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Enantioselective Hydrocyanation of *N*-Protected Aldimines

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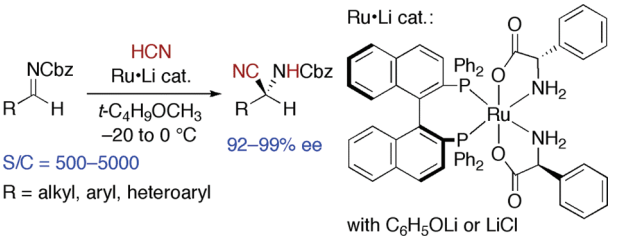
ABSTRACT



Enantioselective hydrocyanation of *N*-benzyloxycarbonyl aldimines catalyzed by a Ru[(*S*)-phgly]$_2$[(*S*)-binap]/C_6H_5OLi system or a bimetallic complex [Li{Ru[(*S*)-phgly]$_2$[(*S*)-binap]}]Cl affords the amino nitriles in 92−99% ee. The reaction is carried out in *tert*-$C_4H_9OCH_3$ with a substrate-to-catalyst molar ratio in the range of 500−5000 at −20 to 0 °C. Primary, secondary, and tertiary alkyl imines as well as the aryl and heteroaryl substrates are smoothly cyanated to produce the desired products in high yield.

Catalytic enantioselective hydrocyanation of aldimines (Strecker-type reaction) is a facile and straightforward method to produce optically active α-amino nitriles, which are readily transformed to the proteinogenic and the non-proteinogenic α-amino acids.[1] Both natural-type and unnatural-type amino acids can be selectively prepared by using this asymmetric reaction when two enantiomers of catalysts are available. Chiral organocatalysts[2] and metal-based catalysts[3] have eminently contributed to the progress in this important field of chemistry. However, the development of a catalytic system that shows high activity and enantioselectivity as well as a wide scope of substrates would be desirable from a scientific and practical point of view.

We recently reported asymmetric conjugate addition of HCN to α,β-unsaturated ketones ($R^1CH{=}CHCOR^2$) by using a Ru(phgly)$_2$(binap)/C_6H_5OLi catalyst system.[4,5] A series of aromatic and aliphatic β-cyano ketones was obtained in high ee. The bimetallic species [Li{Ru(phgly)$_2$-(binap)}]$^+$ prepared in situ is expected to act as a chiral Lewis acidic catalyst.[5c] We therefore considered that the π-isoelectronic *N*-alkoxycarbonyl aldimines ($R^1CH{=}NCO_2R^2$) could react with HCN in the presence of the Ru(phgly)$_2$(binap)/Li salt catalyst system to afford the protected amino nitriles in high ee.

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We selected an *N*-benzyloxycarbonyl (Cbz) imine **1a** derived from benzaldehyde according to the reported method[6] as a typical substrate to optimize the reaction conditions (Scheme 1 and Table 1). The reaction of **1a** (1.0 mmol, 0.15 M) and HCN prepared in situ by mixing $(CH_3)_3SiCN$ (3.0 mmol) and CH_3OH (3.0 mmol) in *tert*-$C_4H_9OCH_3$ at 0 °C smoothly proceeded in the presence of Ru[(*S*)-phgly]$_2$[(*S*)-binap] ((*S*,*S*,*S*)-**3**: 2.0 μmol; substrate-to-catalyst molar ratio (S/C) = 500) and C_6H_5OLi (0.10 M in THF, 2.0 μmol) to afford (*R*)-**2a** in 97% ee quantitatively in 30 min (Table 1, entry 1). An even higher ee value of 98% was achieved at −20 °C (entry 2). A high level of enantioselectivity was obtained in the reaction even at 25 °C (entry 3).[7] The enantioselectivity was decreased under the substrate concentration higher than 0.15 M, although the lower concentration little affected the stereoselective outcome (entries 4 and 5). A comparable result was obtained by using isolated HCN[8] instead of the in situ formed one, suggesting that the reaction is the net hydrocyanation without substantial influence by the existing silicone compounds (entry 6). A bimetallic salt [Li{Ru[(*S*)-phgly]$_2$-[(*S*)-binap]}]Cl ((*S*,*S*,*S*)-**4**)[5c] prepared from (*S*,*S*,*S*)-**3** and LiCl also acted as a highly enantioselective catalyst for this reaction without additives, but the catalytic activity was lower than that of the (*S*,*S*,*S*)-**3**/C_6H_5OLi system (entry 7 vs entry 1). The high catalytic efficiency of (*S*,*S*,*S*)-**3**/C_6H_5OLi system achieved complete conversion of the cyanation with an S/C of 2500 (1 h) and 5000 (2 h) affording **2a** in 95 and 96% ee, respectively (entries 8 and 9).

Scheme 1. Enantioselective Hydrocyanation of *N*-Cbz Aldimine **1a** with the **3**/C_6H_5OLi Catalyst System or **4**

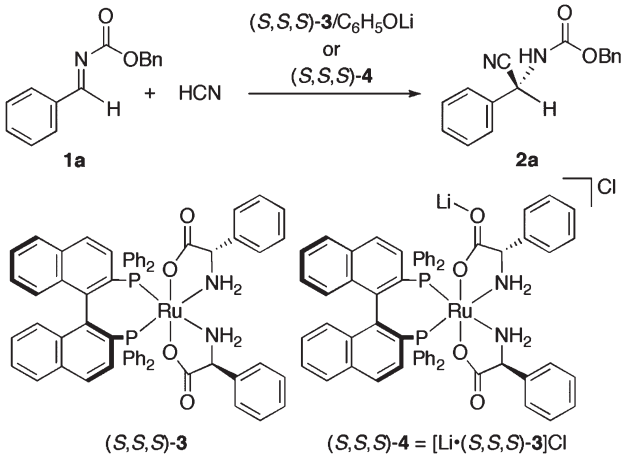

Table 1. Enantioselective Hydrocyanation of *N*-Cbz Aldimine **1a**[a]

entry	$[\mathbf{1a}]_0$, M	S/C[b]	temp, °C	time, h	% yield[c]	% ee[d]
1	0.15	500	0	0.5	99	97
2	0.15	500	−20	0.5	98	98
3	0.15	500	25	0.5	98	89
4	0.45	500	0	0.5	100	94
5	0.05	500	0	0.5	100	97
6[e]	0.15	500	0	0.5	98	96
7[f]	0.15	500	0	20	53	98
8[g]	0.15	2500	0	1	99	95
9[h]	0.15	5000	0	2	95	96

[a] Unless otherwise stated, reactions were conducted using **1a** (1.0 mmol) and HCN (3.0 mmol) in *tert*-$C_4H_9OCH_3$ with a solid (*S*,*S*,*S*)-**3** and C_6H_5OLi (100 mM in THF). **3**:C_6H_5OLi = 1:1. HCN was in situ prepared from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Substrate-to-catalyst (**3**) molar ratio. [c] Isolated yield of **2a**. [d] Determined by chiral HPLC analysis. [e] Isolated HCN was used. [f] **4** was used instead of the **3**/C_6H_5OLi system as a catalyst. [g] Reaction using 5.1 mmol of **1a**. [h] Reaction using 10.0 mmol of **1a**.

The enantioselective hydrocyanation catalyzed by the (*S*,*S*,*S*)-**3**/C_6H_5OLi system or (*S*,*S*,*S*)-**4** was applied to a series of *N*-protected aldimines (Scheme 2). These results are summarized in Table 2. Cbz was the most preferable protective group in terms of stereoselectivity (Table 2, entry 1). The cyanation of *tert*-butoxycarbonyl- and benzoyl-protected aldimines, **1b** and **1c**, with the **3**/C_6H_5OLi system resulted in a somewhat lower ee of products (entries 2 and 3). Both the reaction rate and enantioselectivity were significantly decreased in the reaction of *N*-benzyl imine **1d** (entry 4).

N-Cbz imines of 2-, 3-, and 4-methylbenzaldehydes, **1e**, **1f**, and **1h**, were smoothly cyanated under the typical conditions with the **3**/C_6H_5OLi catalyst system to produce the amino nitriles, **2e**, **2f**, and **2h**, in the same ee of 97%

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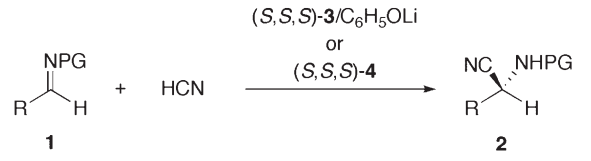
Scheme 2. Enantioselective Hydrocyanation of Aldimines **1** with the **3**/C_6H_5OLi Catalyst System or **4**



1 **2**

a: R = C_6H_5, PG = Cbz
b: R = C_6H_5, PG = Boc
c: R = C_6H_5, PG = Bz
d: R = C_6H_5, PG = Bn
e: R = 2-$CH_3C_6H_4$, PG = Cbz
f: R = 3-$CH_3C_6H_4$, PG = Cbz
g: R = 3-BrC_6H_4, PG = Cbz
h: R = 4-$CH_3C_6H_4$, PG = Cbz
i: R = 4-$CH_3OC_6H_4$, PG = Cbz
j: R = 4-$CF_3C_6H_4$, PG = Cbz
k: R = 2-furyl, PG = Cbz
l: R = 2-thienyl, PG = Cbz
m: R = *n*-C_3H_7, PG = Cbz
n: R = *cyclo*-C_6H_{11}, PG = Cbz
o: R = *tert*-C_4H_9, PG = Cbz

(Table 2, entries 5, 6, and 9). The reactions of a 3-bromophenyl imine **1g** with an S/C of 500 at 0 and −20 °C afforded **2g** in 98% ee and 99% ee, respectively (entries 7 and 8). A substrate with an electron-donating CH_3O group at the C4-position **1i** was converted to **2i** with high stereoselectivity (entry 10). However, an imine bearing an electron-withdrawing CF_3 moiety **1j** was reacted under the same conditions to give **2j** in only 19% ee (entry 11). A noncatalytic NC^- addition to the imine was considered to be a main reason for the low ee value of the product. This problem was solved just by using the less basic Ru·Li bimetallic complex **4** instead of the **3**/C_6H_5OLi system. The ee value of **2j** was dramatically increased to 97% (entry 12). The cyanation of 2′-furyl and 2′-thienyl imines, **1k** and **1l**, catalyzed by the **3**/C_6H_5OLi system quantitatively afforded the amino nitriles, **2k** and **2l**, in 92 and 97% ee, respectively, without injury at the heteroaromatic rings (entries 13 and 14). Complete conversion in the reaction of **1l** with an S/C of 5000 was achieved in 3 h with maintenance of high enantioselectivity (entry 15).

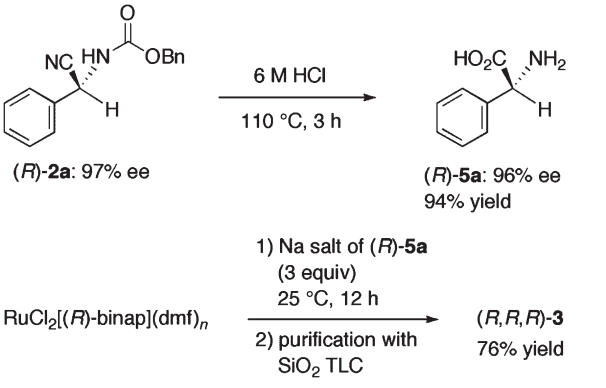
Asymmetric hydrocyanation of imines derived from aliphatic aldehydes is difficult, so that only limited catalyst systems have achieved high enantioselectivity.[1−3] An *N*-Cbz imine of butanal, a primary alkyl aldehyde, **1m** smoothly reacted with HCN in the presence of the **3**/C_6H_5OLi catalyst system (S/C = 500, 0 °C, 30 min) to afford **2m** in 80% ee (Table 2, entry 16).[9] The ee value of **2m** jumped up to 96% when bimetallic complex **4** was used as a catalyst (entry 17).[10] The cyclohexyl imine **1n**, a secondary alkyl imine, was converted to **2n** in 92% ee (0 °C) and 95% ee (−20 °C) with the **3**/C_6H_5OLi catalyst system (entries 18 and 19). A slightly higher selectivity at 0 °C was obtained in the reaction with the catalyst **4** (entry 20). A tertiary alkyl imine **1o** was also cyanated with high enantioselectivity without detectable loss of the reaction rate (entries 21 and 22). The reaction with an S/C of 5000 was completed in 2 h (entry 23).

Table 2. Enantioselective Hydrocyanation of Aldimines **1**[a]

entry	1	cat.[b]	S/C[c]	temp, °C	time, h	% yield[d]	% ee[e]
1	**1a**	**A**	500	0	0.5	99	97
2	**1b**	**A**	500	0	0.5	99	91
3	**1c**	**A**	500	0	0.5	91	86
4	**1d**	**A**	500	0	18	95	−14[f]
5	**1e**	**A**	500	0	0.5	97	97
6	**1f**	**A**	500	0	0.5	97	97
7	**1g**	**A**	500	0	0.5	98	98
8	**1g**	**A**	500	−20	0.5	95	99
9	**1h**	**A**	500	0	0.5	96	97
10	**1i**	**A**	500	0	0.5	96	97
11	**1j**	**A**	500	0	0.5	98	19
12	**1j**	**B**	500	0	2	93	97
13	**1k**	**A**	500	0	0.5	96	92
14	**1l**	**A**	500	0	0.5	98	97
15	**1l**[g]	**A**	5000	0	3	93	96
16	**1m**[h]	**A**	500	0	0.5	59[i]	80
17	**1m**[h]	**B**	500	0	2	72[i]	96
18	**1n**	**A**	500	0	0.5	86	92
19	**1n**	**A**	500	−20	0.5	89	95
20	**1n**	**B**	500	0	2	93	94
21	**1o**	**A**	500	0	0.5	99	92
22	**1o**	**A**	500	−20	0.5	98	96
23	**1o**[g]	**A**	5000	0	2	100	93

[a] Unless otherwise stated, reactions were conducted using **1** (1.0 mmol, 0.15 M) and 3 equiv of HCN in *tert*-$C_4H_9OCH_3$ with a catalyst. HCN was in situ prepared from $(CH_3)_3SiCN$ and CH_3OH in a 1:1 ratio. [b] Catalyst: **A**: (*S*,*S*,*S*)-**3** and C_6H_5OLi (100 mM in THF). **3**:C_6H_5OLi = 1:1. **B**: (*S*,*S*,*S*)-**4**. [c] Substrate-to-catalyst molar ratio. [d] Isolated yield of **2**. [e] Determined by chiral GC or HPLC analysis. [f] The opposite enantiomer was the major product. [g] Reaction using 10 mmol of **1**. [h] Crude **1m** was used as a substrate. [i] Yield in two steps from the precursor of **1m**.

Scheme 3. Hydrolysis of (*R*)-**2a** and Preparation of (*R*,*R*,*R*)-**3**



The cyanated product (*R*)-**2a** in 97% ee was readily converted to (*R*)-phenylglycine ((*R*)-**5a**) in 96% ee with an acidic treatment (Scheme 3). Then (*R*,*R*,*R*)-**3** was prepared from $RuCl_2$[(*R*)-binap](dmf)$_n$[11] and a sodium salt of (*R*)-**5a** according to our reported method (see the Supporting Information for details).[5] The diastereomeric

(9) **1m** was used as a crude compound due to its instability under purification conditions. The isolated yield of **2m** in two steps from the precursor of **1m** is indicated in Table 2.

(10) An *N*-arylsulfonyl primary alkyl imine was cyanated at 0 °C with 96% enantioselectivity catalyzed by a chiral quaternary ammonium salt (S/C = 100). See ref 2l for details.

byproducts, (*R*,*R*,*S*)-**3** and (*R*,*S*,*S*)-**3**, were easily removed with a silica-gel preparative TLC.

In conclusion, we have reported the highly reactive and enantioselective hydrocyanation of *N*-Cbz imines with our original Ru(phgly)$_2$(binap)/C_6H_5OLi system or the bimetallic complex [Li{Ru(phgly)$_2$(binap)}]Cl as a catalyst. The reactions with an S/C of 500−5000 were conducted under mild conditions (−20 to 0 °C) to afford the chiral amino nitriles in up to 99% ee. A series of aromatic, heteroaromatic, and alkyl-substituted imines was cyanated with equally high enantioselectivity. Achievement of the highest level of enantioselectivity for the reaction of a primary alkyl imine is noteworthy. An aromatic nitrile product was hydrolyzed to the amino acid with maintenance of the enantiomeric purity. Thus, the chiral Ru·Li complex is among the best catalysts in terms of reactivity, enantioselectivity, and scope of the substrate to our knowledge.

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Supporting Information Available. Procedures for asymmetric hydrocyanation of *N*-protected aldimines **1**, NMR, GC, and HPLC behavior, $[\alpha]_D$ values of products, and preparative method of the chiral Ru complex (*R*,*R*,*R*)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.