An Asymmetric Cyanation Reaction and Sequential Asymmetric Cyanation–Nitroaldol Reaction Using a [YLi_3{tris(binaphthoxide)}] Single Catalyst Component: Catalyst Tuning with Achiral Additives**

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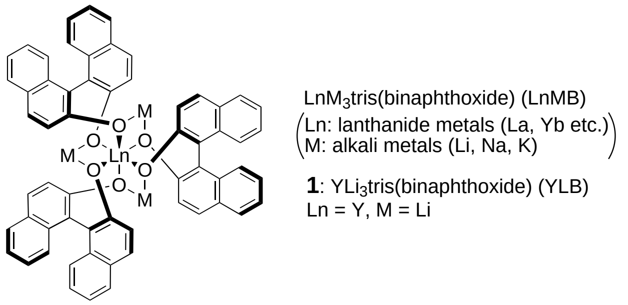
Chiral catalysts are generally designed and optimized to promote one specific asymmetric reaction.[1] The increasing demand for efficient and environmentally benign synthetic processes, however, requires the development of chiral catalysts that promote sequential, mechanistically different, asymmetric reactions. In regard to achiral organometallic reagents, our group and others recently reported multiple actions of a single-metal catalyst component.[2,3] Asymmetric sequential reactions, in which mechanistically different asymmetric reactions were involved, were achieved only by using two sets of chiral catalyst species.[4] In general, the chiral environment suitable for two distinct asymmetric reactions is different, which makes the development of asymmetric sequential reactions with a single catalyst component highly challenging. We report herein the first example of an asymmetric sequential reaction with a multifunctional [YLi_3{tris(binaphthoxide)}] (YLB; **1**, Scheme 1)[5] single catalyst component, in which tuning of the chiral catalyst by achiral additives had a key role in constructing a proper chiral environment for each asymmetric reaction;[6,7] the cyanation and nitroaldol reactions. The strategy is summarized in Figure 1.



Scheme 1. Structure of heterobimetallic [LnM_3{tris(binaphthoxide)}] and **1** (Ln = Y, M = Li).

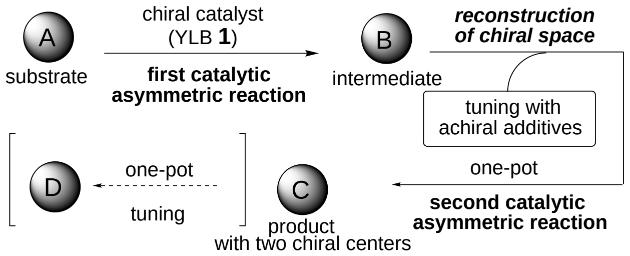
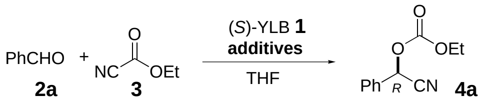


Figure 1. Chiral catalyst tuning strategy with achiral additives for tandem asymmetric catalysis.

We previously developed families of lanthanide heterobimetallic asymmetric catalysts, [LnM_3{tris(binaphthoxide)}] (LnMB, Scheme 1),[5] which promote various asymmetric reactions, such as the nitroaldol reaction.[5a] To develop a novel sequential asymmetric reaction, we first planned to survey new types of asymmetric reactions using LnMB catalysts. On the basis of previous cyanation reactions utilizing Ln−CN active species as a cyanide source,[8] we investigated an asymmetric cyanation reaction of aldehyde with heterobimetallic LnMB catalysts.

The initial screening of both CN sources and metal sources revealed that commercially available ethyl cyanoformate (**3**)[9] and (*S*)-**1** prepared from [$Y(HMDS)_3$] (HMDS = hexadimethylsilazide), (*S*)-binol, and BuLi,[5b] were promising candidates for catalysis of asymmetric reactions.[10] With **1** (10 mol%), H_2O (10 mol%), and **3**, cyanation of the aldehyde **2a** proceeded at −60 °C to afford **4a** in 84% yield and 58% *ee* (Table 1, entry 1). Interestingly, without addition of H_2O, no reaction proceeded (entry 2). To fine-tune the chiral environment, various achiral additives were surveyed and $Ar_3P(O)$ **5** was determined to be the most suitable in terms of enantioselectivity. Addition of both H_2O and $Ph_3P(O)$ (**5a**; 10 mol%) significantly improved both the reaction rate and enantioselectivity (entry 4). The best selectivity was obtained by adding 30 mol% of H_2O (entry 6). The use of the $Ar_3P(O)$ (**5**) was optimized; [2,6-$(CH_3O)_2C_6H_3]_3P(O)$ (**5b**) had the best reactivity and selectivity (entry 7). Moreover, by adding 10 mol% of BuLi, the reaction proceeded smoothly at −78 °C to afford **4a** in 94% *ee* (entry 8). The optimized

Table 1. Catalyst tuning for first reaction: asymmetric cyanation reaction with **1**.



Entry	H_2O [mol%]	Additives $Ar_3P(O)$ [mol%][b]		BuLi [mol%]	*t* [h]	*T* [°C]	Yield [%]	*ee* [%]
1	10	–	0	0	9	−60	84	58
2	0	–	0	0	7.5	−60	0	–
3	0	**5a**	10	0	8.5	−60	93	64
4	10	**5a**	10	0	2.5	−60	88	83
5	20	**5a**	10	0	2.5	−60	74	88
6	30	**5a**	10	0	2.5	−60	54	89
7	30	**5b**	10	0	1.5	−60	97	92
8	30	**5b**	10	10	2	−78	96	94

[a] Reaction conditions: **3** (1.2 equiv), **1** (10 mol%); [b] **5a**: Ar = phenyl, **5b**: Ar = 2,6-dimethoxyphenyl.

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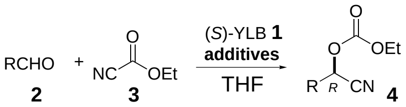
reaction conditions for cyanation, **1** (10 mol%), H_2O (30 mol%), BuLi (10 mol%), $Ar_3P(O)$ **5b** (10 mol%), and **3** (1.2 equiv), were applicable to various aldehydes (Table 2). In all cases, good yields and *ee* values were achieved using aromatic aldehydes (entries 1–2), α,β-unsaturated aldehydes (entries 3–4), α-unsubstituted (entries 5–6), α-monosubstituted (entries 7–10), and α,α-disubstituted aliphatic aldehydes (entry 11). To our knowledge, the present system has one of the broadest substrate generalities yet reported.[11] In addition, a preliminary survey revealed that the reaction proceeded smoothly with lower catalyst loading (entry 8 and entry 9), maintaining good reactivity and selectivity. On the basis of previous cyanation reactions that used Ln−CN active species,[8] we speculate that a similar nucleophilic Y−CN active species is involved in the present system. Detailed mechanistic investigations are in progress.

After developing this novel asymmetric cyanation reaction, we then applied YLB to sequential asymmetric reactions by combining the cyanation reaction with the previously reported asymmetric nitroaldol reaction,[5a] in which Li-binaphthoxide functioned as a Brønsted base to deprotonate CH_3NO_2. As expected, the optimized chiral environment constructed by YLB, and $Ar_3P(O)$ **5b** was not suitable for the nitroaldol reaction at all. As shown in Table 3, YLB and H_2O promoted the nitroaldol reaction of **2a** to afford **7** in 62% *ee* (entry 1).[12,13] However, the *ee* value dropped dramatically to 11% on the addition of **5b** (entry 2). This phenomenon is not surprising in asymmetric catalysis, which makes tandem asymmetric catalysis with a single catalyst component highly challenging. We thought that further elaborate tuning of the YLB with the aid of additional achiral additives might enable us to reconstruct a chiral environment of YLB **1** suitable for a second asymmetric nitroaldol reaction. Indeed, addition of the Li cation to the catalyst systems was effective for the reconstruction. With $LiBF_4$ (30 mol%), a similar *ee* value (59%) was obtained even in the presence of **5b** (entry 3). Currently, we speculate that Li cations interact with **5b**, which leads to the dissociation of **5b** from **1** and the reconstruction of the chiral space.

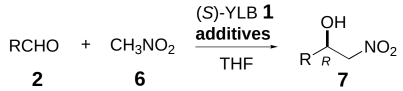
Table 2. A novel catalytic asymmetric cyanation reaction with optimized additives.



Entry		Aldehyde (R)	Product	Cat. [x mol%]	t [h]	Yield [%]	ee [%]
1	**2a**	Ph	**4a**	10	2	96	94
2	**2b**	1-naphthyl	**4b**	10	2	97	90
3	**2c**	(*E*)-$CH_3(CH_2)_2CH{=}CH$	**4c**	10	3	100	92
4	**2d**	(*E*)-PhCH=CH	**4d**	10	3	100	91
5	**2e**	$CH_3(CH_2)_4$	**4e**	10	3	93	94
6	**2f**	CH_3CH_2	**4f**	10	2	79[b]	92
7	**2g**	$(CH_3)_2CH$	**4g**	10	2	88[b]	98
8	**2g**	$(CH_3)_2CH$	**4g**	5	2	82[b]	96
9[c]	**2g**	$(CH_3)_2CH$	**4g**	1	9	96	90
10	**2h**	$c\text{-}C_6H_{11}$	**4h**	10	2	97	96
11	**2i**	$(CH_3)_3C$	**4i**	10	3	93	87

[a] Reaction conditions: **3** (1.2 equiv), (*S*)-**1** (*x* mol%), H_2O (3*x* mol%), BuLi (*x* mol%), **5b** (*x* mol%), THF, −78°C, Ar = 2,6-dimethoxyphenyl. [b] The yield of product isolated was lower because the product was volatile. [c] The reaction was performed on a 6.0 mmol scale. 1.8 mol% of BuLi was used.

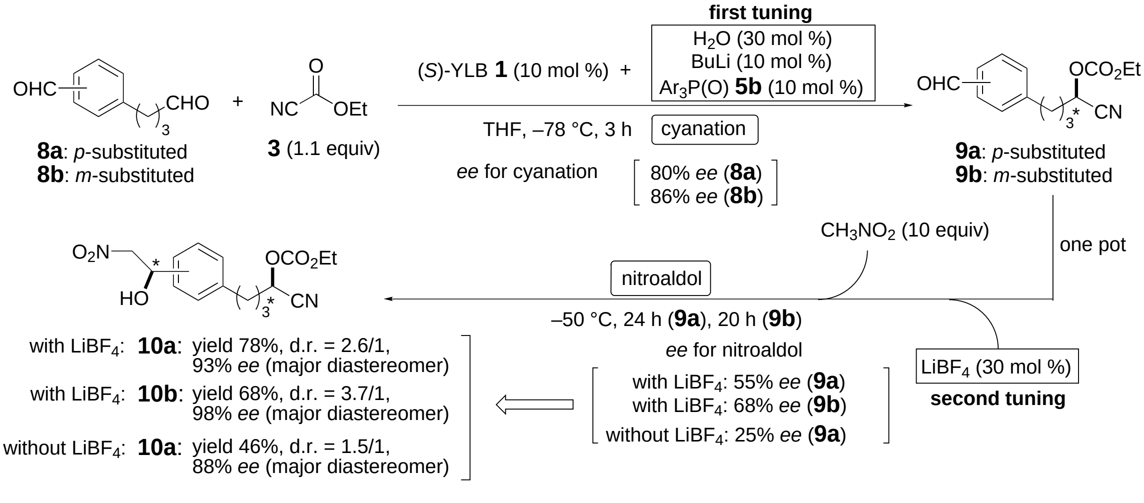
Table 3. Catalyst tuning for second reaction: asymmetric nitroaldol reaction with **1**.



Entry		Aldehyde (R)	Product	$Ar_3P(O)$ **5b** [mol%]	$LiBF_4$ [mol%]	t [h]	Yield [%]	ee [%]
1	**2a**	Ph	**7a**	0	0	20	82	62
2	**2a**	Ph	**7a**	10	0	20	68	11
3	**2a**	Ph	**7a**	10	30	20	84	59
4	**2j**	$4\text{-}CH_3\text{-}C_6H_4$	**7j**	10	0	26	51	11
5	**2j**	$4\text{-}CH_3\text{-}C_6H_4$	**7j**	10	30	26	84	62

[a] Reaction conditions: **6** (10 equiv), (*S*)-**1** (10 mol%), H_2O (30 mol%), THF, −40 °C.

Finally, by tuning the YLB catalyst with achiral additives (H_2O, **5b**, BuLi, and $LiBF_4$), a novel sequential asymmetric cyanation–nitroaldol reaction was performed (Scheme 2).



Scheme 2. Sequential catalytic asymmetric cyanation–nitroaldol reaction with and without adequate catalyst tuning.

Chemoselective cyanation reaction of the aliphatic aldehyde group in the dialdehyde **8** was performed at −78 °C using **1**, H_2O, BuLi, **5b**, and **3**. $LiBF_4$ was then added to the reaction mixture, followed by the addition of CH_3NO_2 (10 equiv). The mixture was stirred at −50 °C for 24 h (**9a**) and 20 h (**9b**) to afford the desired product **10**. The *ee* values of the major diastereomers were 93% (**10a**: yield 78%, d.r. = 2.6/1) and 98% (**10b**: yield 68%, d.r. = 3.7/1), respectively. Without a second tuning with $LiBF_4$, the yield (46%:**10a**), d.r. (1.5/1: **10a**), and *ee* value (88%: **10a**) decreased, which supports the effectiveness of the catalyst tuning strategy to achieve tandem asymmetric catalysis with a single chiral catalyst component. Calculated *ee* values for the second nitroaldol reaction itself were 55% *ee* (**9a** with $LiBF_4$), 68% *ee* (**9b** with $LiBF_4$), and 25% *ee* (**9a** without $LiBF_4$), respectively (Scheme 2).

In summary, we have developed a new, highly enantioselective cyanation reaction and successfully demonstrated the first tandem asymmetric catalysis with a single YLB catalyst component. Tuning the chiral environment in YLB with achiral additives such as $Ar_3P(O)$ (**5**) and $LiBF_4$ had a key role in the present sequential asymmetric cyanation–nitroaldol reactions. The strategy can be regarded as a chiral "allosteric enzyme" model and would, in principle, lead to tandem asymmetric catalysis to promote more than two mechanistically distinct asymmetric reactions in one pot with a single catalyst component (Scheme 1), creating the possibility for a more efficient and environmentally benign synthesis of optically active, complex molecules. Efforts to improve the second nitroaldol reaction and mechanistic investigations to clarify the exact roles of achiral additives are currently in progress.

Experimental Section

To tris(2,6-dimethoxyphenyl)phosphane oxide (**5b**) (27.6 mg, 0.06 mmol) in a test tube was added an (*S*)-YLB/H_2O solution (2.0 mL, 30 mM in THF, 0.06 mmol). The solution was stirred at room temperature. After completely dissolving **5b**, *n*BuLi (0.06 mmol) was added to the mixture. This catalyst solution was cooled down to −78 °C, dialdehyde **8a** (0.6 mmol) and ethyl cyanoformate (**3**) (0.66 mmol) were added and stirred at −78 °C. After stirring for 3 h, $LiBF_4$ (90 μL, 2.0 M in THF, 0.18 mmol) was added and the mixture was stirred at −50 °C for 30 min. Then, CH_3NO_2 (325 μL, 6.0 mmol) was added and the mixture was stirred at −50 °C. After stirring for 24 h, 1 M aq. HCl was added to the solution and the organic components extracted with diethyl ether. The organic layer was washed with brine and dried over Na_2SO_4. After evaporating the solvent, the residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate = 6/1) to give **10a** (156.6 mg, 0.47 mmol, yield 78%, d.r. = 2.6/1, 93% *ee* for major diastereomer) as a colorless oil.

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[10] Other heterobimetallic LnMB complexes (Ln = La, Sm, Gd etc, M = Li, Na, and K) gave less satisfactory results even with additives **5a** and/or **5b** (< 80% *ee*).

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[12] Nitroaldol reactions of benzaldehyde (**2a**) catalyzed by LnMB (Figure 1) generally afford **7a** only in modest *ee* values: LLB (Ln = La, M = Li) 37% *ee*, EuLB (Ln = Eu, M = Li) 72% *ee* (best result among species of general formula LnMB). Thus, the result with **1** (62% *ee*, Table 3, entry 1) is relatively good among LnMB complexes. See ref. [5a].

[13] For comparison with a sequential reaction, BuLi was not added in these experiments. In the first cyanation reaction, LiOH generated in situ from BuLi and H_2O would be consumed by the reaction with **3**.

A Trigonal-Bipyramidal Ferric Aqua Complex with a Sterically Hindered Salen Ligand as a Model for the Active Site of Protocatechuate 3,4-Dioxygenase[**]

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Protocatechurate 3,4-dioxygenase (3,4-PCD) has been found in soil bacteria and is known to play a role in degrading aromatic molecules in nature.[1,2] The enzyme is classified as an intradiol dioxygenase and cleaves catechol analogues bound to the iron(III) site into aliphatic products with incorporation of both atoms of molecular oxygen. It has been proposed that the enzyme does not activate an iron-bound oxygen molecule, but rather induces an iron-bound catecholate to react with O_2.[2] Therefore, knowledge of the structure and electronic state of the iron site is essential to under-

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