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Enantioselective Hydrocyanation of Aldehydes Catalyzed by [Li{Ru(phgly)$_2$(binap)}]X (X = Cl, Br)

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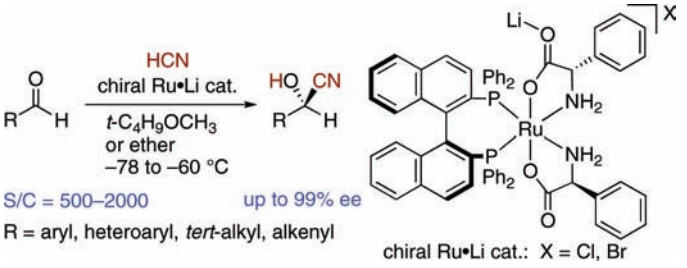
ABSTRACT



Novel bimetallic complexes [Li{Ru[(*S*)-phgly]$_2$[(*S*)-binap]}]X (X = Cl, Br) are readily synthesized by mixing Ru[(*S*)-phgly]$_2$[(*S*)-binap] and LiX. A single-crystal X-ray analysis reveals the structure. These bimetallic complexes efficiently catalyze asymmetric hydrocyanation of aldehydes with a substrate-to-catalyst molar ratio of 500−2000 at −78 to −60 °C. A range of aromatic, heteroaromatic, and α,β-unsaturated aldehydes as well as a *tert*-alkyl aldehyde is converted to the cyanohydrins in high enantiomeric excess (up to 99%).

Enantioselective hydrocyanation of aldehydes is one of the most direct and efficient methods to produce optically active cyanohydrins,[1] which are useful intermediates for the synthesis of biologically important compounds, including β-amino alcohols and α-hydroxy carboxylic acid derivatives.[2,3] This asymmetric transformation catalyzed by oxynitrilase has been used for the practical synthesis of such compounds.[3,4] On the other hand, investigations of artificial catalysts for this reaction have been limited. The cyclic dipeptide *cyclo*-[(*S*)-phenylalanyl-(*S*)-histidyl] reported by Inoue and co-workers is an exception.[5−7] Benzaldehyde and HCN react with the dipeptide catalyst at a substrate-to-catalyst molar ratio (S/C) of 50 to give mandelonitrile in 97% yield and 97% ee. A Ti(IV) complex with a modified

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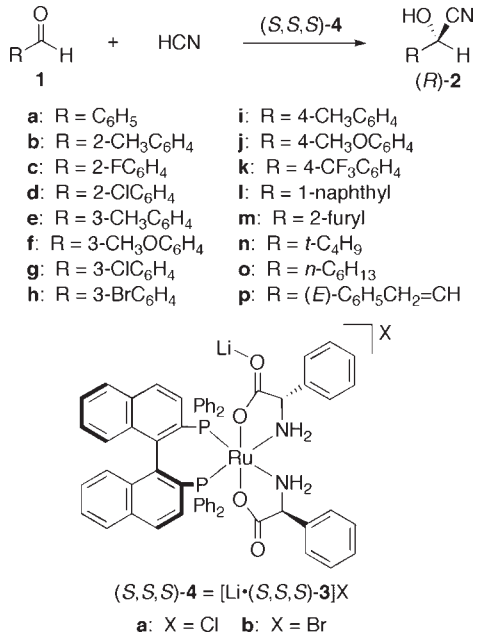
Scheme 1. Asymmetric Hydrocyanation of Aldehydes **1**



dipeptide ligand also developed by Inoue catalyzes this reaction (S/C = 10), resulting in the cyanohydrin in 83% yield and 90% ee.[8] Both examples demonstrate the great potential of nonenzymatic catalysts for enantioselective hydrocyanation of aldehydes. However, these catalysts still have the following drawbacks: (1) the catalyst loadings are relatively high (S/C < 50), and (2) aldehyde substrates that react at a high optical yield of >90% are limited to benzaldehyde, its derivatives with an electron-donating group at the 3 or 4 position, and 2-naphthaldehydes.

We have recently reported that a novel combined catalyst of Ru(phgly)$_2$(binap) and a Li compound effects the asymmetric addition of $(CH_3)_3SiCN$ to aldehydes and α-keto esters.[9,10] The corresponding silylated cyanohydrins are obtained in up to 99% ee quantitatively. Spectroscopic analysis suggested that in situ formed [Li{Ru(phgly)$_2$-(binap)}]$^+$ acts as a chiral Lewis acid to activate the carbonyl moiety of substrates. These observations prompted us to isolate the chiral bimetallic salts [Li{Ru(phgly)$_2$(binap)}]X (X = Cl, Br) (**4**, Scheme 1) and to utilize these compounds as the catalysts for enantioselective hydrocyanation of aldehydes.

The desired [Li{Ru[(*S*)-phgly]$_2$[(*S*)-binap]}]Cl [(*S*,*S*,*S*)-**4a**] was readily prepared as follows: Ru[(*S*)-phgly]$_2$[(*S*)-binap] [(*S*,*S*,*S*)-**3**] (204 mg, 199 μmol), which was prepared according to our previous report,[9] and LiCl (0.10 M solution in THF, 2.60 mL, 260 μmol) were mixed in

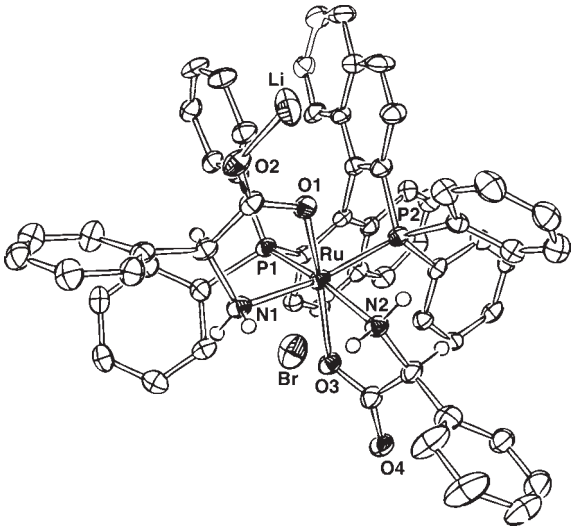


Figure 1. ORTEP drawing of (*S*,*S*,*S*)-**4b**. Selected distances (Å) and bond angles (deg): Ru−O1 2.108(4), Ru−O3 2.110(4), Ru−N1 2.209(4), Ru−N2 2.117(5), Ru−P1 2.283(1), Ru−P2 2.271(2), Li−O2 1.940(1); O1−Ru−O3 162.6(1), N1−Ru−N2 89.3(1), P1−Ru−P2 89.0(5). Only amino and methyne protons of PhGly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

THF (4 mL) at ambient temperature. The solution was left for 10 h and then kept at −11 °C for 7 h, resulting in the precipitation of (*S*,*S*,*S*)-**4a** as a yellow crystal (197 mg, 93%) (see the Supporting Information). The Br salt (*S*,*S*,*S*)-**4b** was obtained as a needle-like crystal in the same manner. Single-crystal X-ray analysis revealed that **4b** has a Ru center with a distorted octahedral geometry in which two carboxylate oxygens connect at the apical positions [O(1)−Ru−O(3) = 163°] (Figure 1). The Li$^+$ is located close to a carbonyl oxygen (O(2)−Li distance = 1.92 Å), and the Br$^-$ is placed between two nitrogen atoms. The ^{31}P{^{1}H} NMR measurement in THF-d_8 indicated a singlet signal at δ 54.1 ppm. The ^{1}H NMR signal of a PhGly amino proton centered at δ 4.32 ppm was notably shifted lower than that of the corresponding signal of **3** (without Li$^+$) at δ 3.92 ppm (see the Supporting Information). This behavior suggests that the Ru complex **3** maintains the interaction with Li$^+$ in the solution phase.

Benzaldehyde (**1a**) was selected as a standard substrate to examine the catalytic efficiency of **4** in enantioselective hydrocyanation of aldehydes (Scheme 1). HCN prepared by mixing $(CH_3)_3SiCN$ (1.48 g, 14.9 mmol) and CH_3OH (481 mg, 15.0 mmol) at 0 °C smoothly reacted with **1a** (530 mg, 5.0 mmol) in $tC_4H_9OCH_3$ (38 mL) at −78 °C in the presence of (*S*,*S*,*S*)-**4a** (10.8 mg, 10 μmol, S/C = 500) to afford (*R*)-**2a** in 95% ee and 96% isolated yield (Table 1, entry 1).[11] The highest levels of catalytic activity and enantioselectivity for this reaction were achieved. Three equivalents of HCN to **1a** were required to obtain the product in high yield under these conditions. The yield was decreased to <80% by using 2 equiv of HCN (entry 2). The reaction using isolated HCN prepared as described in the literature[12] gave a comparable result in the presence of

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(10) PhGly = phenylglycinate, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

Table 1. Asymmetric Hydrocyanation of Benzaldehyde (**1a**)[a]

entry	HCN[b]	catalyst	solvent	% yield[c]	% ee[d]
1	**A** (3)	**4a**	t-$C_4H_9OCH_3$	96	95
2	**A** (2)	**4a**	t-$C_4H_9OCH_3$	78	95
3	**B** (3)	**4a**[e]	t-$C_4H_9OCH_3$[f]	97	93
4	**A** (3)	**3**	t-$C_4H_9OCH_3$	<1[g]	nd[h]
5	**A** (3)	LiCl	t-$C_4H_9OCH_3$	1[g]	
6	**A** (3)	**3** + LiCl	t-$C_4H_9OCH_3$	78	94
7	**A** (3)	**4b**	t-$C_4H_9OCH_3$	83	95
8	**A** (3)	**4a**	$(C_2H_5)_2O$	62	96
9	**A** (3)	**4a**	toluene	4[g]	nd[h]
10	**A** (3)	**4a**	CH_2Cl_2	1[g]	nd[h]

[a] Unless otherwise stated, reactions were carried out using **1a** (5.0 mmol) and HCN in solution (38 mL) with a catalyst (10 μmol, S/C = 500) at −78 °C for 18 h. [b] **A**: HCN was in situ prepared from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. **B**: Isolated HCN was used. The HCN/**1a** molar ratio is in parentheses. [c] Isolated yield of **2a**. [d] Data of (*R*)-**2a** determined by chiral HPLC analysis. [e] $(C_2H_5)_3N$ (10 equiv to **4a**) was added. [f] Reaction using **1a** (2.5 mmol) in 19 mL of solvent. [g] Determined by ^1H NMR analysis. [h] Not determined.

a catalytic amount of $(C_2H_5)_3N$ (**1a**/amine = 50:1) (entry 3). The amine may accelerate the proton migration in this system. It is worth noting that this reaction is the net hydrocyanation without substantial assistance from silicone compounds. The Ru complex **3** or LiCl alone feebly catalyzed the cyanation under the typical reaction conditions (entries 4 and 5). An in situ prepared catalyst from **3** and LiCl in a 1:1 ratio gave **2a** in 94% ee, although the reactivity was insufficient (entry 6). These results clearly indicate that the Li/Ru complexation is crucial to achieve high catalytic activity, although the nature of this catalyst is unclear. The use of Br salt **4b** as a catalyst also gave **2a** in 95% ee and in somewhat lower chemical yield than the reaction with **4a** (entry 7, see also entry 1). The reaction rate of the cyanation with **4a** was slowed in ether (entry 8). No significant reactivity was observed in less polar toluene and CH_2Cl_2 (entries 9 and 10).

A series of aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes were converted to the chiral cyanohydrins in high ee (Scheme 1 and Table 2). The reaction of 2-methylbenzaldehyde (**1b**) and the in situ formed HCN with (*S*,*S*,*S*)-**4a** (S/C = 500) in t-$C_4H_9OCH_3$ at −78 °C for 18 h gave the *R* cyanohydrin, (*R*)-**2b**, in 97% ee and 89% isolated yield (entry 2). The enantioselectivity was even higher than that obtained in the reaction of **1a** (95% ee, entry 1), although the reaction rate was slowed. When the reaction of **1b** was carried out by the use of **4b** instead of **4a**, the adduct **2b** was quantitatively obtained in the same ee (entry 3). 2-Fluoro- and 2-chlorobenzaldehydes, **1c** and **1d**,

Table 2. Asymmetric Hydrocyanation of Aldehydes with Ru·Li Combined Catalysts (*S*,*S*,*S*)-**4**[a]

entry	1	4	S/C[b]	temp, °C	time, h	% yield[c]	% ee[d]
1	**1a**	**4a**	500	−78	18	96	95
2	**1b**	**4a**	500	−78	18	89 (78)	97[e]
3	**1b**	**4b**	500	−78	18	96	97
4	**1c**	**4a**	500	−78	18	97	92
5	**1d**	**4a**	500	−78	18	98 (84)	91[e]
6	**1d**	**4b**	500	−78	18	98	93
7	**1e**	**4a**	500	−78	18	90	95
8	**1f**	**4a**	500	−78	24	96	94
9	**1g**	**4a**	500	−78	18	98 (68)	98[e]
10[f]	**1g**	**4a**	500	−78	18	98	95
11	**1g**	**4a**	2000	−78	18	91	96
12	**1h**	**4a**	500	−78	18	98 (92)	99[e]
13	**1i**	**4a**	500	−70	24	82	95
14	**1j**	**4a**	500	−60	24	82	93
15	**1k**	**4a**	500	−78	18	96 (91)	96[e]
16	**1l**	**4a**	500	−78	18	93	91
17	**1l**	**4b**	500	−78	18	99 (90)	94[e]
18	**1m**	**4a**	500	−70	24	89	92
19	**1n**	**4a**	500	−78	18	91[g]	94[h]
20	**1o**	**4a**	500	−78	18	42	57[h]
21	**1p**	**4a**	500	−70	48	95	92

[a] Unless otherwise stated, reactions were carried out using **1** (5.0 mmol) and HCN (15 mmol) in t-$C_4H_9OCH_3$ (38 mL) with a combined complex (*S*,*S*,*S*)-**4**. HCN was in situ prepared from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Substrate-to-catalyst molar ratio. [c] Isolated yield of (*R*)-**2**. The yield after recrystallization is shown in parentheses. [d] Data of (*R*)-**2** determined by chiral HPLC analysis. [e] The product in >99% ee was obtained after recrystallization. [f] Reaction of **1g** (2.5 mmol) and isolated HCN in t-$C_4H_9OCH_3$ (19 mL). [g] Yield after conversion to the acetate by treatment with $(CH_3CO)_2O$ and pyridine. [h] Determined by chiral GC analysis after conversion to the acetate.

were cyanated with **4a**, affording **2c** and **2d** in 92% and 91% ee, respectively (entries 4 and 5). The ee of **2d** was increased to 93% in the reaction catalyzed by **4b** (entry 6). The reaction of 3-methyl and 3-methoxy aldehydes, **1e** and **1f**, showed selectivity comparable with that in the reaction of **1a** (entries 7 and 8). The excellent ee of the product (>98%) was achieved in the cyanation of 3-chloro and 3-bromo aldehydes, **1g** and **1h** (entries 9 and 12). The high reactivity of **1g** allowed performance of the cyanation with an S/C of 2000 to afford **2g** in 96% ee and 91% isolated yield (entry 11). The comparable result was obtained in the reaction catalyzed by **4a** using isolated HCN with $(C_2H_5)_3N$ (entry 10). Benzaldehydes with electron-donating groups at the 4 position, **1i** and **1j**, required higher temperature conditions for obtaining a >80% chemical yield but yielded an ee of >93% (entries 13 and 14). The higher reactivity and enantioselectivity were observed in the cyanation of aldehyde with an electron-attracting CF_3 group **1k** (entry 15). The cyanation of 1-naphthaldehyde (**1l**) catalyzed by **4a** and **4b** smoothly proceeded to give **2l** in 91% ee and 94% ee, respectively (entries 16 and 17). The reaction of 2-furancarbaldehyde (**1m**) was slow, but **2m** in 92% ee and 89% yield was obtained at −70 °C for 24 h (entry 18). Pivalaldehyde (**1n**), a *tert*-alkyl aldehyde, was cyanated with **4a** to afford the adduct **2n** in 94% ee and 91% yield (entry 19).[13] The reactivity and enantioselectivity

(11) The bimetallic salt **4a** did not catalyze the reaction of **1a** and acetone cyanohydrin. For asymmetric reaction of aldehydes and acetone cyanohydrin with high enantioselectivity, see: (a) Ooi, T.; Takaya, K.; Miura, T.; Ichikawa, H.; Maruoka, K. *Synlett* **2000**, 1133–1134. (b) Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H.; Maruoka, K. *Tetrahedron* **2001**, *57*, 867–873. (c) Takaki, J.; Egami, H.; Matsumoto, K.; Saito, B.; Katsuki, T. *Chem. Lett.* **2008**, *37*, 502–503.

(12) Glemser, O. In *Handbook of Preparative Inorganic Chemistry*, 2nd ed.; Brauer, G., Riley, R. F., Eds.; Academic Press: New York, 1963; pp 658−660.

in the reaction of the primary alkyl aldehyde **1o** was significantly decreased (entry 20). The cyanation of cinnamaldehyde (**1p**) exclusively gave the 1,2-adduct **2p** in 92% ee (entry 21). The high regioselectivity is noteworthy and also a benefit for synthetic applications.

In summary, the newly devised bimetallic complexes [Li{Ru(phgly)$_2$(binap)}]X (**4**; X = Cl, Br) act as excellent catalysts for asymmetric hydrocyanation of aldehydes. The structure of **4b** (X = Br) was determined by an X-ray crystallographic analysis. The reaction is conducted with an S/C of 500−2000. A series of aromatic, heteroaromatic, α,β-unsaturated aldehydes, as well as a *tert*-alkyl aldehyde, are converted to the cyanohydrins in high ee (up to 99%). Thus, these findings represent a significant improvement in the reactivity, enantioselectivity, and scope of substrates for hydrocyanation of aldehydes with artificial catalysts.

(13) Asymmetric hydrocyanation of **1m** and **1n** with the dipeptide catalyst *cyclo*-[(*S*)-phenylalanyl-(*S*)-histidyl] gave the corresponding cyanohydrins in 42% ee and 58% ee, respectively (see ref 5).

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Supporting Information Available. Preparative methods and properties of bimetallic complexes **4**, procedures for asymmetric hydrocyanation of aldehydes **1**, NMR, GC, and HPLC behavior, $[\alpha]_D$ values of products, and X-ray crystallographic data of complex **4b** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.