Asymmetric Hydrocyanation

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Asymmetric Hydrocyanation of α,β-Unsaturated Ketones into β-Cyano Ketones with the [Ru(phgly)$_2$(binap)]/C$_6$H$_5$OLi Catalyst System**

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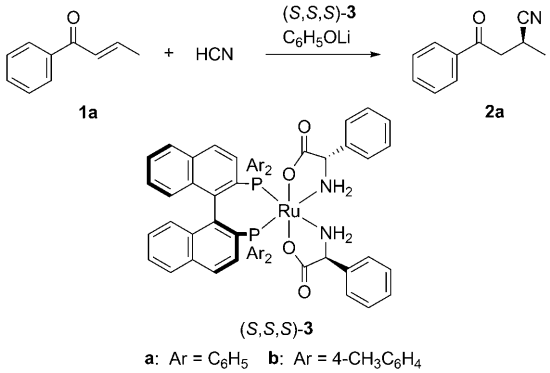
Catalytic asymmetric hydrocyanation of α,β-unsaturated ketones into the corresponding chiral β-cyano ketones is a challenging scientific endeavor. Four major hurdles must be cleared before this reaction can be realized: 1) use of HCN as a cyanide source,[1] 2) high 1,4-addition selectivity over 1,2-addition, 3) sufficient enantioface selectivity and, 4) high catalytic activity (low catalyst loading). Recently, Shibasaki and co-workers reported pioneering studies on asymmetric 1,4-addition of cyanide to the conjugate enones catalyzed by chiral Gd and Sr compounds.[2–5] A wide range of 1,4-adducts were obtained in high enantiomeric excess (*ee*), but two equivalents of a *tert*-C$_4$H$_9$(CH$_3$)$_2$SiCN/2,6-dimethylphenol system were required as a cyanide source to achieve the best catalyst performance.[6] Furthermore, the substrate-to-catalyst molar ratio (S/C) of 10–200 in these reactions was relatively low.[2]

Our research group recently reported the asymmetric cyanation of aldehydes and α-keto esters catalyzed by our original [Ru(phgly)$_2$(binap)]/Li salt systems.[7,8] The corresponding cyanated products were obtained in high *ee*. The spectroscopic analysis suggested that the bimetallic species [Li·Ru(phgly)$_2$(binap)]$^+$ acted as a chiral Lewis acidic catalyst. Herein, we describe the efficient asymmetric conjugate addition of HCN to α,β-unsaturated ketones catalyzed by the combined system of [Ru(phgly)$_2$(binap)] and C$_6$H$_5$OLi. The reaction was carried out with an S/C of 200–1000 at −20–0 °C to afford the β-cyano ketones in up to 98% *ee*.

1-Phenyl-2-buten-1-one (**1a**) was selected as a typical enone substrate to optimize the reaction conditions (Scheme 1 and Table 1). The [Ru{(*S*)-phgly}$_2${(*S*)-binap}] ((*S*,*S*,*S*)-**3a**) complex was prepared according to the method described in our previous report.[7] The reaction of **1a** (1.0 mmol) and HCN prepared by mixing (CH$_3$)$_3$SiCN (1.5 mmol) and CH$_3$OH (1.5 mmol) was conducted in *tert*-C$_4$H$_9$OCH$_3$ (6 mL) with (*S*,*S*,*S*)-**3a** (20 mM in THF, 2.0 μmol, S/C = 500) and C$_6$H$_5$OLi (20 mM in THF, 2.0 μmol) at 25 °C for 1 hour and gave (*R*)-3-cyano-1-phenyl-1-butanone ((*R*)-**2a**) in 89% yield and 89% *ee* (Table 1, entry 1). Notably, no 1,2-addition product was observed. The reaction catalyzed only by C$_6$H$_5$OLi gave racemic **2a** in 35% yield (Table 1, entry 2). No conversion was observed in the reaction with **3a** in the absence of C$_6$H$_5$OLi (Table 1, entry 3). The use of a **3a**/C$_6$H$_5$OLi system in a 1:0.5 or 1:2 ratio afforded **2a** in 53%



Scheme 1. Asymmetric hydrocyanation of 1-phenyl-2-buten-1-one (**1a**) with **3** and C$_6$H$_5$OLi.

Table 1: Asymmetric hydrocyanation of 1-phenyl-2-buten-1-one (**1a**).[a]

Entry	**1a**/**3a**/PhOLi	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][b]
1	500:1:1	*t*BuOMe	25	1	89	89
2	500:0:1	*t*BuOMe	25	1	35	–[c]
3	500:1:0	*t*BuOMe	25	1	<1	n.d.
4	500:1:0.5	*t*BuOMe	25	1	53	90
5	500:1:2	*t*BuOMe	25	1	>99	82
6	500:1:1	Et$_2$O	25	1	80	83
7	500:1:1	*n*-hexane	25	1	21	56
8	500:1:1	CH$_2$Cl$_2$	25	1	<1	n.d.
9	500:1:1	toluene	25	1	44	64
10	500:1:1	*t*BuOMe	0	5	99	93
11[d]	500:1:1	*t*BuOMe	0	5	99	93
12[e]	500:1:1	*t*BuOMe	0	5	98	90
13	1000:1:1	*t*BuOMe	0	5	98	90
14	2000:1:1	*t*BuOMe	0	5	<1	n.d.
15	500:1:1	*t*BuOMe	−20	18	96	97

[a] Unless otherwise stated, the reactions were carried out using **1a** (1.0 mmol) and HCN (1.5 mmol) in solvent (6 mL) with (*S*,*S*,*S*)-**3a** (20 mM in THF) and C$_6$H$_5$OLi (20 mM in THF) in the ratio given in the Table. HCN was prepared in situ from (CH$_3$)$_3$SiCN and CH$_3$OH in a 1:1 ratio. [b] Data for (*S*)-**2a** were determined by GC on a chiral stationary phase. [c] A racemic product was obtained. [d] Isolated HCN was used. [e] **3b** was used as a catalyst. n.d. = not determined.

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yield and 90% *ee*, and >99% yield and 82% *ee*, respectively (Table 1, entries 4 and 5). These observations suggested that **3a** and C_6H_5OLi smoothly formed the 1:1 bimetallic species, $[Li{\cdot}Ru(phgly)_2(binap)]^+$,[7,8] and the chiral species had a higher reactivity than that of achiral C_6H_5OLi alone. The solvent of choice was *tert*-$C_4H_9OCH_3$, while $(C_2H_5)_2O$ gave a slightly less satisfactory result (Table 1, entry 6). The yield and enantioselectivity were significantly decreased in less polar solvents (Table 1, entries 7–9). The cyanation at 0°C was completed in 5 hours and afforded the adduct in 93% *ee* (Table 1, entry 10). The same result was obtained by using the isolated HCN prepared according to the method described in the literature,[9] despite the very low catalyst loading (S/C = 500; Table 1, entry 11). This high reactivity at the low catalyst loading is the important point of difference between Shibasaki's system and the present system.[2,6] We chose the HCN formed in situ for use in this study for operational and safety reasons. The [Ru(phgly)$_2$(tol-binap)] (**3b**) exhibited a similar efficiency (Table 1, entry 12).[10] The high catalytic activity of the **3a**/C_6H_5OLi system allowed us to conduct the cyanation with an S/C of 1000 at 0°C (Table 1, entry 13). The reaction with an S/C of 2000 did not proceed (Table 1, entry 14). The excellent *ee* value of 97% was achieved in the reaction at −20°C, although the reaction took longer to achieve completion (Table 1, entry 15).[11]

Thus, we selected the reaction conditions using **1a** and 1.5 equivalents of HCN prepared from $(CH_3)_3SiCN$ and CH_3OH in *tert*-$C_4H_9OCH_3$ with **3a** and C_6H_5OLi (**3a**/C_6H_5OLi = 1:1) at an S/C of 500 at 0°C or −20°C when a higher *ee* value for the product was required (see the Experimental Section). The 1,4-adduct **2a** was quantitatively isolated by column chromatography on silica gel for a reaction carried out on a 3 mmol scale (Table 2, entries 1 and 2). Phenyl ketones ($R^1 = C_6H_5$ in Scheme 2) with alkyl substituents at the β position (R^2), **1b**–**1g**, reacted with HCN catalyzed by the **3a**/C_6H_5OLi system under the standard conditions and afforded the corresponding β-cyano ketones in 90–96% *ee* (Table 2, entries 3–6, 9, and 10). Although the reactivity of **1c** and **1d** with long alkyl chains was somewhat lower, the enones substituted by secondary and tertiary alkyl groups, **1e**–**1g**, showed reactivity comparable to that of the methyl-substituted ketone **1a**. The cyanation of **1e** with an S/C of 1000 at 0°C or with an S/C of 500 at −20°C proceeded smoothly and gave **2e** in 92% *ee* and 98% *ee*, respectively (Table 2, entries 7 and 8). Chalcone (**1h**), a β-phenyl enone, was much less reactive than the corresponding β-alkyl substrates, but the cyanation product **2h** was obtained in 92% *ee* and 88% yield in the reaction with an S/C of 200 for 47 hours (Table 2, entry 11).[12]

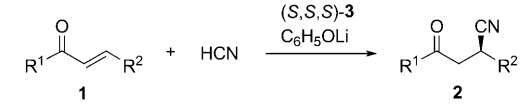
A series of substituted phenyl ketones, **1i**–**1o**, was applied to the asymmetric hydrocyanation. The 2′-Cl phenyl ketone **1i** was treated with **3a** under the typical reaction conditions and gave **2i** in 82% *ee* (Table 2, entry 12). A high enantioselectivity of 95% was achieved in the cyanation of the 3′-Cl substrate **1j** (Table 2, entry 13). The phenyl ketones with an electron-donating CH_3O group at the 3′- or 4′-position, **1k** and **1o**, showed lower reactivity (Table 2, entries 14 and 20). However, an excellent *ee* value of 98% was observed in the reaction of **1k**. The cyanation of substrates with an electron-withdrawing Cl, CF_3, or CH_3OCO group at the 4′-position, **1l**–**1n**, was faster than the reaction of unsubstituted ketone **1a** with maintaining high enantioselectivity (Table 2, entries 15, 16, and 19). The 4′-CF_3 ketone **1m** smoothly reacted with an S/C of 1000 at 0°C or with an S/C of 500 at −20°C and afforded **2m** in 94% *ee* and 98% *ee*, respectively (Table 2, entries 17 and 18).

The cyanation of 2′-naphthyl ketone **1p** under the standard conditions was completed in 12 hours and gave **2p** in 93% *ee* (Table 2, entry 21). The 2′-furyl and 2′-thienyl

Table 2: Asymmetric hydrocyanation of α,β-unsaturated ketones **1**.[a]

Entry	1	S/C[b]	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**1a**	500	0	5	**2a**, 99	94
2	**1a**	500	−20	24	**2a**, 98	97
3	**1b**	500	0	3	**2b**, 98	95
4	**1c**	500	0	18	**2c**, 94	93
5	**1d**	500	0	18	**2d**, 97	90
6	**1e**	500	0	3	**2e**, 99	96
7	**1e**	1000	0	5	**2e**, 98	92
8	**1e**	500	−20	18	**2e**, 98	98
9	**1f**	500	0	5	**2f**, 98	95
10	**1g**	500	0	5	**2g**, 99	96
11	**1h**	200	0	47	**2h**, 88	92
12	**1i**	500	0	5	**2i**, 96	82
13	**1j**	500	0	5	**2j**, 97	95
14	**1k**	200	0	12	**2k**, 96	98
15	**1l**	500	0	3	**2l**, 96	95
16	**1m**	500	0	2	**2m**, 97	96
17	**1m**	1000	0	5	**2m**, 96	94
18	**1m**	500	−20	12	**2m**, 98	98
19	**1n**	500	0	3	**2n**, 97	95
20	**1o**	200	0	12	**2o**, 99	91
21	**1p**	500	0	12	**2p**, 99	93
22	**1q**	500	0	3	**2q**, 98	95
23	**1r**	500	0	5	**2r**, 97[e]	95
24	**1s**	200[f]	0	24	**2s**, 80[g]	93

[a] Unless otherwise stated, reactions were conducted using **1** (3.0 mmol) and HCN (4.5 mmol) in *tert*-$C_4H_9OCH_3$ (18 mL) with a solid (*S*,*S*,*S*)-**3a** and C_6H_5OLi (60 mM in THF). **3a**/C_6H_5OLi = 1:1. HCN was prepared in situ from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Substrate-to-catalyst (**3a**) molar ratio. [c] Yield of isolated **2**. [d] Determined by GC or HPLC on a chiral stationary phase. [e] Contaminated by about 1% of an unidentified compound. [f] **3b** was used as a catalyst. [g] The yield determined by GC methods was 99%.

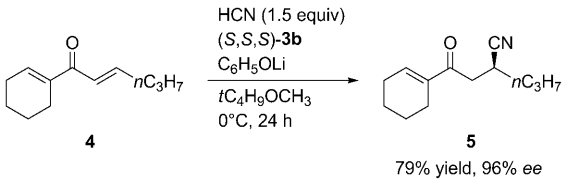


a: $R^1 = C_6H_5$, $R^2 = CH_3$
b: $R^1 = C_6H_5$, $R^2 = nC_3H_7$
c: $R^1 = C_6H_5$, $R^2 = nC_6H_{13}$
d: $R^1 = C_6H_5$, $R^2 = CH_2CH(CH_3)_2$
e: $R^1 = C_6H_5$, $R^2 = CH(CH_3)_2$
f: $R^1 = C_6H_5$, $R^2 = cyclo C_6H_{11}$
g: $R^1 = C_6H_5$, $R^2 = tC_4H_9$
h: $R^1 = C_6H_5$, $R^2 = C_6H_5$
i: R^1 = 2-ClC_6H_4, $R^2 = CH_3$
j: R^1 = 3-ClC_6H_4, $R^2 = CH_3$
k: R^1 = 3-$CH_3OC_6H_4$, $R^2 = CH_3$
l: R^1 = 4-ClC_6H_4, $R^2 = CH_3$
m: R^1 = 4-$CF_3C_6H_4$, $R^2 = CH_3$
n: R^1 = 4-$CH_3OCOC_6H_4$, $R^2 = CH_3$
o: R^1 = 4-$CH_3OC_6H_4$, $R^2 = CH_3$
p: R^1 = 2-naphthyl, $R^2 = CH_3$
q: R^1 = 2-furyl, $R^2 = CH_3$
r: R^1 = 2-thienyl, $R^2 = CH_3$
s: $R^1 = CH_3$, $R^2 = nC_3H_7$

Scheme 2. Asymmetric hydrocyanation of α,β-unsaturated ketones **1** to the β-cyano ketones **2**.

ketones, **1q** and **1r**, were converted into the 1,4-adducts, **2q** and **2r**, with 95% *ee* in both cases (Table 2, entries 22 and 23). The reaction of 3-hepten-2-one (**1s**), an aliphatic enone, with the **3a**/C_6H_5OLi system was slow, but the cyanation with an S/C of 200 at 0°C for 24 hours afforded **2s** in 99% yield and 93% *ee* when **3b** was used instead of **3a** (Table 2, entry 24).[11] The chiral Gd and Sr catalysts reported by Shibasaki exhibit wider applicability to the reaction of aliphatic and β,β-disubstituted enones.[2]

The **3b**/C_6H_5OLi catalyst was applied to the regioselective cyanation of a dialkenyl ketone. When cyclohexenyl pentenyl ketone **4** was subjected to the cyanation conditions, the monocyanated product **5** (at the pentenyl group) was obtained in 96% *ee* (Scheme 3). The regioselectivity was estimated to be greater than 99%.



Scheme 3. Regioselective cyanation of dienone **4**.

The Ru complex **3a** was so robust that it was recovered by column chromatography on silica gel from the reaction mixture in the open air, and was reusable as a cyanation catalyst with the addition of fresh C_6H_5OLi. As shown in Table 3, **3a** could be used five times in the cyanation of **1a**

Table 3: Recycled use of **3a** in the hydrocyanation of **1a**.[a]

Run number[b]	Conversion [%][c]	Yield [%][d]	*ee* [%][c]
1	>99	97	93
2	>99	93	94
3	>99	99	93
4	>99	99	93
5	>99	99	92

[a] Reactions were conducted using **1a** (10 mmol) and HCN (15 mmol) in *tert*-$C_4H_9OCH_3$ (60 mL) at 0°C for 5 h with a solid (*S*,*S*,*S*)-**3a** and C_6H_5OLi (50 mM in THF). **1a**/**3a**/C_6H_5OLi = 500:1:1 (initial). HCN was prepared in situ from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Number of times the catalyst was used. [c] Determined by GC on a chiral stationary phase. [d] Yield of isolated **2a**.

with an initial S/C of 500 at 0°C with maintaining high enantioselectivity. The total turnover number was about 2500. The notable robustness and reusability of **3a** make it suitable for practical use.

In addition, different α,β-unsaturated ketones **1** were cyanated sequentially with this catalyst-reuse procedure. Table 4 lists the results. The catalyst efficiency and enantioselectivity for all runs were comparable to those of the regular single-run reactions shown in Table 2.

In summary, we have reported here the efficient enantioselective conjugate addition of HCN into the α,β-unsaturated ketones to afford the β-cyano ketones catalyzed by our original [Ru(phgly)$_2$(binap)]/C_6H_5OLi system. The reaction was carried out with an S/C in the range of 200–1000 at −20°C→0°C. A series of aryl-, hetero-aryl-, and alkyl-substituted enones was converted into the 1,4-addition products in up to 98% *ee* without formation of a detectable amount of the 1,2-adducts. The reaction of cyclohexenyl pentenyl ketone afforded the monocyanated product at the less-hindered site in high regio- and enantioselectivity. The robust [Ru(phgly)$_2$(binap)] complex can be reused with addition of fresh C_6H_5OLi without loss of the stereoselectivity. We hope these findings will contribute to the progress of synthetic organic chemistry.

Table 4: Sequential hydrocyanation of different substrates.[a]

Run number[b]	1	*t* [h]	Yield [%][c]	*ee* [%][d]
1	**1n**	3	96	93
2	**1p**	12	96	90
3	**1j**	5	98	96
4	**1l**	3	95	95
5	**1k**[e]	12	99	96

[a] Reactions were conducted using **1** (8.2 mmol) and HCN (11.8 mmol) in *tert*-$C_4H_9OCH_3$ (48 mL) at 0°C with a solid (*S*,*S*,*S*)-**3a** and C_6H_5OLi (50 mM in THF). **1**/**3a**/C_6H_5OLi = 500:1:1 (initial). HCN was prepared in situ from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Number of times the catalyst was used. [c] Yield of isolated **2**. [d] Determined by GC or HPLC on a chiral stationary phase. [e] Reaction using **1k** (3.2 mmol) and HCN (4.8 mmol) in *tert*-$C_4H_9OCH_3$ (19 mL).

Experimental Section

The typical procedure for the hydrocyanation of 1-phenyl-2-buten-1-one (**1a**): **Caution**: $(CH_3)_3SiCN$ and HCN that is formed in situ must be used in a well-ventilated fume hood owing to their high toxicity. Ruthenium complex (*S*,*S*,*S*)-**3a** (6.2 mg, 6.1 μmol)[7,8] was placed in a 50 mL Schlenk flask, and the air present in this apparatus was replaced by argon. Anhydrous CH_3OH (146 mg, 4.6 mmol) was added to this flask, and the mixture was cooled to 0°C. Then $(CH_3)_3SiCN$ (445 mg, 4.5 mmol) was added in a dropwise manner, and the mixture was stirred for 15 min. To the solution containing HCN, anhydrous *tert*-$C_4H_9OCH_3$ (18 mL) and C_6H_5OLi (60 mM in THF, 100 μL, 6.0 μmol) were added at 0°C, and the mixture was stirred for 30 min. Then **1a** (447 mg, 3.1 mmol) was added to this solution in a dropwise manner over 5 min, and the reaction mixture was stirred for 5 h. After the solvent and the volatile compounds were evaporated under reduced pressure, the residue was purified by column chromatography on silica gel to give (*S*)-**2a** (colorless oil, 531 mg, 99% yield, 94% *ee*). $[\alpha]_D^{24} = -6.7\ deg\,cm^3\,g^{-1}\,dm^{-1}$ (c = 1.07 g cm^{-3}, $CHCl_3$); literature[2a] $[\alpha]_D^{25} = -6.2\ deg\,cm^3\,g^{-1}\,dm^{-1}$ (c = 0.6 g cm^{-3}, $CHCl_3$), 88% *ee* (absolute configuration was unreported); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, 3H, J = 6.8 Hz, CH_3), 3.23 (dd, 1H, J = 6.5, 17.0 Hz, C*H*H), 3.31–3.40 (m, 1H, CHCN), 3.43 (dd, 1H, J = 6.2, 17.0 Hz, CH*H*), 7.48–7.51 (m, 2H, aromatic H), 7.60–7.63 (m, 1H, aromatic H), 7.95–7.97 ppm (m, 2H, aromatic H); ^{13}C NMR (67.7 MHz, $CDCl_3$): δ = 17.8 (CH_3), 20.5 (CH), 42.2 (CH_2), 122.6 (C), 128.0 (CH), 128.8 (CH), 133.8 (CH), 135.8 (C), 195.1 ppm (C); HRMS (ESI): m/z calcd for $C_{11}H_{11}ClNO$: 208.05292 $[M+Cl]^-$; found: 208.05292. The *ee* value of **2a** was determined by GC on a chiral stationary phase using an InertCap CHIRAMIX column (0.25 mm × 30 m, depth of film = 0.25 μm, GL Science); carrier gas: helium (217 kPa); column temp: 170°C heating to 179°C at a rate of 0.5°C min^{-1}; injection temp; 250°C; retention time (t_R) of (*R*)-**2a**: 17.5 min (3.1%), t_R of (*S*)-**2a**: 16.5 min (96.9%). The *ee* value was not changed by purification with column chromatography. The absolute

configuration was determined after conversion to 2-methyl-4-oxo-4-phenylbutanoic acid in 55% *ee*. $[\alpha]_D^{26} = -18.4\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.592\ g\,cm^{-3}$, $CHCl_3$); literature[13] $[\alpha]_D^{20} = -32.5\ deg\,cm^3\,g^{-1}\,dm^{-1}$ ($c = 0.69\ g\,cm^{-3}$, $CHCl_3$) for the *S* enantiomer.

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[10] Tol-binap = 2,2′-bis(di-4-tolylphosphanyl)-1,1′-binaphthyl.

[11] The β-amino ketones **2a** in 88% *ee* and **2s** in 92% *ee* were obtained by Shibasaki's Gd system (see reference [2a]).

[12] The conjugate addition of $(CH_3)_3SiCN$ to **1h** catalyzed by a chiral sodium phosphate with an S/C of 5 gave **2h** in 71% *ee*. See: J. Yang, S. Wu, F.-X. Chen, *Synlett* **2010**, 2725 – 2728.

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