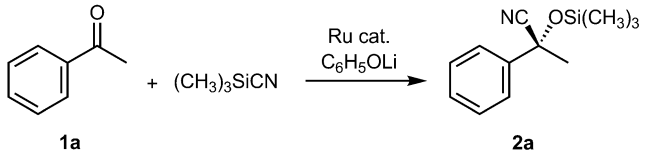
The enantioselective reaction of prochiral ketones and $(CH_3)_3SiCN$ (cyanosilylation) is among the most direct and reliable methods to produce optically active tertiary cyanohydrin derivatives, which are versatile intermediates for the synthesis of both natural and artificial biologically active compounds.[1] Many chiral organometallic catalysts and organocatalysts have been applied to this important transformation.[2–6]

Three major requirements for the development of an efficient asymmetric cyanosilylation of ketones are as follows: (i) high catalytic activity (low catalyst loading), (ii) high enantioselectivity, and (iii) a wide range of applications for substrates. Regarding the first item, the substrate-to-catalyst molar ratio (S/C), an indication of catalytic activity, of the reported reactions was usually in the range of 5–200. An exception was the use of the chiral salen/Ti(IV) complex, which realized the reaction of 4′-methylacetophenone with an S/C of 1000 (room temperature, 4 days) to give the silylated cyanohydrin in 52% *ee*.[2d] A salen/Al(III) complex and an *N*-oxide (co-catalyst) system also cyanated acetophenone (S/C = 1000, −20 °C, 16 days, 99% yield) and 3-methyl-2-butanone (S/C = 1000, −20 °C, 36 h, 80% yield) to afford the chiral products in 94% *ee* and 90% *ee*, respectively.[4b]

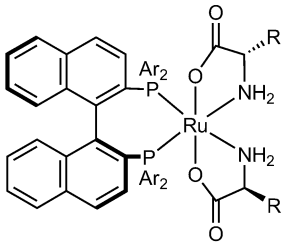
With respect to the second requirement, several catalysts with well-designed chiral structures have achieved high enantioselectivity in recent years.[1–6] The enantioselectivity of 98% obtained in the cyanation of 2′-methylacetophenone with a chiral thiourea catalyst (S/C = 20, −78 °C, 36 h, 96% yield)[6d] and the reaction of phenylglyoxal diethyl acetal catalyzed by a *Cinchona* alkaloid derivative (S/C = 50, −50 °C, 18 h, 96% yield)[6a] are noteworthy.

Concerning the third requirement, ketone compounds are roughly classified into simple (unfunctionalized) ketones and functionalized ones. Alkyl aryl ketones and dialkyl ketones are typical examples of simple ketones. Functionalized ketones have a wide variation in their structures. Among them, α-heterosubstituted ketones have features significantly different from those of simple ketones with respect to enantioselectivity, because α-heterosubstituted ketones tend to behave as bidentate ligands, forming five-membered chelate structures with catalyst metals or metal cations. This behavior notably influences the reaction mechanism and the mode of enantioface se-

Table 1. Asymmetric cyanosilylation of acetophenone (**1a**).[a]



1a **2a**



(*S*,*S*,*S*)-**3**

a: Ar = R = C_6H_5 **c**: Ar = C_6H_5, R = $CH_2CH(CH_3)_2$
b: Ar = 3,5-$(CH_3)_2C_6H_3$, R = C_6H_5 **d**: Ar = C_6H_5, R = $C(CH_3)_3$

Entry	**3**	**1a**:**3**:Li[b]	Temp. [°C]	Time [h]	Yield [%][c]	*ee* [%][c]
1	**3a**	1000:1:1	−40	6	>99	86
2	**3a**	1000:1:0.5	−40	6	97	86
3	**3a**	1000:1:2	−40	6	>99	85
4	**3a**	1000:1:3	−40	6	93	73
5	**3a**	1000:1:1	−20	2	>99	80
6	**3a**	1000:1:1	0	1	>99	69
7	**3a**	1000:1:1	−60	18	97	90
8	**3a**	3000:1:1	−40	18	99	84
9	**3b**	1000:1:1	−40	6	98	89
10	**3c**	1000:1:1	−40	6	92	51
11	**3d**	1000:1:1	−40	6	36	1

[a] The reactions were conducted using **1a** (5.0 mmol, 0.42 M) and 1.2 equiv. of $(CH_3)_3SiCN$ in *t*-$C_4H_9OCH_3$ with Ru complex (*S*,*S*,*S*)-**3** and C_6H_5OLi.
[b] **1a**:**3**:C_6H_5OLi molar ratio.
[c] Determined by chiral GC analysis.

lection. Therefore, only a limited number of chiral catalysts has achieved high enantioselectivity in the cyanosilylation of both simple and functionalized ketones. Catalyst systems combining a chiral oxazaborolidinium ion and a phosphine oxide are representative examples that catalyze the cyanosilylation of 4′-nitroacetophenone (S/C = 10, 45 °C, 10 days, 83% yield) and methylglyoxal dimethyl acetal (S/C = 10, 25 °C, 2 days, 92% yield) to give both cyanated products in 96% *ee*.[4c]

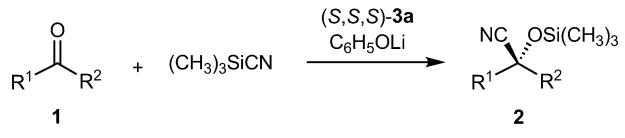
We recently reported the asymmetric cyanosilylation of aldehydes[7] and α-keto esters[8] with our original [Ru(PhGly)$_2$(BINAP)]-Li_2CO_3 or C_6H_5OLi catalyst system [PhGly = phenylglycinate, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl: the structures are given in the Scheme of Table 1]. For example, the reaction of α-keto esters, a class of functionalized ketones, was completed with an S/C of 1000 at −60 °C, and with an S/C of 10,000 at −50 °C in 18 h in both cases.[8] A series of aromatic, hetero-aromatic, aliphatic, and α,β-unsaturated α-keto esters was converted to the silylated cyanohydrins in up to 99% *ee*. The spectroscopic studies suggested that a novel bimetallic species [Li{Ru(PhGly)$_2$(BINAP)}]CN, in which [Li{Ru(PhGly)$_2$(BINAP)}]$^+$ acts as a chiral Lewis acid, efficiently catalyzes the reaction. We herein describe our studies on the enantioselective cyanosilylation of several simple and heterosubstituted ketones catalyzed by bimetallic systems consisting of amino acid/BINAP/Ru(II) complexes and C_6H_5OLi for achieving high catalytic activity, enantioselectivity, and amenable to a wider range of substrates.

Results and Discussion

Simple Ketones

We selected acetophenone (**1a**), a simple aromatic ketone, as the standard substrate to optimize the catalyst structure and the reaction conditions (Table 1). [Ru{(*S*)-PhGly}$_2${(*S*)-BINAP}] [(*S*,*S*,*S*)-**3a**] was prepared in two steps from commercial [$RuCl_2(\eta^6$-$C_6H_6)]_2$ according to the method described in our previous report.[7] Ru complexes **3b**–**3d** were prepared with basically the same methods (see the Experimental Section). The reaction of **1a** (620 mg, 5.2 mmol, 0.42 M) and 1.2 equiv. of $(CH_3)_3SiCN$ with (*S*,*S*,*S*)-**3a** (5,1 mg, 5.0 μmol, S/C = 1000) and C_6H_5OLi (100 mM in THF, 50 μL, 5.0 μmol) in *tert*-$C_4H_9OCH_3$ at −40 °C was carried out for 6 h to produce the *R* silylated cyanohydrin, (*R*)-**2a**, in 86% *ee* quantitatively (Table 1, entry 1). A 1:1 ratio of **3a** and C_6H_5OLi gave the best result in terms of reactivity and enantioselectivity. When a 2:1 **3a**-C_6H_5OLi system was used as a catalyst, the reaction rate was slightly slowed (entry 2). The enantioselectivity was decreased with an increase in the proportion of C_6H_5OLi in the catalyst system (entries 3 and 4). The higher *ee* value of **2a** was obtained in the reaction at lower temperature, but a longer reaction period was required (entries 1, 5–7). The high catalytic activity of the **3a**-C_6H_5OLi system allowed quantitative conversion in the reaction with an S/C of 3000 at −40 °C in 18 h (entry 8). The highest turnover number for this reaction so far reported was achieved. Use of **3b** with a sterically more demanding XylBINAP[9] instead of BINAP slightly increased the enantioselectivity at the cost of the reactivity (entries 1 and 9). The structure of the amino acid moiety in the Ru complex **3** significantly influenced the enantioselectivity as well as the catalytic activity. Thus, Ru(Leu)$_2$(BINAP) (**3c**) and Ru(*t*-Leu)$_2$(BINAP) (**3d**) coupled with C_6H_5OLi catalyzed the cyanation of **1a** under the typical conditions to give **2a** in only 51% *ee* (92% yield) and 1% *ee* (36% yield), respectively (entries 10 and 11).[9]

Table 2. Asymmetric cyanosilylation of simple ketones **1**.[a]



1 **2**

a: $R^1 = C_6H_5$, $R^2 = CH_3$
b: $R^1 = 3\text{-}CH_3C_6H_4$, $R^2 = CH_3$
c: $R^1 = 4\text{-}CH_3C_6H_4$, $R^2 = CH_3$
d: $R^1 = 2\text{-}ClC_6H_4$, $R^2 = CH_3$
e: $R^1 = 3\text{-}ClC_6H_4$, $R^2 = CH_3$
f: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = CH_3$
g: $R^1 = 3\text{-}CH_3OC_6H_4$, $R^2 = CH_3$
h: $R^1 = 4\text{-}CH_3OC_6H_4$, $R^2 = CH_3$
i: $R^1 = C_6H_5$, $R^2 = i\text{-}C_3H_7$
j: $R^1 = cyclo\text{-}C_6H_{11}$, $R^2 = CH_3$
k: $R^1 = n\text{-}C_5H_{11}$, $R^2 = CH_3$

Entry	1	3	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	**3a**	−40	6	99	86
2	**1a**	**3a**	−60	18	97	90
3	**1b**	**3a**	−40	8	91	88
4	**1c**	**3a**	−40	24	97	83
5	**1d**	**3a**	−60	4	99	82
6	**1e**	**3a**	−60	4	99	87
7	**1f**	**3a**	−60	7	99	86
8	**1g**	**3a**	−40	6	93	83
9	**1h**	**3a**	−40	6	92	80
10	**1i**	**3a**	−40	18	99	53
11	**1i**	**3b**	−40	18	96	60
12	**1i**	**3d**	−40	18	85	15
13	**1j**	**3a**	−40	24	97	50
14	**1j**	**3b**	−40	24	91	63
15	**1j**	**3d**	−40	24	89	7
16	**1k**	**3a**	−40	10	99	32
17	**1k**	**3b**	−40	10	99	40
18	**1k**	**3d**	−40	10	99	−18[d]

[a] The reactions were conducted using **1** (5.0 mmol, 0.42 M) and 1.2 equiv. of $(CH_3)_3SiCN$ in $t\text{-}C_4H_9OCH_3$ with Ru complex (*S*,*S*,*S*)-**3** and C_6H_5OLi. **1**:**3**:C_6H_5OLi = 1000:1:1.
[b] Isolated yield.
[c] Determined by chiral GC analysis.
[d] (*S*)-**2a** was the major product.

We have previously reported that the **3a**-Li compound systems efficiently catalyze the asymmetric hydrocyanation of aldehydes,[10] α,β-unsaturated ketones (conjugate addition),[11] and *N*-protected aldimines.[12] However, the reaction of **1a** and 3 equiv. of HCN prepared *in situ* by mixing $(CH_3)_3SiCN$ and CH_3OH with the **3a**-C_6H_5OLi catalyst system (S/C = 1000, 0 °C, 48 h) gave the cyanohydrin in only 59% yield and 2% *ee*.

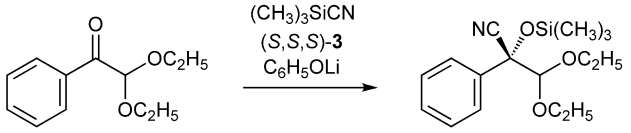
The **3**-C_6H_5OLi catalyst system was applied to the asymmetric cyanosilylation of a series of simple ketones. The results are summarized in Table 2. All reactions were conducted at −60 °C to −40 °C with an S/C of 1000. The highest *ee* value of 90% was obtained in the cyanation of **1a** at −60 °C catalyzed by the **3a**-C_6H_5OLi system (entry 2). Acetophenones with electron-donating CH_3 and CH_3O groups at the 3′ and 4′ positions, **1b**, **1c**, **1g**, and **1h**, were converted to the corresponding silylated cyanohydrins in 80–88% *ee* (entries 3, 4, 8, and 9). The reactions of 2′-, 3′-, and 4′-chloroacetophenones, **1d**–**1f**, at −60 °C were completed in 4–7 h to give the products in 82–87% *ee* (entries 5–7). The enantioselectivity of the cyanation of sterically hindered isobutyrophenone (**1i**) with the **3a**-C_6H_5OLi catalyst system was significantly lower than that of the reaction of **1a** (entries 1 and 10). Use of the **3b**-C_6H_5OLi system slightly increased the *ee* value of **2i** to 60%, but the number was down to 15% with the **3d**-C_6H_5OLi system (entries 11 and 12).

Simple aliphatic ketones are difficult substrates to cyanate with high enantioselectivity, because the two similar alkyl groups connected at each side of the carbonyl moiety are hard to differentiate. Thus, the *ee* value of 63% obtained in the reaction of cyclohexyl methyl ketone (**1j**) with the **3b**-C_6H_5OLi catalyst system was the highest (Table 2, entries 13–15). 2-Heptanone (**1k**), a primary alkyl ketone, was converted with the **3a**-C_6H_5OLi and **3b**-C_6H_5OLi systems to **2k** in 32% *ee* and 40% *ee*, respectively (entries 16 and 17). The sense of enantioselection was reversed in the reaction by using the **3d**-C_6H_5OLi system (entry 18). The bifunctional chiral Ti(IV) complexes and a chiral salen/Al(III)-*N*-oxide system were reported to catalyze the cyanation of secondary alkyl methyl ketones with ≥ 90% enantioselectivity.[2c,4b]

α,α- and β,β-Dialkoxy Ketones

We applied the **3**-C_6H_5OLi catalyst systems to the asymmetric cyanosilylation of α,α-dialkoxy ketones, which are one of the representative classes of α-heterosubstituted ketones. Phenylglyoxal diethyl acetal (**4a**), an aromatic α,α-dialkoxy ketone, was the substrate of choice to examine the cyanation conditions (Table 3). The reaction of **4a** (624 mg, 3.0 mmol, 0.3 M) and a 2 equiv. of $(CH_3)_3SiCN$ with (*S*,*S*,*S*)-**3a** (3.0 μmol, S/C = 1000) and C_6H_5OLi (3.0 μmol) in *tert*-$C_4H_9OCH_3$ at −40 °C was completed in 1 h to produce the silylated cyanohydrin (*R*)-**5a** in 92% *ee* (entry 1). The sense of enantioselection was the same as that in the reaction of aromatic simple ketones (see Table 2). The *ee* value of product **5a** was much higher than that of the unfunctionalized silylated cyanohydrin **2i**, which has structural similarity to **5a** (see Table 2, entry 10). The bulkiness of the substituents (R) of the amino acid ligands on **3** seemed to significantly affect the enantioselectivity. Thus, the reactions with the $Ru(Leu)_2$ complex **3c** [R = $CH_2CH(CH_3)_2$] and the $Ru(t\text{-}Leu)_2$ complex **3d** [R = $C(CH_3)_3$] afforded the product **5a** in 85% *ee* and 93% *ee*, respectively (entries 2 and 3). Interestingly, the excellent *ee* value of 98% was achieved when a 2.5:1 **3d**-C_6H_5OLi system was used as catalyst (entry 4). In the absence of the Li compound, little conversion was observed

Table 3. Asymmetric cyanosilylation of phenylglyoxal diethyl acetal (**4a**).[a]



4a **5a**

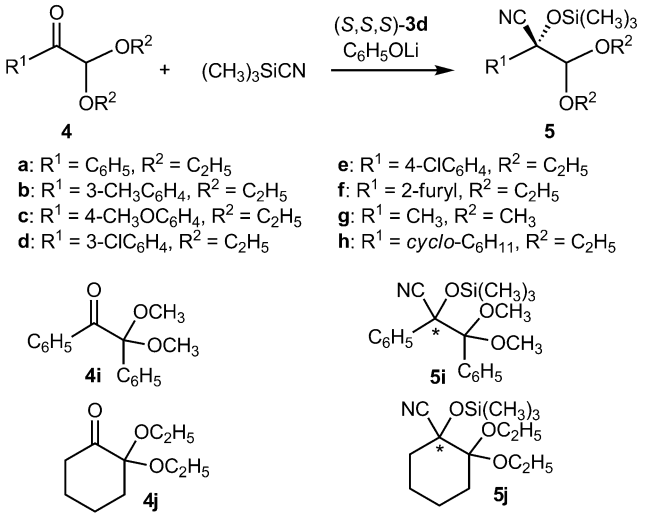
Entry	**3**	**4a**:**3**:Li[b]	Temp. [°C]	Yield [%][c]	*ee* [%][c]
1	**3a**	1000:1:1	−40	>99	92
2	**3c**	1000:1:1	−40	>99	85
3	**3d**	1000:1:1	−40	>99	93
4	**3d**	1000:1:0.4	−40	>99	98
5	**3d**	1000:1:0	−40	<1	nd[d]
6[e]	**3d**	5000:1:0.4	−40	>99[f]	98
7[e,g]	**3d**	10000:1:0.4	−40	>99[h]	97
8	**3d**	1000:1:0.4	0	>99	95

[a] Unless otherwise stated, the reactions were carried out using **4a** (2.1–3.0 mmol, 0.3 M) and 2 equiv. of $(CH_3)_3SiCN$ in t-$C_4H_9OCH_3$ with Ru complex (*S*,*S*,*S*)-**3** (2.1–3.0 μmol) and C_6H_5OLi for 1 h.
[b] **1a**:**3**:C_6H_5OLi molar ratio.
[c] Determined by chiral GC analysis.
[d] Not determined.
[e] 15.6 mmol of **4a** was used.
[f] The isolated yield was 98%.
[g] The reaction was conducted using 0.8 M of **4a** for 2 h.
[h] The isolated yield was 99%.

(entry 5). The cyanations with an S/C of 5000 and 10,000 were completed in 1 h and 2 h, respectively, to yield **5a** without loss of enantioselectivity (entries 6 and 7). It was noteworthy that a high level of enantioselectivity was also observed in the reaction at 0 °C (entry 8). This is the most active and enantioselective catalyst for cyanosilylation of α,α-dialkoxy ketones so far reported.[13,14] Hydrocyanation of **4a** catalyzed by the **3d**-C_6H_5OLi system (3 equiv. of HCN, S/C = 1000, −40 °C, 48 h) afforded the cyanohydrin in 92% yield and 51% *ee*.

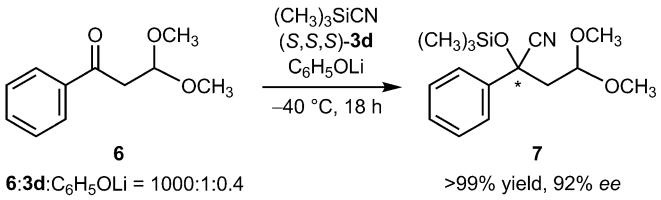
A series of α,α-dialkoxy ketones **4** was cyanated by using the 2.5:1 **3d**-C_6H_5OLi catalyst system (Table 4). The reaction of 3-methylphenyl ketone **4b** with an S/C of 1000 at −40 °C proceeded smoothly to give quantitatively the cyanated product **5b** in the same *ee* as that of **5a** (entries 1 and 2). The excellent *ee* value of 99% was achieved in the cyanation of the electron-rich 4-methoxyphenyl ketone **4c**, although the reaction rate was relatively slow (entry 3). The phenyl ketone bearing an electron-withdrawing Cl at the 3′ position (**4d**) was quantitatively converted to **5d** in 98% *ee* within 1 h under the regular conditions (entry 4). The high reactivity of **4d** allowed complete conversion in the cyanation with an S/C of 5000 in 1 h (entry 5). The *ee* value of **5d** in the reaction at 0 °C was 90% (entry 6). The enantioselectivity in the reaction of 4-chlorophenyl ketone **4e** was somewhat lower, but the reaction rate was also high (entry 7). The 2-furyl ketone **4f** was among the best substrates for this transformation (entry 8). The desired product **5f** in 99% *ee* was quantitatively obtained in 2 h. It is worth noting that the cyanation of methylglyoxal dimethyl acetal (**4g**), a primary alkyl α,α-dialkoxy ketone, with the **3d**-C_6H_5OLi-system under the typical conditions afforded quantitatively the desired product **5g** in 98% *ee* (entry 9).[14] The reactivity and enantioselectivity were significantly decreased in the cyanation of the cyclohexyl ketone **4h** (entry 10). A sterically hindered α,α-dialkoxy-α-phenyl ketone **4i** was also quantitatively cyanated at −20 °C in 30 h to give **5i** in 90% *ee* (entry 11). Notably, high reactivity and enan-

Table 4. Asymmetric cyanosilylation of α,α-dialkoxy ketones **4**.[a]



Entry	**4**	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**4a**	−40	1	>99 (95)	98
2	**4b**	−40	2	>99 (99)	98
3	**4c**	−40	6	>99 (96)	99
4	**4d**	−40	1	>99 (97)	98
5	**4d**[d]	−40	1	>99 (99)	97
6	**4d**	0	1	>99 (100)	90
7	**4e**	−40	1	>99 (99)	91
8	**4f**	−40	2	>99 (99)	99
9	**4g**	−40	4	>99 (95)	98
10	**4h**	−40	31	>99 (96)	74
11	**4i**	−20	30	>99 (96)	90
12	**4j**	−40	2	>99 (98)	98

[a] Unless otherwise stated, the reactions were conducted using **4** (2.9–3.1 mmol, 0.3 M) and a 2 equiv. of $(CH_3)_3SiCN$ in t-$C_4H_9OCH_3$ with Ru complex (*S*,*S*,*S*)-**3d** (3.0–3.1 μmol) and C_6H_5OLi. **4**:**3d**:C_6H_5OLi = 1000:1:0.4.
[b] Determined by chiral GC analysis. The isolated yield is given in parenthesis.
[c] Determined by chiral GC or HPLC analysis.
[d] **4d**:**3d** = 5000:1.



Scheme 1. Asymmetric cyanosilylation of a β,β-dialkoxy ketone **6**.

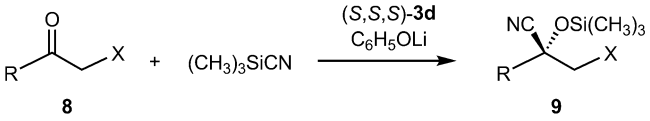
tioselectivity were achieved in the cyanation of 2,2-diethoxycyclohexanone (**4j**), a cyclic ketonic substrate (entry 12).

The **3d**-C_6H_5OLi catalyst system was also effective for the asymmetric cyanosilylation of a β,β-dialkoxy ketone **6** (Scheme 1). The functionalized silylated cyanohydrin **7** in 92% *ee* was quantitatively obtained under the typical conditions.

α-Alkoxy and α-Amino Ketones

2-Methoxyacetophenone (**8a**), an α-alkoxy ketone, is also an appropriate ketonic substrate for this asymmetric cyanosilylation (Table 5). The feature of reacting with high enantioselectivity under catalysis with the combined system of the Ru(*t*-Leu)$_2$ complex **3d** and C_6H_5OLi is similar to that of the reaction of phenylglyoxal diethyl acetal (**4a**: see Table 3). Thus, **8a** (410 mg, 2.7 mmol, 0.1 M) and 2 equiv. of $(CH_3)_3SiCN$ reacted with (*S*,*S*,*S*)-**3d** (2.9 μmol, S/C = 930) and C_6H_5OLi (3.0 μmol) in *tert*-$C_4H_9OCH_3$ at −40 °C for 2 h to afford the cyanated product (*R*)-**9a** in 97% *ee* quantitatively (entry 1). This is the first example of enantioselective cyanosilylation of α-alkoxy aromatic ketones to the best of our knowledge. Use of the 2.5:1 **3d**-C_6H_5OLi system, which gives the highest enantioselectivity for the reaction of **4a** (Table 3, entry 4), resulted in a somewhat slower reaction rate, although the product **9a** in 98% *ee* was obtained quantitatively (entry 2). The reaction with an S/C of 3000 was completed in 17 h with maintenance of a high level of enantioselectivity (entry 3). The cyanated product **9a** in an acceptable *ee* of 86% was obtained at 0 °C (entry 4). The ketonic substrates with an electron-donating CH_3O and an electron-withdrawing Cl at the 4′ position, **8b** and **8c**, were cyanated with the same level of reactivity and stereoselectivity (entries 5 and 6). Notably, methoxyacetone (**8d**), an aliphatic ketone, was quantitatively converted to the cyanohydrin derivative **9d** in 97% *ee* with the same catalyst (entry 7).[15] The low isolated yield was due to the volatility of **9d**. The reaction of the methyl ketone with a methoxymethyl ether moiety **8e** was relatively slow, but a high *ee* value of the product was attained (entry 8). The reaction of 1-(dimethylamino)acetone (**8f**), an α-amino ketone, showed medium enantioselectivity (entry 9).

Table 5. Asymmetric cyanosilylation of α-alkoxy and α-amino ketones **8**.[a]



a: R = C_6H_5, X = OCH_3
b: R = 4-$CH_3OC_6H_4$, X = OCH_3
c: R = 4-ClC_6H_4, X = OCH_3
d: R = CH_3, X = OCH_3
e: R = CH_3, X = OCH_2OCH_3
f: R = CH_3, X = $N(CH_3)_2$

Entry	8	Temp. [°C]	Time [h]	Yield [%][b]	*ee* [%][c]
1	**8a**	−40	2	95	97
2	**8a**[d]	−40	3	96	98
3	**8a**[e]	−40	17	92	95
4	**8a**	0	1	98	86
5	**8b**	−40	2	97	96
6	**8c**	−40	2	94	98
7[f]	**8d**	−40	5	58	97[g]
8	**8e**	−40	20	87	91
9	**8f**	−40	20	76	69

[a] Unless otherwise stated, the reactions were conducted using **8** (2.7–3.3 mmol, 0.1 M) and 2 equiv. of $(CH_3)_3SiCN$ in *t*-$C_4H_9OCH_3$ with Ru complex (*S*,*S*,*S*)-**3d** (2.9–3.3 μmol) and C_6H_5OLi. **8**:**3d**:C_6H_5OLi = 930–1000:1:1.
[b] Isolated yield. The yields determined by GC analysis were >99% except in the case of entries 7 and 8.
[c] Determined chiral GC or HPLC analysis.
[d] **8a**:**3d**:C_6H_5OLi = 1000:1:0.4.
[e] **8a**:**3d**:C_6H_5OLi = 3000:1:1.
[f] (*R*,*R*,*R*)-**3d** and 3 equiv. of $(CH_3)_3SiCN$ to **8d** were used.
[g] (*S*)-**9d** was obtained.

Conclusions

The bimetallic catalyst systems of amino acid/BINAP/Ru(II) complexes and C_6H_5OLi achieve highly reactive and enantioselective cyanosilylation of a wide range of ketones. The selection of amino acid ligand is crucial to achieve high enantioselectivity and applicability for substrates. Thus, the system Ru(PhGly)$_2$(BINAP)-C_6H_5OLi catalyzes the reaction of acetophenone derivatives to afford the silylated tertiary cyanohydrins in up to 90% *ee*. When the Ru(*t*-Leu)$_2$(BINAP)-C_6H_5OLi catalyst is used for the cyanation of α,α- and β,β-dialkoxy ketones as well as α-alkoxy ketones, the cyanated products are obtained in up to 99% *ee*. The excellent catalytic activity of the bimetallic systems is reflected in turnover numbers of 10,000, 3000, and 3000 in the cyanation of dialkoxy ketones, simple ketones, and α-alkoxy ketones, respectively, in the best cases.

Experimental Section

General

The commercially available substrates **1a–k**, **4a**, **4g**, **4i**, **8a**, **8d** and **8f** were used after distillation. The substrates **4b–f**, **4h**,[6a] **4j**,[16] **6**,[17] **8b**, **8c**, and **8e**[18] were prepared in accordance with the procedures in the literature. $(CH_3)_3SiCN$ was purchased from Wako Chemical Industries, Ltd. and distilled before use. Anhydrous *t*-$C_4H_9OCH_3$, THF, DMF, pentane, CH_2Cl_2, and methanol were purchased from Kanto Chemical Co., Inc. and used without further purification. The ruthenium complexes (*S,S,S*)-**3b–d** were synthesized with the same procedure as used for (*S,S,S*)-**3a**.[7] C_6H_5OLi (1.0 M in THF) was purchased from Aldrich Co. and diluted with anhydrous THF before use. NMR spectra were recorded on a JEOL JNM-ECS400 or LA400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, 161.7 MHz for ^{31}P NMR) spectrometer. The chemical shifts are reported downfield from TMS ($\delta = 0$ ppm) for ^{1}H NMR. For ^{13}C NMR, the chemical shifts are reported in a scale relative to the solvent used as an internal reference. Carbon multiplicity was assigned by DEPT experiments. ^{31}P NMR was carried out with phosphoric acid as an external standard.

Preparation of Ruthenium Complex 3[7]

The preparation of (*S,S,S*)-**3a** illustrates the typical reaction procedure. $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (258 mg, 0.52 mmol) and (*S*)-BINAP (661 mg, 1.06 mmol) were placed in a 100-mL Schlenk flask. After the air in the flask had been replaced with argon, degassed DMF (15 mL) was added, and the mixture was heated at 100 °C for 10 min with stirring to give a reddish brown solution. After the solution had cooled to 25 °C, a degassed methanol solution (30 mL) of sodium (*S*)-phenylglycinate (533 mg, 3.08 mmol) was added and the mixture was stirred for 12 h. Water (50 mL) was added to the solution to precipitate a yellowish orange solid. The collected precipitates were dissolved in CH_2Cl_2 (40 mL), washed with water (50 mL × 3), and dried over $MgSO_4$. After filtration and removal of the solvent, the residue was purified by preparative TLC (silica gel; eluent: ethyl acetate; $R_f = 0.45$–0.61). Reprecipitation with a mixture of CH_2Cl_2 (10 mL) and pentane (100 mL) afforded (*S,S,S*)-**3** as a light yellow powder; yield: 787 mg (74%); mp (decomp) 223 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.45$ (br s, 2H, N*H*H), 3.23 (brs, 2H, NH*H*), 3.63 (t, 2H, $J = 8.3$ Hz, 2PhC*H*), 6.24 (d, 2H, $J = 9.3$ Hz, aromatic H), 6.50 (m, 6H, aromatic H), 6.71 (m, 6H, aromatic H), 7.07–7.67 (m, 24H, aromatic H), 8.06 (m, 4H, aromatic H); ^{31}P NMR (161.7 MHz, $CDCl_3$): $\delta = 52.3$ (s); HR-MS (ESI): $m/z =$ 1024.2123, calcd. for $C_{60}H_{48}N_2O_4P_2Ru$ $[M]^+$: 1024.2149.

Ru[(*S*)-PhGly]$_2$[(*S*)-XylBINAP] [(*S,S,S*)-3b]

This complex was prepared by the same procedure as used for **3a**. The reaction of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (76 mg, 0.15 mmol), (*S*)-XylBINAP (250 mg, 0.34 mmol), and sodium (*S*)-phenylglycinate (101 mg, 0.58 mmol) gave (*S,S,S*)-**3b**; yield: 0.18 g (0.16 mmol, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.67$ (s, 12H, CH_3), 2.27 (br. t, 2H, N*H*H), 2.42 (s, 12H, CH_3), 3.18 (br, dd, 2H, NH*H*), 3.70 (br. t, 2H, PhC*H*), 5.96 (s, 2H, aromatic H), 6.24 (d, 2H, $J =$ 8.8 Hz, aromatic H), 6.67–6.82 (m, 10H, aromatic H), 7.11–7.23 (m, 10H, aromatic H), 7.51–7.81 (m, 8H, aromatic H), 8.10–8.15 (m, 2H, aromatic H); ^{31}P NMR (161.7 MHz, $CDCl_3$): $\delta = 52.3$ (s); HR-MS (ESI): $m/z = 1136.3376$, calcd for $C_{68}H_{64}N_2O_4P_2Ru$ $[M]^+$: 1136.3404.

Ru[(*S*)-Leu]$_2$[(*S*)-BINAP] [(*S,S,S*)-3c]

This complex was prepared by the same procedure as used for **3a**. The reaction of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (250 mg, 0.50 mmol), (*S*)-BINAP (633 mg, 1.02 mmol), and sodium (*S*)-leucinate (475 mg, 3.10 mmol) gave (*S,S,S*)-**3c**; yield: 0.75 g (0.76 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.29 (d, 6H, $J = 6.6$ Hz, CH_3), 0.66 (d, 6H, $J = 6.3$ Hz, CH_3), 1.03–1.13 (m, 4H, $(CH_3)_2CH$ & C*H*H), 1.81–1.89 (m, 2H, CH*H*), 2.38–2.41 (m, 4H, N*H*H and COCH), 3.25–3.29 (m, 2H, NH*H*), 6.25 (d, 2H, $J = 8.5$ Hz, aromatic H), 6.43–6.52 (m, 6H, aromatic H), 6.72 (t, 2H, $J = 7.6$ Hz, aromatic H), 7.02–7.06 (m, 4H, aromatic H), 7.15 (t, 2H, $J = 7.6$ Hz, aromatic H), 7.47–7.61 (m, 10H, aromatic H), 7.78–8.23 ppm (m, 6H, aromatic H); ^{31}P NMR (161.7 MHz, $CDCl_3$): $\delta =$ 52.0 (s); HR-MS (ESI): $m/z = 984.2771$, calcd. for $C_{56}H_{56}N_2O_4P_2Ru$ $[M]^+$: 984.2774.

Ru[(*S*)-*t*-Leu]$_2$[(*S*)-BINAP] [(*S,S,S*)-3d]

This complex was prepared by the same procedure as used for **3a**. The reaction of $[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ (251 mg, 0.50 mmol), (*S*)-BINAP (643 mg, 1.03 mmol), and sodium (*S*)-*tert*-leucinate (475 mg, 3.10 mmol) gave (*S,S,S*)-**3c**; yield: 0.72 g (0.73 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.65 (s, 18H, CH_3), 1.88–2.18 (m, 4H, NH_2), 3.03 (m, 2H, C*H*CH_3), 6.27 (d, 2H, $J = 8.8$ Hz, aromatic H), 6.49 (m, 6H, aromatic H), 6.73 (m, 2H, aromatic H), 7.02 (brm, 4H, aromatic H), 7.16 (m, 2H, aromatic H), 7.47–7.61 (m, 10H, aromatic H), 7.93 (m, 2H, aromatic H), 8.03 (br, 4H, aromatic H); ^{31}P NMR (161.7 MHz, $CDCl_3$): $\delta = 52.6$ (s); HR-MS (ESI): $m/z = 984.2772$, calcd. for $C_{56}H_{56}N_2O_4P_2Ru$ $[M]^+$: 984.2774.

General Procedure for Asymmetric Cyanosilylation of Ketones

Caution: *$(CH_3)_3SiCN$ must be handled with utmost care: it is highly flammable, and causes death by inhalation, by contact with the skin, or if swallowed. It produces HCN gas on contact with water.*[19]

The cyanosilylation of **1a** illustrates the typical reaction procedure. The ruthenium complex (*S,S,S*)-**3a** (5.1 mg, 5.0 μmol) was placed in a 50-mL Schlenk flask, and the air present in this apparatus was replaced by argon. Anhydrous *t*-$C_4H_9OCH_3$ (10 mL), $(CH_3)_3SiCN$ (0.75 mL, 6.0 mmol), and C_6H_5OLi (100 mM in THF, 50 μL, 5.0 μmol, S/C = 1000) were added to this flask, and the mixture was stirred at −40 °C for 30 min. Then **1a** (0.62 g, 5.2 mmol) was added to the solution, and the reaction mixture was stirred for 6 h. After the solvent and the volatile compounds were evaporated under reduced pressure at ambient temperature, the residue was suspended in pentane (40 mL).[20] The mixture was filtered through a celite pad,[21] and the filtrate was concentrated under reduced pressure. The crude product was purified by short-path distillation to give (*R*)-**2a** as a colorless oil; yield: 1.13 g (5.16 mmol, 99%); 86% *ee*; bp 65 °C/20 Pa;

$[\alpha]_D^{24}$: +20.6 deg cm^3 g^{-1} dm^{-1} (*c* 1.02, $CHCl_3$), {lit.[2m] $[\alpha]_D^{28}$: −19.0 deg cm^3 g^{-1} dm^{-1} (*c* 1.01, $CHCl_3$, *R* enantiomer in 88% *ee*)}; EI-MS: *m*/*z* (relative intensity) = 219.17 (0.4), 204.14 (96), 177.12 (100), 105.06 (56); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.18 [s, 9H, $Si(CH_3)_3$], 1.86 (s, 3H, CH_3), 7.35–7.42 (m, 3H, aromatic H), 7.54–7.56 (m, 2H, aromatic H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 1.0 (CH_3), 33.5 (CH_3), 71.6 (C), 121.6 (C), 124.6 (CH), 128.6 (CH), 142.0 (C); chiral GC analysis [Chirasil Dex (0.32 mm × 25 m); carrier gas: helium (114 kPa); column temp: 110 °C; injection temp: 180 °C]: t_R of (*S*)-**2a** = 10.6 min (7.0%), t_R of (*R*)-**2a** = 11.0 min (93.0%).

Supporting Information

Procedures for the asymmetric cyanosilylation of ketones, the NMR, GC, and HPLC behavior, $[\alpha]_D$ values and the determination of the absolute configuration of products are available in the Supporting Information.

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[14] A chiral oxazabororidinium ion-phosphine oxide system-catalyzed cyanosilylation of methylglyoxal dimethyl acetal (**4g**: S/C = 10, 25 °C, 2 days) to give the product in 92% yield and 96% *ee*. See: ref.[4c]
[15] Cyanosilylation of methoxy acetone (**8d**) with a chiral thiourea catalyst (S/C = 20, −78 °C, 8 h) gave the product in 81% yield and 88% *ee*, see ref.[6d]
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[20] Alternatively, hexane could be used to make a suspension of the ruthenium complex (*S,S,S*)-**3a** and the lithium salt.
[21] Since (*S,S,S*)-**3b–d** show some solubility to pentane or hexane, removal of the ruthenium and/or the lithium components was carried out by a silica gel short-path column (30 mm × 100 mm).

