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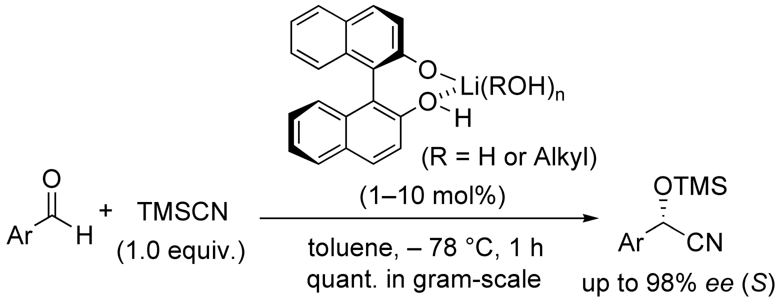

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Chiral Lithium Binaphtholate Aqua Complex as a Highly Effective Asymmetric Catalyst for Cyanohydrin Synthesis

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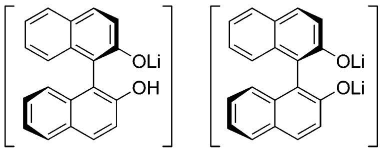
The catalytic asymmetric cyanation of aldehydes to give cyanohydrins is a versatile synthetic method in organic chemistry.[1−7] Upon transformation, optically active cyanohydrins give important intermediates not only in natural product chemistry but also in the fields of biology and pharmaceuticals.[6] However, in contrast to the development of chiral Lewis acid catalysis,[1] examples of asymmetric cyanation to aldehydes with trimethylsilylcyanide (TMSCN) catalyzed by a chiral Lewis base[3] are still limited to Kagan's pioneering work.[7] We report here the highly enantioselective cyanation of aromatic aldehydes by chiral lithium binaphtholates **1** and **2** in the presence of a catalytic amount of water or alcohol as a co-activator (Chart 1), which is a simple and inexpensive catalyst suitable for the aim of process chemistry to give gram-scale cyanohydrins in minimum solvent successfully.

Chart 1. Chiral Lithium Binaphtholate Complexes



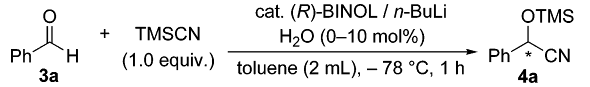
(*R*)-**1** (*R*)-**2**

First, monolithium catalyst (*R*)-**1** prepared in situ from 1:1 of (*R*)-1,1′-bi-2-naphthol ((*R*)-BINOL) and *n*-BuLi in toluene was used to convert 1 mmol of benzaldehyde (**3a**) into the corresponding cyanohydrin (**4a**) with TMSCN (1.0 equiv) at −78 °C for 1 h (Table 1). (*S*)-**4a** was obtained quantitatively in 23% ee with 1 mol % of (*R*)-**1** (entry 1).[8] Interestingly, 10 mol % of (*R*)-**1** gave 58% ee of (*R*)-**4a** along with a changeover of enantioselectivity (entry 2). Next, an attempt with (*R*)-**2** prepared in situ from 1 mol % of (*R*)-BINOL and 2 mol % of *n*-BuLi gave (*R*)-**4a** almost quantitatively with 65% ee (entry 3).[8] Here again, 10 mol % of (*R*)-**2** gave 26% ee of **4a** in (*S*)-form with a changeover in absolute stereochemistry (entry 4).[9]

For these interesting results, we suspected that the coexistence of adventitious moisture including the catalyst and/or solvent may have caused the opposite results regarding the enantiomeric excess. Thus, we next intended to add a small amount of H_2O to confirm whether water affects the activity of the *well-dried* catalyst.[5b,10] 1 mol % of (*R*)-**1** or (*R*)-**2** with a catalytic amount of water turned the sense of enantioselectivity of **4a** into (*S*)-form (entries 5 and 7 versus 1[8] and 3[8]). Higher catalytic activity was observed with 10 mol % of (*R*)-**1**$\cdot(H_2O)_n$ rather than (*R*)-**2**$\cdot(H_2O)_n$: 95% ee (entry 6) versus 88% ee (entry 8). More or less than the optimized amount of water gradually decreased catalytic activity (see Supporting Information). We could rule out the possibility of the addition to aldehyde with HCN, which was generated from TMSCN and H_2O, because low catalytic activity (60% yield, 44% ee (*S*)) was observed with (*R*)-**1**/HCN.[11] Other protic additives such as *i*-PrOH and *t*-BuOH were also effective, but not superior to H_2O.

Encouraged by the effect of catalytic water, we next examined other lithium sources in place of *n*-BuLi to generate corresponding protic compounds in situ by complexation with (*R*)-BINOL (Table 2). As expected, the release of H_2O after complexation of LiOH with (*R*)-BINOL was quite effective and gave (*S*)-**4a** with 95% ee (entry 1). Regarding the effect of H_2O in Table 1, $LiOH\cdot H_2O$ had lower catalytic activity than LiOH and gave (*S*)-**4a** with 78% ee (entry 2), while Li_2O or LiOAc[12] showed no reactivity. Eventually, LiOEt, $LiOPr^i$, and $LiOBu^t$ were found to be highly effective, and the enantioselectivity of (*S*)-**4a** was increased up to 97% ee (entries 3−6). $LiOPr^i$ was such a highly active precursor at promoting cyanation of **3a** (10 mmol) with 1 mol % catalyst loading in minimum solvent (2 mL) that the gram scale of (*S*)-**4a** was obtained practically with 90% ee almost quantitatively (entry 4). Again, BINOL−$2LiOPr^i$ catalyst showed lower catalytic activity than BINOL−$LiOPr^i$ catalyst (entry 5).

Table 1. Enantioselective Cyanation Catalyzed by (*R*)-1 or (*R*)-2



entry	(*R*)-BINOL (mol %)	*n*-BuLi (mol %)	H_2O (mol %)	yield (%)	ee (%)
1	1	1	−	>99	23 [*R*]
2	10	10	−	>99	58 **[*S*]**
3	1	2	−	99	65 [*R*]
4	10	20	−	99	26 **[*S*]**
5	1	1	0.3	>99	58 **[*S*]**
6	10	10	3	95	95 **[*S*]**
7	1	2	1	>99	25 **[*S*]**
8	10	20	10	>99	88 **[*S*]**

Table 2. Effect of Lithium Source upon (*R*)-1 Catalyzed Enantioselective Cyanation[a]

$$\mathbf{3a} + \underset{\text{(1.0 equiv.)}}{\text{TMSCN}} \xrightarrow[\text{toluene (2 mL), – 78 °C, 1 h}]{(R)\text{-BINOL / lithium source (10 mol\% each)}} (S)\text{-}\mathbf{4a}$$

entry	lithium source	yield (%)	ee (%)	entry	lithium source	yield (%)	ee (%)
1	LiOH	98	95	4	$LiOPr^i$	>99 [98][b]	97 [90][b]
2	$LiOH\cdot H_2O$	93	78	5[c]	$LiOPr^i$	97	58
3	LiOEt	94	97	6	$LiOBu^t$	97	96

[a] 1 mmol scale of **3a**. [b] 1 mol % of (*R*)-BINOL−$LiOPr^i$ was used for 10 mmol of **3a**. [c] 10 mol % of (*R*)-BINOL and 20 mol % of $LiOPr^i$ was used.

Next, the cyanation of other aldehydes with TMSCN was examined with $LiOPr^i$ and (*R*)-BINOL (i.e., (*R*)-**1**$\cdot$*i*-PrOH) (Table 3). Aromatic aldehydes with an electron-withdrawing group or an electron-donating group gave the corresponding (*S*)-**4** with high enantioselectivities up to 97% ee almost quantitatively (entries 2−12). α- or *β*-Naphthaldehydes (**3m**, **3n**) and 3-furylaldehyde (**3o**) bearing a heterocycle also gave excellent results up to 98% ee (entries 13−15). Double cyanation of isophthaldehyde (**3p**) proceeded smoothly to give *dl*-product (*S*,*S*)-**4p** in 85% yield with 98% ee (entry 16). Notably, even 1−3 mol % of our simple BINOL−Li catalyst in minimum solvent (2 mL) could afford the various corresponding cyanohydrins **4** almost quantitatively with high enantioselectivities in practically useful gram scale (10 mmol). (*R*)-**1**$\cdot$*i*-PrOH showed low enantioselectivity for aliphatic aldehydes.

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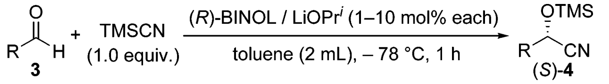
Table 3. Cyanation of Aldehydes Catalyzed by (*R*)-1·*i*-PrOH[a]



entry	R (**3**)	yield (%)	ee (%)
1	Ph (**3a**)	>99 [98][b]	97 [90][b]
2	*p*-FC_6H_4 (**3b**)	92	96
3	*m*-FC_6H_4 (**3c**)	97	93
4	*p*-ClC_6H_4 (**3d**)	98 [99][b]	92 [91][b]
5	*m*-ClC_6H_4 (**3e**)	83	91
6	*p*-BrC_6H_4 (**3f**)	98 [95][d]	93 [90][d]
7	*m*-BrC_6H_4 (**3g**)	96	87
8	*p*-$CF_3C_6H_4$ (**3h**)	97	82
9	*m*-$CF_3C_6H_4$ (**3i**)	99	86
10	*m*-MeC_6H_4 (**3j**)	96 [97][c]	95 [90][c]
11	*m*-$MeOC_6H_4$ (**3k**)	93 [93][d]	97 [95][d]
12	3,5-$(MeO)_2C_6H_3$ (**3l**)	99 [92][d]	97 [97][d]
13	α-naphthyl (**3m**)	95	81
14	*β*-naphthyl (**3n**)	96	95
15	3-furyl (**3o**)	96 [93][d]	98 [93][d]
16	*m*-$CHOC_6H_4$ (**3p**)	85[e]	98[e]

[a] 10 mol % each of (*R*)-BINOL and LiOPr^i for 1 mmol of **3** was used unless otherwise noted. [b] 1 mol % each of (*R*)-BINOL and LiOPr^i was used for 10 mmol of aldehyde. [c] 2 mol % each of (*R*)-BINOL and LiOPr^i was used for 5 mmol of aldehyde. [d] 3 mol % each of (*R*)-BINOL and LiOPr^i was used for 3.3 mmol of aldehyde. [e] Isolated yield and enantioselectivitiy for *dl*-product. Other 15% yield was *meso* product.

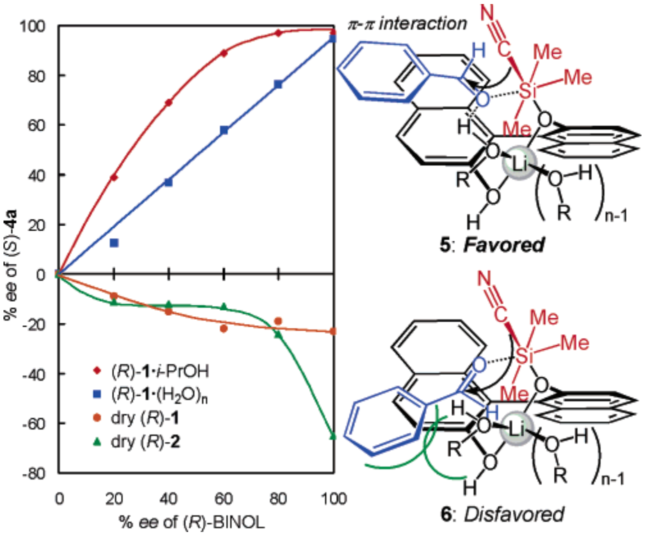


Figure 1. Nonlinear effect (left) and proposed transition states for the cyanation of ArCHO with (*R*)-**1**·$(ROH)_n$ (R = H or alkyl) (right).

This drawback, however, strongly suggests that the existence of a weak interaction such as *π*−*π* stacking between the aromatic aldehydes and (*R*)-BINOL should play a key role in the transition state of cyanation.

Finally, we turned our attention to the characteristics of the active BINOL−Li catalyst and the mechanistic aspects. On the basis of the lack of a nonlinear effect (NLE) between the ee of (*S*)-**4a** and the ee of (*R*)-**1**·$(H_2O)_n$ (10 mol %) (Figure 1, ■), the active structure of monolithium binaphtholate aqua complexes in our catalysis is different from "dry" (*R*)-**1** and (*R*)-**2**,[13] which have the respective NLE leading to (*R*)-**4a** (Figure 1, ● and ▲). One possibility is that the presence of hydroxyl compounds just as water would promote the dissociation of oligomeric BINOL−Li complexes into highly active monomeric species. In fact, almost the same reactivities (>90% yield) with (*R*)-**1**·$(H_2O)_n$ were exhibited with no relation to enantiomeric excess of (*R*)-BINOL (see Supporting Information). Monolithium binaphtholate alcohol complex (i.e., (*R*)-**1**·*i*-PrOH) showed a large positive NLE (Figure 1, ◆). This can be interpreted that (*R*)-**1**·*i*-PrOH may be a mixture of an active monomeric species and inactive oligomeric species.[14] Although a further investigation of mechanistic aspects is required to acquire a full understanding, our postulated transition states are shown on the basis of a monomeric structure or a complex strikingly similar to this species (Figure 1 and Supporting Information). Taking advantage of the detailed studies on hypervalent silicon intermediates,[15] we found that transition state assembly **6** is less favorable because of (1) steric repulsion between the aryl group of aldehyde and ROH coordinating to the Li center and (2) little overlap of *π*−*π* stacking between aromatic aldehyde and a binaphthyl plane of (*R*)-BINOL. On the other hand, **5** avoids this repulsion and shows adequate *π*−*π* interaction and hydrogen bonding, to eventually give (*S*)-**4**.

In summary, we have developed a highly enantioselective cyanation of aromatic aldehydes using a simple and inexpensive chiral lithium binaphtholate aqua or alcohol complexes. The cyanation is suitable for process chemistry to ensure the practical gram-scale cyanohydrin synthesis in minimum solvent. Further investigations into understanding the role of water and alcohol to enhance the catalytic activity are in progress.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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