

# [Ru(phgly)<sub>2</sub>(binap)]/Li<sub>2</sub>CO<sub>3</sub>: A Highly Active, Robust, and Enantioselective Catalyst for the Cyanosilylation of Aldehydes\*\*

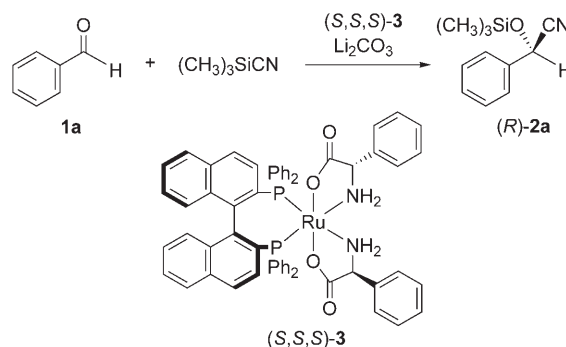
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The enantioselective cyanosilylation of aldehydes is one of the most efficient and general methods for producing optically active cyanohydrin derivatives, which can be readily converted into biologically important compounds, including  $\beta$ -amino alcohols and  $\alpha$ -hydroxycarboxylic acid derivatives.<sup>[1]</sup> A variety of chirally modified catalysts have been utilized for this asymmetric transformation, and some of them have achieved high enantioselectivity.<sup>[1,2]</sup> However, the development of a highly active and robust chiral catalyst for this reaction is challenging.

We and other research groups have reported that simple lithium salts, such as LiCl,<sup>[3]</sup> LiClO<sub>4</sub>,<sup>[4]</sup> and lithium alkoxides,<sup>[5]</sup> show high catalytic activity for the cyanosilylation of carbonyl compounds. We expected that the combination of a lithium salt and a metal complex with appropriate chiral ligands would form an efficient catalyst system for this asymmetric reaction. Herein we disclose a highly active, robust, and enantioselective catalyst consisting of [Ru(phgly)<sub>2</sub>(binap)] (phgly = phenylglycinate, binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl) and Li<sub>2</sub>CO<sub>3</sub> for the cyanosilylation of aldehydes. The reaction is conducted with a substrate-to-catalyst ratio (S/C) of 10000:1 at  $-78$  to  $-70$  °C, and 100000:1 at  $-40$  °C. A series of aromatic, aliphatic, and  $\alpha,\beta$ -unsaturated aldehydes can be converted into silylated cyanohydrins in up to 98 % *ee* by using this system.

[Ru((S)-PhGly)<sub>2</sub>((S,S,S)-3)] ((S,S,S)-3; Scheme 1)<sup>[6]</sup> was isolated in 74 % yield by treatment of [RuCl<sub>2</sub>{(S)-binap}-(dmf)]<sub>n</sub> (oligomeric form)<sup>[7]</sup> and 3.0 equivalents of the (S)-PhGly sodium salt in a DMF/CH<sub>3</sub>OH mixed solvent at 25 °C for 12 h (see the Experimental Section). This complex was so robust that it could be purified by chromatography on silica gel in air, and could be stored in a vial at room temperature. The <sup>31</sup>P{<sup>1</sup>H} NMR spectrum of (S,S,S)-3 in CDCl<sub>3</sub> shows a singlet at  $\delta$  = 52.3 ppm, which indicates a *trans*-Ru(OCOR)<sub>2</sub> geometry.<sup>[8,9]</sup>

When benzaldehyde (**1a**; 1.05 g, 9.9 mmol) and (CH<sub>3</sub>)<sub>3</sub>SiCN (1.19 g, 12.0 mmol) were treated with (S,S,S)-3



**Scheme 1.** Asymmetric cyanosilylation of benzaldehyde (**1a**).

(20 mm in THF, 50  $\mu$ L, 1.0  $\mu$ mol, S/C 10000:1) and aqueous Li<sub>2</sub>CO<sub>3</sub> (0.10 M, 10  $\mu$ L, 1.0  $\mu$ mol) at  $-78$  °C in (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O (10 mL) for 12 h, the *R* cyanation product (**R**)-**2a** was obtained quantitatively with 97 % *ee* (Scheme 1 and Table 1, entry 1). A 1:1 ratio of complex **3** and Li<sub>2</sub>CO<sub>3</sub> gave the best catalyst performance. The enantioselectivity was slightly

**Table 1:** Asymmetric cyanosilylation of benzaldehyde (**1a**).<sup>[a]</sup>

| Entry | <b>1a</b> /3/Li <sub>2</sub> CO <sub>3</sub> | Solvent                         | Yield [%] <sup>[b]</sup> | <i>ee</i> [%] <sup>[b]</sup> |
|-------|----------------------------------------------|---------------------------------|--------------------------|------------------------------|
| 1     | 10000:1:1                                    | Et <sub>2</sub> O               | > 99                     | 97                           |
| 2     | 10000:1:2                                    | Et <sub>2</sub> O               | > 99                     | 95                           |
| 3     | 10000:1:0.5                                  | Et <sub>2</sub> O               | 98                       | 97                           |
| 4     | 10000:1:0.2                                  | Et <sub>2</sub> O               | 9                        | 98                           |
| 5     | 10000:1:0                                    | Et <sub>2</sub> O               | < 1                      | n.d. <sup>[c]</sup>          |
| 6     | 10000:0:1                                    | Et <sub>2</sub> O               | 47                       | –                            |
| 7     | 10000:1:1                                    | <i>t</i> BuOMe                  | > 99                     | 94                           |
| 8     | 10000:1:1                                    | THF                             | 38                       | 39                           |
| 9     | 10000:1:1                                    | toluene                         | 84                       | 88                           |
| 10    | 10000:1:1                                    | CH <sub>2</sub> Cl <sub>2</sub> | 84                       | 88                           |

[a] Unless otherwise stated, reactions were conducted using **1a** (9.9–10.0 mmol) and (CH<sub>3</sub>)<sub>3</sub>SiCN (12.0 mmol) in solvent (10 mL) with (S,S,S)-3 (20 mm in THF) and aqueous Li<sub>2</sub>CO<sub>3</sub> (0.1 M) at  $-78$  °C for 12 h. [b] Data for (**R**)-**2a** were determined by GC analysis on a chiral stationary phase. [c] Not determined.

lower when the reaction was conducted with a **3**/Li<sub>2</sub>CO<sub>3</sub> ratio of 1:2 (Table 1, entry 2). The reaction rate was slower when the proportion of Li<sub>2</sub>CO<sub>3</sub> was reduced (Table 1, entries 3 and 4). The Ru complex **3** alone was a poor catalyst for the reaction under the standard conditions (Table 1, entry 5), while Li<sub>2</sub>CO<sub>3</sub> showed medium catalytic activity and gave racemic **2a** (Table 1, entry 6).<sup>[10]</sup> When the less Lewis basic salt LiCl or LiOTf was used instead of Li<sub>2</sub>CO<sub>3</sub> (**1a**/3/Li salt 10000:1:1 or 10000:1:2), **2a** was obtained in less than 3 %

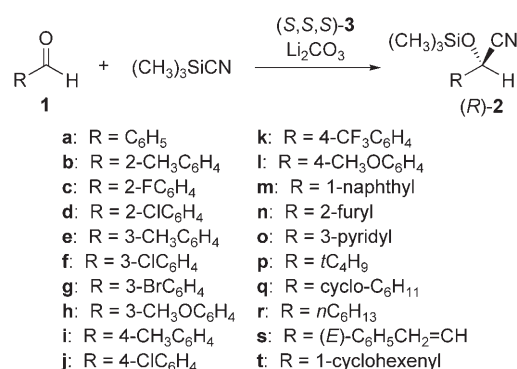
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[\*\*] This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 18350046) and the Innovation Plaza Hokkaido in the Japan Science and Technology Agency (JST). phgly = phenylglycinate, binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200801501>.

yield. These results clearly indicate that the combination of **3** and  $\text{Li}_2\text{CO}_3$  generates a new highly active catalyst for this asymmetric transformation. Similarly reactivity was observed on using  $t\text{C}_4\text{H}_9\text{OCH}_3$  as the solvent under conditions otherwise identical to those shown in Table 1, entry 1, and afforded (*R*)-**2a** in 94% *ee* (Table 1, entry 7). Interestingly, both the reactivity and the enantioselectivity were significantly lower in THF (Table 1, entry 8). The use of toluene or dichloromethane, which are typical solvents for cyanosilylations,<sup>[1,2]</sup> gave lower yields and enantioselectivities than reactions in  $(\text{C}_2\text{H}_5)_2\text{O}$  (Table 1, entries 9 and 10).

A series of aromatic, aliphatic, and  $\alpha,\beta$ -unsaturated aldehydes were converted quantitatively into the cyanohydrin silyl ethers in high enantioselectivity with an S/C ratio of 10000:1 (Scheme 2). The reaction of benzaldehyde (**1a**) and 1.2 equivalents of  $(\text{CH}_3)_3\text{SiCN}$  in  $(\text{C}_2\text{H}_5)_2\text{O}$  at  $-78^\circ\text{C}$  in the presence of (*S,S,S*)-**3** and  $\text{Li}_2\text{CO}_3$  (**3**/ $\text{Li}_2\text{CO}_3$  1:1) was complete



**Scheme 2.** Asymmetric cyanosilylation of aldehydes **1**.

in 12 h. The silylated cyanohydrin (*R*)-**2a** was readily isolated in 98% yield and 97% *ee*, without aqueous workup, simply by concentration of the mixture and a short-path distillation (Table 2; see the Experimental Section). The high catalytic activity of the (*S,S,S*)-**3**/ $\text{Li}_2\text{CO}_3$  system resulted in complete conversion when an S/C ratio of 10000:1 was used at  $-40^\circ\text{C}$  over 24 h, and gave the *R* product with 90% *ee*. The reaction of 2-methylbenzaldehyde (**1b**) gave a comparable enantioselectivity of 96%. Substitution at the C2-position of the aldehydes with F or Cl atoms (**1c** and **1d**) did not significantly affect the enantioselectivity. The cyanation of 3-methylbenzaldehyde (**1e**) was conducted at  $-70^\circ\text{C}$  because of its low reactivity, but the desired product (*R*)-**2e** was obtained in high enantioselectivity. A high *ee* value of 98% was achieved in the cyanation of substrates with Cl or Br atoms at the C3-position (**1f** and **1g**). The reaction of a benzaldehyde with an electron-donating methoxy group at the C3-position (**1h**) at  $-70^\circ\text{C}$  and an S/C ratio of 10000:1 required 24 hours for completion, and afforded (*R*)-**2h** with 95% *ee*. 4-Methyl- and 4-chloro-substituted aldehydes **1i** and **1j** were converted into the *R* products with 97% *ee*. The electron-deficient 4- $\text{CF}_3$ -substituted aldehyde **1k** showed high reactivity, although the enantioselectivity was somewhat lower. A substrate with an electron-donating methoxy group at the C4-position (**1l**) was converted at  $-70^\circ\text{C}$  quantitatively into (*R*)-**2l** with 96% *ee*

**Table 2:** Asymmetric cyanosilylation of aldehydes.<sup>[a]</sup>

| 1                        | Solvent               | S/C <sup>[b]</sup> | T<br>[°C] | t<br>[h] | Yield<br>[%] <sup>[c]</sup> | ee<br>[%] <sup>[d]</sup> |
|--------------------------|-----------------------|--------------------|-----------|----------|-----------------------------|--------------------------|
| <b>1a</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 98                          | 97                       |
| <b>1a</b> <sup>[e]</sup> | $\text{Et}_2\text{O}$ | 100000:1           | $-40$     | 24       | 94                          | 90                       |
| <b>1b</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 18       | 99                          | 96                       |
| <b>1c</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 97                          | 96                       |
| <b>1d</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 97                          | 94                       |
| <b>1e</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 12       | 99                          | 97                       |
| <b>1f</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 98                          | 98                       |
| <b>1g</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 98                          | 98                       |
| <b>1h</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 24       | 97                          | 95                       |
| <b>1i</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 24       | 95                          | 97                       |
| <b>1j</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 12       | 96                          | 97                       |
| <b>1k</b> <sup>[f]</sup> | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 12       | 98                          | 94                       |
| <b>1l</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 24       | 99                          | 96                       |
| <b>1m</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 18       | 97                          | 95                       |
| <b>1n</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-70$     | 18       | 97                          | 93                       |
| <b>1o</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 18       | 91 <sup>[g]</sup>           | 93                       |
| <b>1p</b>                | $\text{Et}_2\text{O}$ | 10000:1            | $-78$     | 18       | 94                          | 93                       |
| <b>1p</b>                | $t\text{BuOMe}$       | 10000:1            | $-78$     | 18       | 92                          | 95                       |
| <b>1q</b>                | $t\text{BuOMe}$       | 10000:1            | $-78$     | 18       | 97                          | 88                       |
| <b>1r</b>                | $t\text{BuOMe}$       | 10000:1            | $-78$     | 18       | 98                          | 70                       |
| <b>1s</b>                | $t\text{BuOMe}$       | 10000:1            | $-78$     | 18       | 93                          | 91                       |
| <b>1t</b>                | $t\text{BuOMe}$       | 10000:1            | $-70$     | 18       | 92                          | 93                       |

[a] Unless otherwise stated, reactions were conducted using **1** (9.7–10.6 mmol) and  $(\text{CH}_3)_3\text{SiCN}$  (12.0 mmol) in solvent (10 mL) with (*S,S,S*)-**3** (20 mM in THF) and aqueous  $\text{Li}_2\text{CO}_3$  (0.1 M); **3**/ $\text{Li}_2\text{CO}_3$  1:1. [b] Substrate-to-catalyst (**3**) ratio. [c] Yield of isolated (*R*)-**2**. Yields determined by GC analysis were >99% in all cases. [d] Data for (*R*)-**2** were determined by GC analysis on a chiral stationary phase. [e] Reaction using 50.7 mmol (5.38 g) **1a** in 50 mL of  $(\text{C}_2\text{H}_5)_2\text{O}$ . [f] Reaction in 20 mL of solvent. [g] Yield after deprotection.

after 24 hours. 1-Naphthaldehyde (**1m**) was also a good substrate, and afforded (*R*)-**2m** with 95% *ee*. The cyanation was applicable to heteroaromatic aldehydes: 2-furancarbaldehyde (**1n**) and 3-pyridinecarbaldehyde (**1o**) were converted into the *R* products with 93% *ee*.

Interestingly, the cyanation of aliphatic aldehydes showed higher enantioselectivity in  $t\text{C}_4\text{H}_9\text{OCH}_3$  than in  $(\text{C}_2\text{H}_5)_2\text{O}$ . Thus, pivalaldehyde (**1p**), a tertiary alkyl aldehyde, was converted into (*R*)-**2p** with 95% *ee* in  $t\text{C}_4\text{H}_9\text{OCH}_3$ , and with 93% *ee* in  $(\text{C}_2\text{H}_5)_2\text{O}$  (Table 2). The sense of enantioselection was the same as that of the reaction of **1a**. The reaction of cyclohexanecarbaldehyde (**1q**) gave a high enantioselectivity of 88%, although *n*-heptanal (**1r**) was converted into **2r** in only 70% *ee*.<sup>[11]</sup> The cyanation of cinnamaldehyde (**1s**) afforded the 1,2-adduct (*R*)-**2s** in 93% yield and 91% *ee*. An even better enantioselectivity of 93% *ee* was achieved in the reaction of 1-cyclohexenecarbaldehyde (**1t**).

ESI mass-spectrometric analysis of a mixture of the Ru complex **3** ( $m/z$  1024), aqueous  $\text{Li}_2\text{CO}_3$  (0.1 M; **3**/ $\text{Li}_2\text{CO}_3$  1:1), and an excess amount of  $(\text{CH}_3)_3\text{SiCN}$  showed prominent signals centered at  $m/z$  1031, which correspond to the Ru-Li bimetallic species  $[\mathbf{3}\text{-Li}]^+$ , and a decrease in the intensity of the signals of **3** (see the Supporting Information).  $^1\text{H}$  NMR analysis ( $[\text{D}_8]\text{THF}$ ) of this mixture also suggested the formation of the  $[\mathbf{3}\text{-Li}]^+$  species. The signal for the PhGly benzylic protons of **3**, which appear at  $\delta = 3.94$  ppm in the absence of  $\text{Li}_2\text{CO}_3$ , was shifted to  $\delta = 4.15$  ppm. A Li cation



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