Catalytic Asymmetric Cyano-Phosphorylation of Aldehydes Promoted by Heterobimetallic YLi_3tris(binaphthoxide) (YLB) Complex

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Abstract: A highly enantioselective cyano-phosphorylation of aldehydes catalyzed by YLi_3tris(binaphthoxide) complex (YLB, **1**) is described. Slow addition of diethyl cyanophosphonate (**4**) to aldehydes **5** in the presence of **1** (10 mol%), H_2O (30 mol%), *tris*(2,6-dimethoxyphenyl)phosphine oxide (10 mol%, **3a**), and BuLi (10 mol%) afforded cyanohydrin *O*-phosphates **6** in up to 98% yield and 97% ee.

Key words: asymmetric catalysis, cyanohydrins, Lewis acid, phosphorylation, yttrium

Catalytic asymmetric cyanation reaction of carbonyl compounds is one of the most powerful tools available to supply useful chiral building blocks. Although various methods have been developed over the last two decades,[1] $(CH_3)_3SiCN$ (TMSCN) and/or HCN are most often used as cyanide sources to afford cyanohydrins and their TMS ethers. The intrinsic instability of cyanohydrins and their TMS ethers, however, is sometimes problematic for further transformations. Therefore, the development of a one-pot cyanation–*O*-protection reaction with a stable protecting group is desirable. To address this issue, we[2] and others[3,4] recently developed a catalytic asymmetric cyano-ethoxycarbonylation reaction of aldehydes[2,3] and ketones[4] using ethyl cyanoformate (**2**) as the cyanide source, affording the chiral cyanohydrin *O*-carbonates in one-pot. In our system, the YLi_3tris(binaphthoxide)[5] complex [YLB (**1**), Figure 1] effectively promoted the reaction in the presence of three additives; H_2O, *tris*(2,6-dimethoxyphenyl)phosphine oxide (**3a**), and BuLi. The cyanohydrin *O*-carbonates were obtained in high yield (up to 100% yield) and ee (up to 98% ee).

To extend the utility of our catalyst system, we investigated the use of other cyanide sources. Cyanohydrin *O*-phosphate is a useful building block found in pesticides.[6] Although efficient one-pot racemic syntheses of cyanohydrin *O*-phosphate were reported two decades ago using diethyl cyanophosphonate (**4**) as the cyanide source,[7] there is only one recent report of catalytic asymmetric cyano-phosphorylation reaction by Nájera, Saá and co-workers.[8] Herein, we disclose a catalytic asymmetric cyano-phosphorylation reaction of aldehydes using YLB (**1**). Cyanohydrin *O*-phosphates were obtained in up to 98% yield and 97% ee.

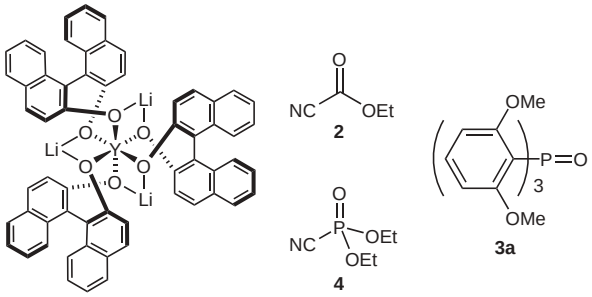

Figure 1 Structures of YLi_3tris(binaphthoxide) [YLB (**1**)], ethyl cyanoformate (**2**), *tris*(2,6-dimethoxyphenyl)phosphine oxide (**3a**), and diethyl cyanophosphonate (**4**)

Initially, we applied the optimized conditions for the catalytic asymmetric cyano-ethoxycarbonylation reaction[2a] to the cyano-phosphorylation reaction. The (*S*)-YLB (**1**, 10 mol%) catalyst with H_2O (30 mol%), $Ar_3P(O)$ (**3a**, 10 mol%), and BuLi (10 mol%) promoted the reaction of **5a** and **4** at –78 °C, affording cyanohydrin *O*-phosphate **6a** in 66% yield and 86% ee with corresponding cyanohydrin (11% yield, Table 1, entry 1). The results shown in entries 2–4 suggested that all three additives [H_2O, $Ar_3P(O)$ **3a**, and BuLi] were essential for good enantioselectivity. During optimization studies, we encountered reproducibility problems both in terms of reactivity and selectivity. We hypothesized that **4** might partially decompose the YLB complex (**1**), because **4** is a good phosphorylating reagent of phenolic OH groups.[9] A slow addition of **4** was effective to overcome the problem. As shown in entry 5, both chemical yield and enantiomeric excess were improved when **4** was added slowly over one hour to the reaction mixture at –78 °C. Cyanohydrin *O*-phosphate **6a** was obtained in 97% yield and 92% ee after two hours under the optimized conditions.

Substituent effects of the phosphine oxide are summarized in Table 2. Triphenylphosphine oxide (**3b**) resulted in a slightly lower ee and reactivity (88% ee, 85% yield, entry 2). *Tris*(2,4,6-trimethoxyphenyl)phosphine oxide (**3c**)[10] afforded comparable enantioselectivity and reactivity (95% yield, 91% ee, entry 3) On the other hand, *tris*(2,4,6-trimethylphenyl)phosphine oxide (**3d**) produced worse results (75% yield, 79% ee, entry 4), indicating the importance of the MeO-group rather than steric bulkiness at the *ortho*-position.

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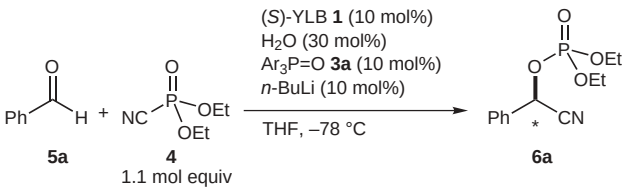
Table 1 Optimization of the Reaction Conditions

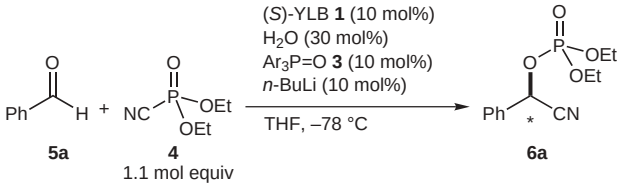


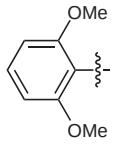
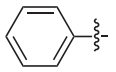
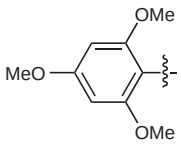
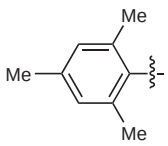
Entry	Additive (mol%) H_2O	$Ar_3P{=}O$ **3a**	BuLi	Time (h)	Yield (%)	ee (%)
1[a]	30	10	10	1	66	86
2	0	10	10	4	58	19
3	30	0	10	4	54	29
4	30	10	0	4	63	75
5[b]	30	10	10	2	97	92

[a] Cyanohydrin (11%) was obtained.
[b] Compound **4** was slowly added over 1 h.

The scope and limitations of the substrates are summarized in Table 3.[11] In all entries, the reactions were performed at –78 °C for two hours with the slow addition of **4**. Aromatic aldehydes gave a high yield (95–98%) and good enantiomeric excess (81–93% ee, entries 1–4).

Table 2 Effects of Phosphine Oxides

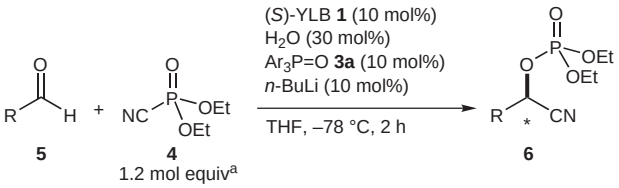


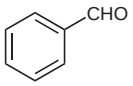
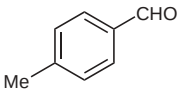
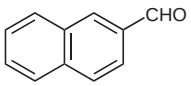
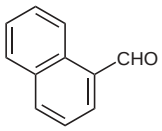
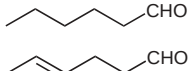
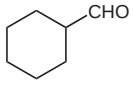
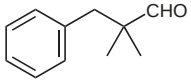
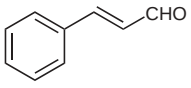
Entry	Ar in $Ar_3P{=}O$		Yield (%)	ee (%)
1		**3a**	97	92
2		**3b**	85	88
3		**3c**	96	91
4		**3d**	75	79

[a] Compound **4** was slowly added over 1 h at –78 °C.

Linear and branched aliphatic aldehydes (entry 5–8) gave good chemical yield (82–90%) and good enantiomeric excess (82–97% ee). Aldehyde **5h** gave the highest enantioselectivity among the aldehydes examined (97% ee, entry 8). On the other hand, aldehyde **5i** gave **6i** in slightly lower enantioselectivity, probably due to the steric factor (entry 9). α,β-Unsaturated aldehydes **5j** gave **6j** in only 24% ee (entry 10), although high enantiomeric excess was obtained in the cyano-ethoxycarbonylation reaction of **5j** (100% yield, 91% ee).[2] The result shown in entry 10 indicated that the catalytic cycle for the cyano-phosphorylation reaction might be different from that for the cyano-ethoxycarbonylation reaction.[12]

Table 3 Catalytic Asymmetric Cyano-Phosphorylation of Aldehydes



Entry	Aldehyde		Product	Yield (%)	ee (%)
1		**5a**	**6a**	97	92
2		**5b**	**6b**	98	93
3		**5c**	**6c**	98	81
4[b]		**5d**	**6d**	95	89
5[b]		**5e**	**6e**	90	92
6		**5f**	**6f**	83	82
7		**5g**	**6g**	82	96
8		**5h**	**6h**	82	97
9		**5i**	**6i**	81	76
10		**5j**	**6j**	71	24

[a] Compound **4** was slowly added over 1 h at –78 °C, and the reaction mixture was stirred further 1 h at –78 °C.
[b] Compound **3c** was used instead of **3a**.

In conclusion, we developed a catalytic asymmetric cyano-phosphorylation reaction promoted by the YLB complex. Cyanohydrin *O*-phosphates were obtained with good yield (up to 98%) and enantiomeric excess (up to 97% ee). Mechanistic studies are now in progress.

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(11) **General Procedure for the Cyano-Phosphorylation Reaction.**
To **3a** (164.6 mg, 0.3 mmol) in a test tube were added the (*S*)-YLB·H_2O solution (5.00 mL, 0.3 mmol, 0.06 M, THF)[2] and BuLi (0.3 mmol) in hexane at r.t. After dissolving **3a** completely, the mixture was cooled to –78 °C, and **5a** (3.0 mmol) in THF (4.50 mL) was added to the catalyst mixture. After stirring for 10 min at –78 °C, **4** (0.55 mL, 3.6 mmol) in THF (0.50 mL) was slowly added to the reaction mixture over 1 h, and the reaction mixture was stirred at –78 °C for additional 1 h. Then, HOAc in THF cooled to –78 °C was added to the solution, and the mixture was diluted with H_2O. The organic component was extracted with EtOAc. The organic layer was washed with sat. aq $NaHCO_3$, H_2O, brine, and dried over Na_2SO_4. After evaporating solvent, the residue was purified by silica gel flash column chromatography (hexane–EtOAc = 7:1) to give **6a** (97% yield, 92% ee, *R*); colorless oil. IR (neat): ν = 1269, 1024 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.16 (dt, $J_{(H,P)}$ = 0.6 Hz, J = 7.0 Hz, 3 H), 1.32 (dt, $J_{(H,P)}$ = 0.6 Hz, J = 7.0 Hz, 3 H), 3.92–3.99 (m, 2 H), 4.12–4.17 (m, 2 H), 6.02 (d, $J_{(H,P)}$ = 8.6 Hz, 1 H), 7.39–7.40 (m, 3 H), 7.49–7.50 (m, 2 H). ^{13}C NMR ($CDCl_3$): δ = 15.8 (d, $J_{(C,P)}$ = 7.3 Hz), 16.0 (d, $J_{(C,P)}$ = 7.1 Hz), 64.6 (d, $J_{(C,P)}$ = 6.3 Hz), 64.8 (d, $J_{(C,P)}$ = 6.1 Hz), 66.5 (d, $J_{(C,P)}$ = 4.1 Hz), 116.1 (d, $J_{(C,P)}$ = 6.3 Hz), 127.5, 129.2, 130.6, 132.4 (d, $J_{(C,P)}$ = 4.1 Hz). ^{31}P NMR ($CDCl_3$): δ = –1.93. LRMS (ESI, MeOH): *m/z* = 292 [M + Na^+]. HRMS (FAB): *m/z* [N + H^+] calcd for $C_{12}H_{17}NO_4P$: 270.0890; found: 270.0894. $[\alpha]_D^{21.7}$ +18.9 (*c* 1.2, $CHCl_3$; 92% ee, *R*); HPLC (DAICEL CHIRALPAK®) AD-H, hexane–2-PrOH = 9:1, flow rate = 1.0 mL/min, retention time 14.5 min (*S*)/17.1 min (*R*). The absolute configuration of **6a** was determined comparing retention time in HPLC analysis with that of the authentic product synthesized from commercially available (*R*)-mandelonitrile (Aldrich Co. Ltd.) with **4**.

(12) Detailed mechanistic studies of asymmetric cyanation reaction using YLB(**1**) and the cyanide source **2** and **4** will be reported elsewhere in due course.