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Asymmetric Cyanosilylation of α-Keto Esters Catalyzed by the [Ru(phgly)$_2$(binap)]–C_6H_5OLi System

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The asymmetric reaction of α-keto esters and $(CH_3)_3SiCN$, catalyzed by a combined system of [Ru{(*S*)-phgly}$_2${(*S*)-binap}] and C_6H_5OLi with a substrate-to-catalyst molar ratio (S/C) of 1000 at –60 °C, affords silylated cyanohydrins in up to 99% *ee*. Cyanosilylation smoothly proceeds with an S/C of 10,000 at –50 °C. The use of Xyl-Binap instead of Binap as a ligand provides better enantioselectivity in some cases. A series of aromatic, hetero-aromatic, aliphatic, and α,β-unsaturated keto esters are converted into the desired products.

Introduction

The development of effective methods for the synthesis of optically active compounds with a multi-functionalized carbon center is highly desirable in the field of modern organic synthesis. To this end, the asymmetric cyanosilylation of ketones is among the most reliable and versatile procedures.[1–6] In the presence of the appropriate chiral catalysts, the tertiary cyanohydrin derivatives are obtained in high enantiomeric excess (*ee*). However, to the best of our knowledge, this asymmetric reaction of α-keto esters, a typical class of functionalized ketones, has not been reported to date.[7–9] The presence of an ester moiety, which can interact with the metal of catalysts, adjacent to the reaction center may introduce difficulty into enantioface selection.

We recently reported the asymmetric cyanosilylation of aldehydes with a novel combined catalyst of [Ru(phgly)$_2$(binap)] and a Li salt.[10,11] The cooperation of a Lewis acidic Li cation and the chiral Ru complex enables this asymmetric transformation to proceed with high catalytic efficiency. Herein we report for the first time the highly enantioselective cyanosilylation of α-keto esters with a catalyst system consisting of the Binap–Ru(phgly)$_2$ complex and C_6H_5OLi. The reaction is conducted with a substrate-to-catalyst molar ratio (S/C) of 1000 at –60 °C, and 10,000 at –50 °C. A series of aromatic, hetero-aromatic, aliphatic, and α,β-unsaturated α-keto esters are converted into the silylated cyanohydrins with an *ee* of up to 99%.

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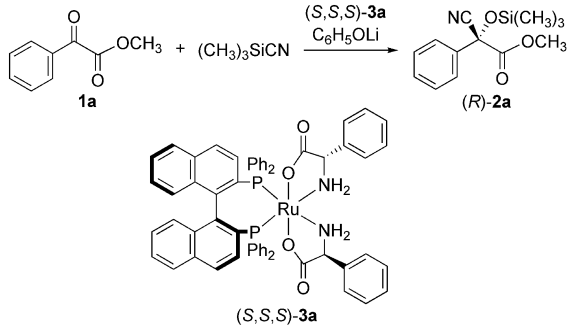
Results and Discussion

[Ru{(*S*)-phgly}$_2${(*S*)-binap}] [(*S*,*S*,*S*)-**3a**] (Scheme 1) was prepared according to the method described in our previous report.[10] We selected methyl benzoylformate (**1a**) as the standard substrate to optimize the reaction conditions. The reaction of **1a** (0.82 g, 5.0 mmol, 0.1 M) and $(CH_3)_3SiCN$ (0.99 g, 10.0 mmol) 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 $tC_4H_9OCH_3$ at –40 °C was completed in 3 h to afford the *R* cyanation product, (*R*)-**2a**, in 97% *ee* (Table 1, Entry 1). Excellent enantioselectivity of 99% was achieved at –60 °C under otherwise identical conditions, although the reaction rate was slower at the lower temperature (Entry 2). Cyanation at –70 °C was not completed within 24 h without an increase in enantioselectivity (Entry 3). Use of 2 equiv. of $(CH_3)_3SiCN$ to **1a** was required for completion of the reaction at –60 °C within 18 h (Entry 2). The yield of **2a** was decreased with decreasing amounts of reagent (Entries 4 and 5). The initial concentration of **1a** affected the enantio-



Scheme 1. Asymmetric cyanosilylation of methyl benzoylformate (**1a**) with **3a** and C_6H_5OLi.

selectivity of this reaction. The *ee* value of 99% with 0.1 M of **1a** decreased to 97% when the concentration of **1a** was increased to 0.8 M (Entries 2, 6, and 7).

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

Entry	[**1a**]$_0$ [M][b]	CN/S[c]	S/C[d]	T [°C]	t [h]	Yield [%][e]	*ee* [%][e]
1	0.1	2.0	1000	–40	3	>99	97
2	0.1	2.0	1000	–60	18	>99	99
3	0.1	2.0	1000	–70	24	97	99
4	0.1	1.5	1000	–60	18	91	99
5	0.1	1.2	1000	–60	18	65	98
6	0.3	2.0	1000	–60	18	>99	98
7	0.8	2.0	1000	–60	18	99	97
8	0.1	2.0	10000	–40	36	>99	97
9	0.3	2.0	10000	–40	18	>99	97
10	0.3	2.0	10000	–50	18	>99	98
11	0.3	2.0	10000	–60	18	69	98
12	0.8	2.0	10000	–50	18	>99	96

[a] Unless otherwise stated, reactions were carried out using **1a** (5–10 mmol) and $(CH_3)_3SiCN$ in *tert*-$C_4H_9OCH_3$ with a Ru complex (*S*,*S*,*S*)-**3a** (1–5 μmol) and C_6H_5OLi. **3a**:C_6H_5OLi = 1:1. [b] Initial concentration of **1a**. [c] Molar ratio of $(CH_3)_3SiCN$ to substrate (**1a**). [d] Substrate-to-catalyst (**3a**) molar ratio. [e] Data for (*R*)-**2a** determined by chiral GC analysis.

The cyanation of **1a** (0.1 M) in the presence of (*S*,*S*,*S*)-**3a** and C_6H_5OLi with an S/C of 10,000 at –40 °C for 36 h afforded (*R*)-**2a** in 97% *ee* quantitatively (Table 1, Entry 8). The reaction rate was increased without loss of the enantioselectivity when a concentration of 0.3 M **1a** was used (Entry 9). A higher *ee* value of 98% was attained when cyanation was conducted at –50 °C (Entry 10). The reaction rate was markedly reduced at –60 °C (Entry 11). Cyanation with 0.8 M of **1a** at –50 °C gave **2a** in 96% *ee* (Entry 12).

Thus, we selected the reaction conditions using **1a** (0.1 M) and 2 equiv. of $(CH_3)_3SiCN$ in *t*$C_4H_9OCH_3$ with (*S*,*S*,*S*)-**3a** and C_6H_5OLi (**3a**:C_6H_5OLi = 1:1) at an S/C of 1000 at –60 °C to afford (*R*)-**2a** in 99% *ee* quantitatively (Table 2, Entry 1; see also Table 1, Entry 2). The desired product was readily isolated in 97% yield by bulb-to-bulb distillation after removal of the metal compounds and excess $(CH_3)_3$-SiCN (See the Experimental Section). When an even higher turnover number (i.e., close to 10,000) is required, we recommend the following conditions: **1a** (0.3 M) in *t*$C_4H_9OCH_3$, $(CH_3)_3SiCN$ (2 equiv.), (*S*,*S*,*S*)-**3a** with C_6H_5OLi (S/C = 10,000), –50 °C (Table 2, Entry 2; see also Table 1, Entry 10).

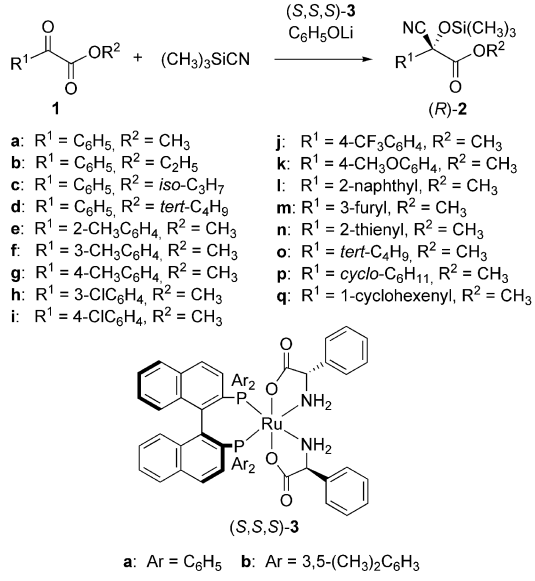
Enantioselectivity was notably influenced by the size of the ester moieties of the substrates (Scheme 2). Methyl ester **1a** was converted to **2a** in 98% *ee* at –50 °C with the **3a**–C_6H_5OLi system (S/C = 10,000) (Table 2, Entry 2). The cyanation of the ethyl ester **1b**, isopropyl ester **1c**, and *tert*-butyl ester **1d** under the same conditions gave **2b**, **2c**, and **2d** in 87%, 49%, and 53% *ee*, respectively (Entries 3–5).

When methyl 2′-methylbenzoate (**1e**) was treated with $(CH_3)_3SiCN$ catalyzed by the (*S*,*S*,*S*)-**3a**–C_6H_5OLi system with an S/C of 1000 at –60 °C, the *R* cyanohydrin product, (*R*)-**2e**, was obtained in 90% *ee* (Scheme 2 and Table 2, Entry 6). Fortunately, the *ee* value was increased to 94% by using [Ru{(*S*)-phgly}$_2${(*S*)-xyl-binap}] [(*S*,*S*,*S*)-**3b**] (Scheme 2)[12] instead of **3a** (Entry 7). Stereo-demanding 3,5-xylyl groups on the phosphorus atoms contributed to form the more suitable chiral enviraonment for this substrate. The reaction of sterically less crowded 3′-methyl- and 4′-methylbenzoylformates, **1f** and **1g**, with the **3a**–C_6H_5OLi catalyst gave the chiral products, **2f** and **2g**, in 97% and 95% *ee*, respectively (Entries 8 and 10). The keto ester **1f** (0.3 M) and $(CH_3)_3SiCN$ were smoothly reacted with an

Table 2. Asymmetric cyanosilylation of α-keto esters **1**.[a]

Entry	**1**	[**1**]$_0$ [M][b]	**3**	S/C[c]	T [°C]	t [h]	Yield [%][d]	*ee* [%][e]
1	**1a**	0.1	**3a**	1000	–60	18	97	99
2	**1a**	0.3	**3a**	10000	–50	18	98	98
3	**1b**	0.3	**3a**	10000	–50	36	97	87
4	**1c**	0.3	**3a**	10000	–50	18	94	49
5	**1d**	0.3	**3a**	10000	–50	24	97	53
6	**1e**	0.1	**3a**	1000	–60	18	98	90
7	**1e**	0.1	**3b**	1000	–60	18	98	94
8	**1f**	0.1	**3a**	1000	–60	18	97	97
9	**1f**	0.3	**3a**	10000	–50	18	95	98
10	**1g**	0.1	**3a**	1000	–60	18	92	95
11	**1h**	0.1	**3a**	1000	–60	18	97	98
12	**1i**	0.1	**3a**	1000	–60	18	98	98
13	**1j**	0.1	**3a**	1000	–60	18	92	92
14	**1k**	0.1	**3a**	1000	–60	18	96	95
15	**1l**	0.1	**3a**	1000	–60	18	97	98
16	**1l**	0.3	**3a**	10000	–50	18	96	97
17	**1m**	0.1	**3a**	1000	–50	18	94	92
18	**1n**	0.1	**3a**	1000	–60	18	99	91
19	**1o**	0.1	**3a**	1000	–60	18	92	88
20	**1o**	0.1	**3b**	1000	–60	18	94	94
21	**1p**	0.1	**3a**	1000	–60	18	98	85
22	**1q**	0.1	**3a**	1000	–60	18	98	97

[a] Unless otherwise stated, reactions were conducted using **1** (5–10 mmol) and 2 equiv. of $(CH_3)_3SiCN$ in *t*$C_4H_9OCH_3$ with a Ru complex (*S*,*S*,*S*)-**3** (1–5 μmol) and C_6H_5OLi. **3**:C_6H_5OLi = 1:1. [b] Initial concentration of **1**. [c] Substrate (**1**)-to-catalyst (**3**) molar ratio. [d] Yield of isolated (*R*)-**2**. Yields determined by GC analysis were >99% in all cases. [e] Data for (*R*)-**2** determined by chiral GC or HPLC analysis.



Scheme 2. Asymmetric cyanosilylation of α-keto esters **1** with **3** and C_6H_5OLi.

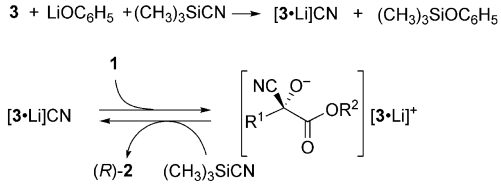
S/C of 10,000 at –50 °C to afford **2f** in 98% *ee* (Entry 9). The chlorinated keto esters at the 3′ or 4′ position, **1h** and **1i**, were quantitatively cyanated with the **3a**–C_6H_5OLi system (S/C = 1000) at –60 °C for 18 h to give **2h** and **2i** in 98% *ee* in both cases (Entries 11 and 12). Substitution of a strongly electron-attracting CF_3 group at the 4′ position (**1j**) decreased the *ee* value of product to 92%, while reactivity was only slightly influenced by this change in the electronic condition (Entry 13). On the other hand, the cyanation of the aromatic ketone bearing an electron-donating CH_3O group at the 4′ position, **1k**, catalyzed by the **3a**–C_6H_5OLi system quantitatively gave **2k** in 95% *ee* under the typical conditions (Entry 14). Methyl 2′-naphthoylformate (**1l**) was found to be a good substrate for this asymmetric reaction, affording the cyantion product **2l** in 98% *ee* quantitatively (Entry 15). High reactivity and enantioselectivity were maintained in the cyanation of **1l** with an S/C of 10,000 at –50 °C (Entry 16).

A 3′-furyl ketone, **1m**, was treated with the **3a**–C_6H_5OLi catalyst (S/C = 1000) at –50 °C due to its low solubility in $tC_4H_9OCH_3$, resulting in the product **2m** in 92% *ee* quantitatively (Entry 17). The hetero-aromatic ring was left intact. The reaction of 2′-thienyl ketone **1n** at –60 °C gave **2n** in 91% *ee* (Entry 18).

The cyanation of methyl pivaloylformate (**1o**), a sterically hindered aliphatic keto ester, smoothly proceeded with the (*S*,*S*,*S*)-**3a**–C_6H_5OLi catalyst (S/C = 1000) at –60 °C to give (*R*)-**2o** in 88% *ee* (Table 2, Entry 19). The sense of enantioface selection was the same as that in the reaction of benzoylformate **1a**. The *ee* value was increased to 94% when the reaction was carried out with the **3b**–C_6H_5OLi catalyst (Entry 20). A secondary alkyl ketone, **1p**, was cyanated with the **3a**–C_6H_5OLi system to give **2p** in 85% *ee* (Entry 21). The reaction of a 1-cyclohexenyl ketone, **1q**, catalyzed by the **3a**–C_6H_5OLi system, afforded **2q** in 97% *ee* quantitatively (Entry 22). No conjugated-addition product was observed.

Comparison of enantioselectivity in the reaction of **1a** (phenyl ketone), **1p** (cyclohexyl ketone), and **1q** (cyclohexenyl ketone) with the **3a**–C_6H_5OLi system (Table 2, Entries 1, 21, and 22) suggested that this catalyst prefers aryl and alkenyl groups (Csp^2 groups) to alkyl groups (Csp^3 groups) from CO_2CH_3 group (Csp^2 group), although the mode of enantioface-selection is unclear.

Here, ESI mass-spectrometric measurement of a 1:1:10 mixture of Ru complex **3a** (*m*/*z* 1024), C_6H_5OLi, and $(CH_3)_3SiCN$ showed prominent signals corresponding to the Ru–Li combined species [**3a**·Li]$^+$ (*m*/*z* 1031) (see the Supporting Information). The same signals were also observed in the measurement of a **3a**–Li_2CO_3–catalyst system.[10] ^1H and ^{13}C NMR analyses of this mixture suggested that $C_6H_5O^-$ quantitatively reacted with $(CH_3)_3SiCN$ to form CN^- and $(CH_3)_3SiOC_6H_5$ (see the Supporting Information). No pentacoordinate Si species $[(CH_3)_3Si(NC)_2]^-$ was observed, although an excess amount of $(CH_3)_3SiCN$ was present.[13] The addition of sufficient amount of keto ester **1a** to this mixture resulted in the disappearance of the $(CH_3)_3SiCN$ signal, together with the appearance of the **2a** product peak. The signal of $(CH_3)_3SiOC_6H_5$ remained unaltered during this procedure. Based on these data, a plausible reaction pathway is depicted in Scheme 3 (nonproductive and minor pathways were not considered in this depiction). The reaction of **3**, C_6H_5OLi, and $(CH_3)_3SiCN$ gives [**3**·Li]CN and $(CH_3)_3SiOC_6H_5$.[14] Keto ester **1** smoothly reacts with [**3**·Li]CN (in which [**3**·Li]$^+$ acts as an efficient chiral Lewis acid) to give the cyanohydrin anion with [**3**·Li]$^+$.[15] This intermediate is silylated spontaneously with $(CH_3)_3SiCN$, resulting in the formation of product, **2**, and the regeneration of [**3**·Li]CN.



Scheme 3. Proposed mechanism for cyanosilylation of α-keto esters **1**.

Conclusions

We report here the first example of the highly reactive and enantioselective cyanosilylation of α-keto esters with a unique [Ru(phgly)$_2$(binap)]–C_6H_5OLi catalyst system. The cyanation smoothly proceeds with an S/C of 1000 at –60 °C and 10,000 at –50 °C. The use of stereo-demanding Xyl-Binap ligand in place of Binap achieves better stereoselectivity in some cases. A series of aromatic, hetero-aromatic, aliphatic, and α,β-unsaturated α-keto esters are converted into the cyanohydrin products in up to 99% *ee*. Spectroscopic analysis suggests that [Li·{Ru(phgly)$_2$(binap)}]CN is a plausible reactive species. Thus, this finding provides an efficient procedure for the constructing of multi-functionalized chiral carbon centers.

Experimental Section

General Procedure for the Cyanosilylation of α-Keto Esters: The cyanosilylation of **1a** illustrates the typical reaction procedure. ***Caution:*** $(CH_3)_3SiCN$ must be used in a well-ventilated hood due to its high toxicity. Ruthenium complex (*S*,*S*,*S*)-**3a** (5.1 mg, 5.0 μmol)[10] was placed in a 500-mL Schlenk flask, and the air present in this apparatus was replaced by argon. Anhydrous *tert*-$C_4H_9OCH_3$ (50 mL), **1a** (0.82 g, 5.0 mmol), and C_6H_5OLi (100 mM in THF, 50 μL, 5.0 μmol) were added to this flask, and the mixture was stirred for 30 min. The resulting yellow solution was cooled down to –60 °C. Then $(CH_3)_3SiCN$ (0.99 g, 10.0 mmol) was added to the solution in a dropwise manner for 15 min, and the reaction mixture was stirred for 18 h. After the solvent and the volatile compounds were evaporated under reduced pressure at ambient temperature, the residue was suspended in hexane (100 mL). The mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure. The crude product was purified by short-path distillation to give (*R*)-**2a** (colorless oil, 1.27 g, 97% yield, 99% *ee*); b.p. 116–119 °C/1.0 Torr. $[\alpha]_D^{24}$ = +24.0 deg cm^3 g^{-1} dm^{-1} (*c* = 1.13 g cm^{-3}, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.26 [s, 9

H, $Si(CH_3)_3$], 3.79 (s, 3 H, OCH_3), 7.40–7.45 (m, 3 H, aromatic H), 7.63–7.67 ppm (m, 2 H, aromatic H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.7 (CH_3), 54.0 (CH_3), 74.8 (C), 117.9 (C), 125.5 (CH), 128.8 (CH), 129.8 (CH), 136.4 (C), 167.5 ppm (C). $C_{13}H_{17}NO_3Si$ (263.10): calcd. C 59.29, H 6.51, N 5.32; found C 59.23, H 6.45, N 5.25. HRMS (EI): *m*/*z* calcd: 263.0978 $[M]^+$, obsd. 263.0970. The *ee* of **2a** was determined by chiral GC analysis: column, InertCap CHIRAMIX (0.25 mm × 30 m, depth of film = 0.25 μm, GL Science); carrier gas: helium (100 kPa); column temp.: 70 °C heating to 135 °C at a rate of 0.5 °C min^{-1}; injection temp.: 220 °C; retention time (t_R) of (*R*)-**2a**: 134.7 min (99.5%), t_R of (*S*)-**2a**: 133.5 min (0.5%). The absolute configuration was determined after conversion to 3-hydroxy-3-phenylazetidin-2-one. $[\alpha]_D^{26}$ = +113 deg cm^3 g^{-1} dm^{-1} (*c* = 0.612 g cm^{-3}, $CHCl_3$); ref.[9] $[\alpha]_D^{25}$ = –57.4 deg cm^3 g^{-1} dm^{-1} (*c* = 0.25 g cm^{-3}, $CHCl_3$), 80% *ee* (*S*).

Supporting Information (see also the footnote on the first page of this article): Preparative method and properties of complex **3b**, procedure for asymmetric cyanosilylation of α-keto esters, analytical data and absolute configuration determination procedure of products **2**, and MS and NMR behavior of catalytic species.

Acknowledgments

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[15] There remains the possibility that $[\mathbf{3}\cdot Li][(CH_3)_3Si(NC)_2]$, formed reversibly, acts as an active species.

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