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Chiral Lanthanum(III)-Binaphthyldisulfonate Complexes for Catalytic Enantioselective Strecker Reaction

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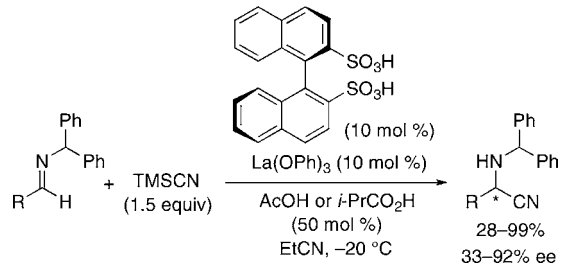
ABSTRACT



A catalytic enantioselective Strecker reaction catalyzed by novel chiral lanthanum(III)−binaphthyl disulfonate complexes was developed. The key to promoting the reactions was a semistoichiometric amount of AcOH or *i*-PrCO$_2$H, which takes advantage of HCN generation in situ. The corresponding cyanation products were obtained in high yields and with high enantioselectivities.

The catalytic enantioselective Strecker reaction is one of the most convenient methods for the synthesis of optically active natural and unnatural α-amino acids.[1] This process usually involves the addition of hydrogen cyanide (HCN) or trimethylsilyl cyanide (TMSCN) to imines, and several chiral organocatalysts[2] and metal catalysts[3] have recently been developed to achieve a high level of enantioselectivity. In particular, chiral binaphthyl derivatives offer great advantages in the design of both organocatalysts and metal catalysts for the Strecker reaction.[4,5] In the course of our studies of chiral binaphthyl chemistry, we recently developed chiral 1,1′-binaphthyl-2,2′-disulfonic acid (BINSA, **1**) as an organocatalyst for the enantioselective direct Mannich-type reaction.[6] BINSA, which has an extremely simple structure, should be a highly promising chiral ligand for metal-mediated

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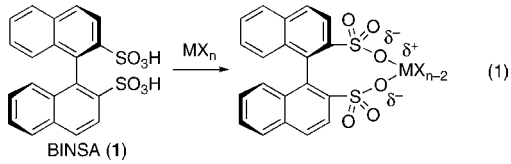
enantioselective catalyses. First, the bidentate electron-withdrawing sulfonate groups should effectively activate the metal center after metal complexation (eq 1). Second, high enantioselectivity may be induced even without any 3,3′-modification of the 1,1′-binaphthyl skeleton, since the $-SO_3H$ substituents of BINSA are sterically more demanding than other 2,2′-substituents of 1,1′-binaphthyl such as −OH and $-CO_2H$. In this paper, we describe the catalytic enantioselective Strecker reaction of aldimines with the use of novel chiral lanthanum(III)−1,1′-binaphthyl 2,2′-disulfonate complexes, which is the first catalysis with **1**−metal complexes.

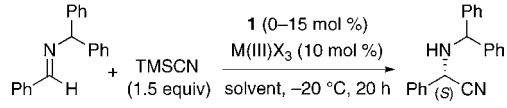


(1)

First, we examined the metal tuning for **1** (10−15 mol %) in the reaction of aldimine **2a** with TMSCN (1.5 equiv) at −20 °C for 20 h (Table 1).[7] Monovalent, divalent, and tetravalent MX_n precursors, such as AgOAc, CuOAc, $Cu(OAc)_2$, $Cu(OMe)_2$, $Pd(OAc)_2$, $Ti(O\text{-}i\text{-}Pr)_4$, $Zr(O\text{-}t\text{-}Bu)_4$, $Hf(O\text{-}t\text{-}Bu)_4$, etc., were not effective, and the corresponding product (**3a**) was obtained in low yields with low enantioselectivities (<20% ee). Interestingly, however, we found that trivalent precursors improved both the yields and the enantioselectivities. In particular, $La(O\text{-}i\text{-}Pr)_3$ and early lanthanide complexes showed moderate enantioselectivities (entries 3−5), while $Sc(O\text{-}i\text{-}Pr)_3$, $Y(O\text{-}i\text{-}Pr)_3$, and late lanthanide complexes showed lower enantioselectivities (entries 1, 2, 7−9).[8,9] When more polar EtCN was used in place of toluene, the solubility of the heterogeneous catalysts was slightly improved to give the same enantioselectivity (entry 10). $La(OPh)_3$ was found to be most effective among the La(III) precursors (LaX) examined (entry 11).[10] Moreover, the enantioselectivity was improved to 65% ee when the ratio of **1** to $La(OPh)_3$ was optimized as 1:1. As expected, the activities of **1** without $La(OPh)_3$ (entry 13) and of $La(OPh)_3$ without **1** (entry 14) were low. A poor result was also observed when $La(OPh)_3$ and (*R*)-BINOL were used (entry 15).

Further optimization was examined by adding protic compounds, since the actual cyanide source has been previously shown to be HCN rather than TMSCN.[3c,d,h,4c,e,i] The addition of protic compounds such as H_2O and PhOH improved the yields of **3a** (Table 2, entries 2 and 3).

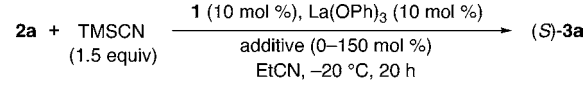
Table 1. **1**-$M(III)X_3$-Catalyzed Strecker Reaction of **2a** with TMSCN[a]



entry	$M(III)X_3$	**1** (mol %)	solvent	yield (%)	ee (%)
1	$Sc(Oi\text{-}Pr)_3$	15	toluene	56	18
2	$Y(Oi\text{-}Pr)_3$	15	toluene	28	0
3	$La(Oi\text{-}Pr)_3$	15	toluene	34	54
4	$Pr(Oi\text{-}Pr)_3$	15	toluene	24	46
5	$Nd(Oi\text{-}Pr)_3$	15	toluene	29	49
6	$Sm(Oi\text{-}Pr)_3$	15	toluene	35	34
7	$Dy(Oi\text{-}Pr)_3$	15	toluene	6	20
8	$Er(Oi\text{-}Pr)_3$	15	toluene	12	10
9	$Yb(Oi\text{-}Pr)_3$	15	toluene	29	10
10	$La(Oi\text{-}Pr)_3$	15	EtCN	27	55
11	$La(OPh)_3$	15	EtCN	38	57
12	$La(OPh)_3$	10	EtCN	22	65
13[b]		10	EtCN	26	13
14[c]	$La(OPh)_3$	0	EtCN	16	
15[d]	$La(OPh)_3$	0	EtCN	9	0

[a] Prior to the reaction, each catalyst was prepared in situ from **1** and MX_3 in the solvent at 60 °C for 1 h. [b] In the absence of MX_3. [c] Reaction time was 20 h. [d] 10 mol % of (*R*)-BINOL was used in place of **1**.

Table 2. Effect of Protic Additives[a]



entry	additive (mol %)	yield (%)	ee (%)	entry	additive (mol %)	yield (%)	ee (%)
1		22	65	7	$i\text{-}PrCO_2H$ (70)	88	74
2	H_2O (50)	46	65	8	$i\text{-}PrCO_2H$ (100)	89	73
3	PhOH (50)	42	53	9	$i\text{-}PrCO_2H$ (150)	69	23
4	AcOH (50)	98	84	10	HCO_2H (50)	46	49
5	$i\text{-}PrCO_2H$ (30)	58	64	11	CF_3CO_2H (50)	34	38
6	$i\text{-}PrCO_2H$ (50)	86	84	12	$t\text{-}BuCO_2H$ (50)	62	73

[a] Prior to the reaction, each catalyst was prepared in situ from **1** and $La(OPh)_3$ in EtCN at 60 °C for 1 h. Then, **2a**, the additive, and TMSCN were poured into the heterogeneous suspension at −20 °C.

Fortunately, we found that 50 mol % of AcOH or $i\text{-}PrCO_2H$ significantly improved the catalytic activity, and **3a** was obtained with 84% ee in good yields (entries 4 and 6). The amount of $i\text{-}PrCO_2H$ was also important, and less or more than 50 mol % of $i\text{-}PrCO_2H$ decreased the catalytic activity (entries 5−9). Other carboxylic acids such as HCO_2H, CF_3CO_2H, and $t\text{-}BuCO_2H$ gave less improvement than AcOH or $i\text{-}PrCO_2H$ (entries 10−12).

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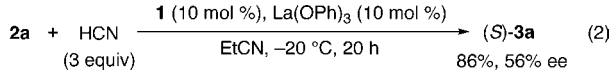
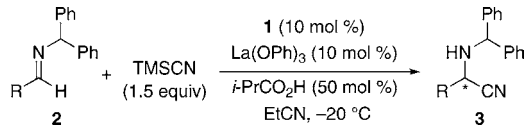
A direct comparison with HCN was also examined (eq 2). The reaction proceeded smoothly when 3 equiv of HCN was used, and **3a** was obtained in 86% yield with 56% ee. Although the enantioselectivity was not as high as under the conditions using TMSCN (Table 2, entry 1), these results strongly suggest that HCN is a key reagent in this reaction.



(2)

Next, we examined the scope of the aldimine substrates in the presence of 10 mol % each of **1** and $La(OPh)_3$, *i*-$PrCO_2H$ or AcOH (50 mol %), and TMSCN (1.5 equiv) in EtCN at −20 °C (Table 3). For *N*-protection, a $CHPh_2$ group

Table 3. 1-$La(OPh)_3$-Catalyzed Strecker Reaction[a]



entry	R	reaction time[b] (h)	yield[b] (%)	ee[b,c] (%)
1	Ph	20 [20]	86 [98]	84 (*S*) [84 (*S*)]
2	4-ClC_6H_4	20 [24]	92 [78]	88 (*S*) [88 (*S*)]
3	4-$MeOC_6H_4$	20 [16]	97 [97]	90 (*S*) [85 (*S*)]
4	3,4-$OCH_2OC_6H_3$	20 [20]	95 [96]	86 [74]
5	3-furyl	20 [18]	99 [96]	86 [80]
6	2-thienyl	86 [96]	97 [83]	92 (*R*) [76 (*R*)]
7	3-thienyl	24 [20]	97 [96]	83 [84]
8	2-Naph	96 [20]	64 [28]	92 (*S*) [85 (*S*)]
9	PhCH=CH	86 [72]	97 [99]	80 (*S*) [64 (*S*)]
10	PhC≡C	92 [96]	68 [79]	52 [66]
11	*t*-Bu	20 [48]	99 [98]	41 (*S*) [33 (*S*)]

[a] Prior to the reaction, the catalyst was prepared in situ from **1** and $La(OPh)_3$ in EtCN at 60 °C for 1 h. Then, **2**, *i*-$PrCO_2H$, and TMSCN were poured into the heterogeneous suspension at −20 °C. [b] Data in brackets are the result when AcOH was used in place of *i*-$PrCO_2H$. [c] Absolute configurations are shown in parentheses.

gave the best result (Supporting Information).[2a,b,j,3c,d,g] The reactions of aromatic and heteroaromatic aldimines bearing electron-withdrawing and electron-donating groups proceeded in high yields with moderate to high enantioselectivities (entries 1−8). In particular, 4-$MeOC_6H_4$-CH=NCHPh$_2$ and 2-thienylCH=NCHPh$_2$ gave each of the products with over 90% ee in high yields (entries 3 and 6). α,β-Unsaturated aldimines gave the corresponding products with moderate to good enantioselectivities (entries 9 and 10), although aliphatic aldimine gave poor enantioselectivity (entry 11).

Finally, we examined the mechanistic aspects. Based on the observation of a positive nonlinear effect between **1** and **3a** (Figure 1), the structure of enantiomerically pure La(III) catalysts in situ might involve a mixture of monomeric and

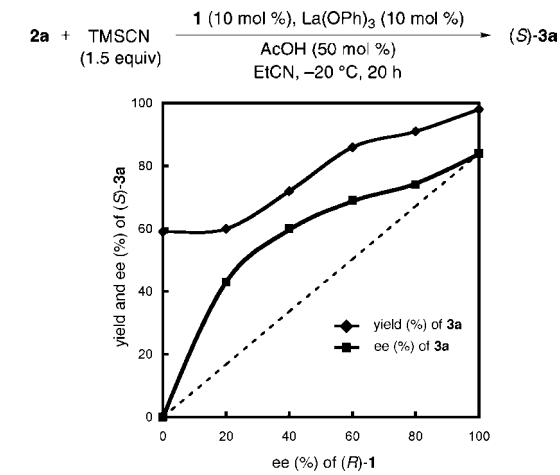


Figure 1. Nonlinear effect between **1** and **3a**.

oligomeric complexes. However, ESI-MS analysis of the catalyst, which was prepared in situ from $La(OPh)_3$ (1 equiv) and **1** (1 equiv) in AcOH (5 equiv) and MeCN, suggested the dominant generation of monomeric La(III) complexes, $[Ar^*(SO_3)_2La(MeCN)_n]^+$ ($Ar^*(SO_3H)_2$ = **1**, n = 1−4). The observed species may be derived from a parent complex $[Ar^*(SO_3)_2La(OAc)(MeCN)_n]^+$,[11] since the p$K_a$ value of HCN is smaller than that of AcOH.[12] Although further investigation is necessary to obtain a clear understanding, postulated catalytic cycles are shown in Figure 2 as a working model. Acidic R′CO_2H (R′ = Me or *i*-Pr) provides a counteranion for La(III) and generates HCN via proton-

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(7) Solubility of the corresponding complexes was low, and the reaction conditions were heterogeneous.

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(10) $La_2(CO_3)_3$, $La(OTs)_3$, and $La(NO_3)_3{\cdot}6H_2O$ showed low catalytic activity with poor enantioselectivity. Moreover, other $La(OAr)_3$ complexes (Ar = Ph, 3,5-xylyl, mesityl, 2,6-$Ph_2C_6H_3$) did not affect the enantioselectivity of **3**.

(11) The possibility of the complexes, $[Ar^*(SO_3)_2La(CN)(MeCN)_n]^+$, cannot be denied.

(12) pK_a of HCN is 12.9 in DMSO and 9.1 in H_2O. The pK_a of AcOH is 12.3 in DMSO and 4.75 in H_2O: Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

(13) For the full generation of HCN (1.5 equiv) in situ, a ratio of R′CO_2H (0.5 equiv) and TMSCN (1.5 equiv) is disputable. PhOH (0.3 equiv) released via ligand exchange and adventitious water also may be involved as protone sources. Moreover, it is notable that the equiliblium among a product, TMSCN, PhOTMS, HCN, and PhOH has been proposed by Shibasaki et al. in ref 4c.

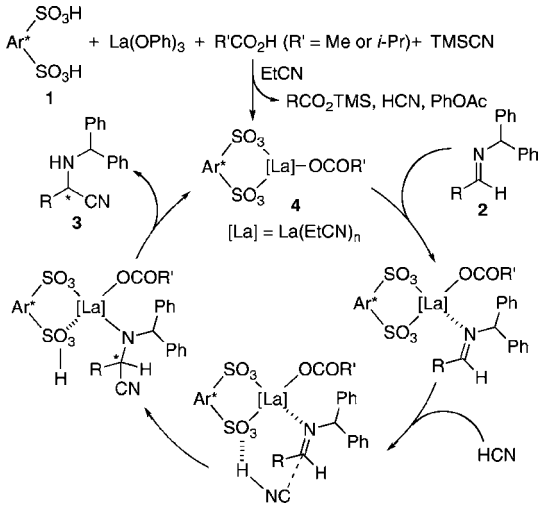

Figure 2. Postulated catalytic cycles.

exchange reactions.[13] First, a possible active EtCN−solvate catalyst [Ar*$(SO_3)_2$La(OCOR′)$(EtCN)_n$] (**4**) would be generated in situ from the mixture of **1**, La$(OPh)_3$, R′CO_2H, and TMSCN, and then aldimine **2** would be continuously activated at the La(III) center. HCN is then added to **2**,[14] and the catalyst would be regenerated and the product (**3**) is released. In the transition states, the *re*-face attack, which leads to (*S*)-products, should be favored without conspicuous steric repulsion between the substrate and the ligand (Figure 3).

In summary, we have developed a catalytic enantioselective Strecker reaction catalyzed by chiral lanthanum(III)-binaphthyldisulfonate complexes. The key to promoting the reactions was a semistoichiometric amount of AcOH or *i*-PrCO_2H, which takes advantage of HCN generation in situ. Further applications of **1**−metal salts to other catalytic enantioselective reactions are now underway.

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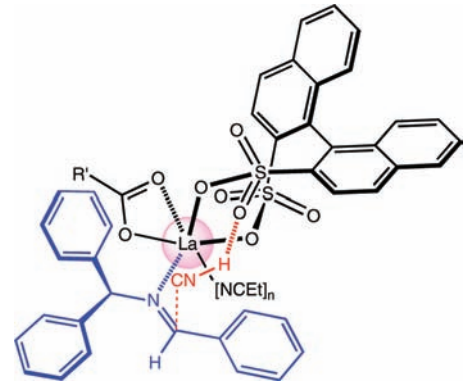

Figure 3. Possible transition states.

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Supporting Information Available: Experimental procedures and spectral data, as well as copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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