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Chiral Lithium Salts of Phosphoric Acids as Lewis Acid–Base Conjugate Catalysts for the Enantioselective Cyanosilylation of Ketones

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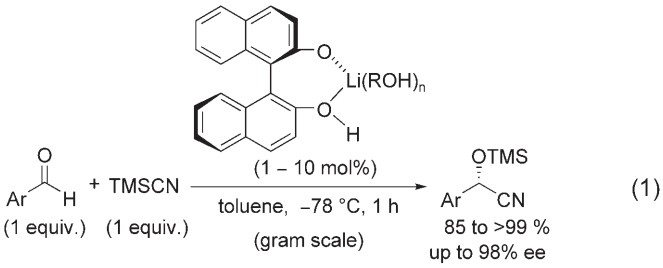
Abstract: The catalytic enantioselective cyanosilylation of aromatic ketones was developed by using chiral lithium salts of (*R*)-BINOL- or (*S*)-BINAM-derived phosphoric acid compounds. In the presence of 10 mol% of chiral conjugate lithium salts, the corresponding tertiary cyanohydrins were obtained in high yields with moderate to high enantioselectivities. This is the first efficient example of asymmetric catalysis using lithium salts of synthetically useful chiral phosphoric acid compounds. A possible catalytic mechanism and transition states are also discussed as a preliminary working hypothesis.

Keywords: asymmetric catalysis; cyanohydrins; cyanosilylation; ketones; lithium; phosphoric acids

Over the past decade considerable attention has been centered on the catalytic enantioselective synthesis of optically active tertiary cyanohydrins from ketones and trimethylsilyl cyanide (TMSCN) or hydrogen cyanide.[1,2] Optically active tertiary cyanohydrins are synthetically important building blocks that can be transformed into not only natural products but also biologically and pharmaceutically active compounds.[3] However, although several outstanding catalysts have been developed for the cyanation of aldehydes, the catalytic enantioselective cyanation of ketones is still limited.[1,2,4–13] This problem is partially due to the extremely low reactivity associated with conspicuous steric and electronic constraint between ketones and nucleophiles, and the difficulty of controlling the enantiofacial stereoselectivity of ketones.

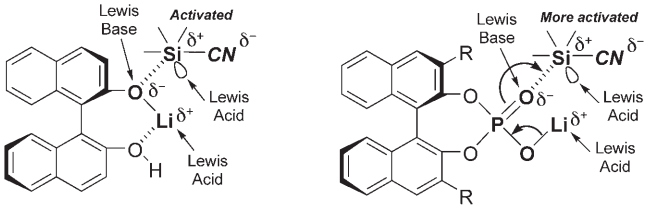
As a pioneering work, Kagan has developed the addition of TMSCN to aldehydes catalyzed by a *dry* chiral lithium binaphtholate as a Lewis base catalyst where intermediates of hypervalent silicate might be responsible.[14] As an extension of this work, we also reported a highly efficient secondary cyanohydrin synthesis using chiral lithium binaphtholate aqua and/or alcohol complexes as Lewis base catalysts [Eq. (1)].[15]



(1)

Unfortunately, however, this catalytic system could not be applied to the synthesis of tertiary cyanohydrins from ketones: the reactions could scarcely proceed at −78 °C in low yields, but higher temperatures of up to −40 °C gave racemates or quite low enantioenriched products in high yields. We assumed that this low catalytic activity was due to then inadequate Lewis basicity of the lithium binaphtholate, and thus stronger Lewis basicity would be needed to activate TMSCN to react with inactive ketones.

To overcome this difficulty in catalytic enantioselective tertiary cyanohydrin synthesis, we designed simple chiral lithium salts of phosphoric acids,[16] which were derived from 2,2′-binaphthol (BINOL) (Figure 1). Lithium phosphate complexes (Figure 1b) as Lewis acid–base catalysts[17] should be more efficient than lithium binaphtholate complexes (Figure 1a) for three reasons. (1) Based on our recent developments in the organozinc addition to aldehydes and ketones using 3,3′-diphosphoryl-BINOLs and L-



(a) Lithium binaphtolate (b) Lithium phosphate

Figure 1. Design of chiral lithium phosphate complexes as Lewis acid-base conjugate catalysts.

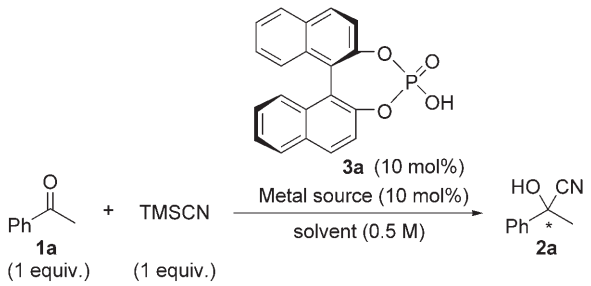
valine-derived phosphoramide as chiral ligands,[18] the conjugate P=O moiety with Lewis acidic metal centers can act as a Lewis base to activate nucleophiles such as TMSCN.[19,20] In general, the P=O moiety in phosphoric acids [$R_2P(=O)OH$] shows a relatively high basicity[21] and, moreover, this basicity should increase through the ionic conjugation of Li–O–P=O in the corresponding lithium salts [$R_2P(=O)OLi$]. (2) Since silicon compounds tend to form highly Lewis acidic complexes with five or six valences,[22] ketones can be doubly activated by Si and Li centers. A favored six-membered chelation ring may be formed in a lithium phosphate, in contrast to a less-favored four-membered chelation ring in a lithium binaphtholate. (3) Based on recent developments in the chemistry of chiral phosphoric acids by Alper, Inanaga, Akiyama, Terada, and others, it should be possible to design BINOL-derived phosphoric acids with 3,3′-disubstitution in the binaphthyl skeleton.[23,24]

First, the cyanosilylation of acetophenone (**1a**) with TMSCN (1 equiv. each) was examined in the presence of chiral phosphoric acid **3a** and *n*-BuLi (10 mol% each) (Table 1). The reactions proceeded, albeit slowly, at room temperature in dichloromethane or THF (entries 1 and 2), while the desired product **2a** was obtained with low enantioselectivity in moderate yields even at −40 °C in Et_2O or toluene (entries 3 and 4).[25] The yield of **2a** was improved to 82% with 36% *ee* under higher concentration (1.0 M) conditions in toluene (entry 5). As a lithium source in place of *n*-BuLi, LiO-*i*-Pr was not effective (entry 6),[26] and other alkaline metal salts such as NaO-*t*-Bu and KO-*t*-Bu were also not effective (entries 7 and 8).

Next, we examined the effect of 3,3′-disubstitution in the (*R*)-BINOL-derived phosphoric acids (**3**) (Table 2). The enantioselectivities of (*S*)-**2a** gradually increased with the use of compounds **3b** (R = Me) and **3c** (R = Br) (entries 2 and 3). Interestingly, compound **3d** (R = Ph) dramatically improved the enantioselectivity of (*R*)-**2a** up to 86% *ee* with a change in the absolute stereochemistry (entry 4). To achieve higher enantioselectivity, we examined other candidates with large aromatic groups. However, **3e** (R = 1-Naph), **3f** (R = 3,5-$Me_2C_6H_3$), **3g** (R = 3,5-$Mes_2C_6H_3$), **3h** (R = 4-PhC_6H_4), and **3i** (R = 2-*i*-$PrOC_6H_4$) gave (*R*)-**2a** with low enantioselectivities (0–31% *ee*) (entries 5–9).[27]

Under the optimized reaction conditions using **3d**, the cyanosilylation of other ketones was examined (Table 3). Aromatic ketones with an electron-withdrawing group gave the corresponding (*R*)-products

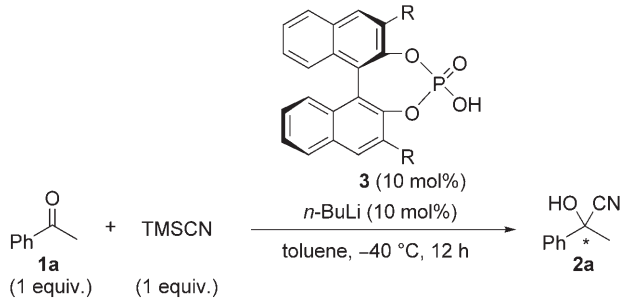
Table 1. Enantioselective cyanosilylation of acetophenone (**1a**) catalyzed by an alkaline metal salt of chiral phosphoric acid **3a**.



Entry	Metal source	Solvent	Temperature	Time [h]	Yield [%]	*ee* [%] (Configuration)
1	*n*-BuLi	CH_2Cl_2	r.t.	24	<3	–
2	*n*-BuLi	THF	r.t.	12	54	10 (*S*)
3	*n*-BuLi	Et_2O	−40 °C	9	45	26 (*S*)
4	*n*-BuLi	toluene	−40 °C	12	48	31 (*S*)
5[a]	*n*-BuLi	toluene	−40 °C	12	82	36 (*S*)
6	LiO-*i*-Pr	toluene	−40 °C	12	49	13 (*S*)
7[b]	NaO-*t*-Bu	toluene	0 °C	15	13	26 (*R*)
8[b]	KO-*t*-Bu	toluene	r.t.	24	28	7 (*R*)

[a] Concentration was 1.0 M.
[b] 20 mol% of catalysts were used. *t*-BuOH was removed during the catalyst preparation.

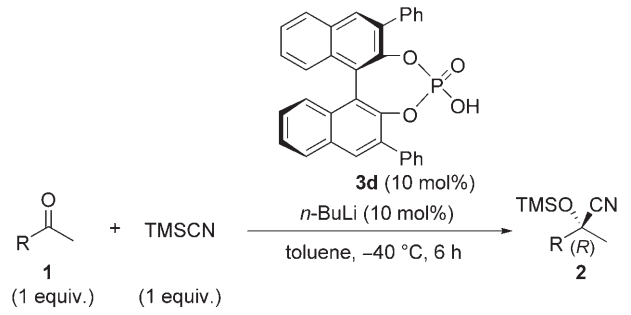
Table 2. Effect of 3,3′-disubstitution of (*R*)-BINOL-derived chiral phosphoric acid.[a]



Entry	**3** (R)	Yield [%]	*ee* [%] (Configuration)
1	**3a** (H)	82	36 (*S*)
2	**3b** (Br)	95	40 (*S*)
3	**3c** (Me)	99	54 (*S*)
4	**3d** (Ph)	96	86 (*R*)
5	**3e** (1-Naph)	30	0
6	**3f** (3,5-$Me_2C_6H_3$)	78	11 (*R*)
7	**3g** (3,5-$Mes_2C_6H_3$)	86	29 (*R*)
8	**3h** (4-PhC_6H_4)	73	9 (*R*)
9	**3i** (2-*i*-$PrOC_6H_4$)	69	31 (*R*)

[a] Reactions were examined at 1.0 M toluene.

Table 3. Catalytic enantioselective cyanosilylation of ketones using lithium salt of **3d**.

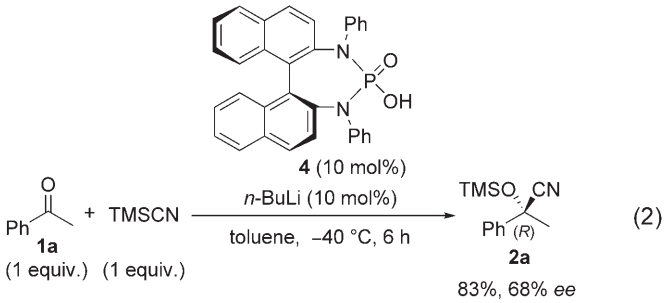


Entry	**1** (R)	Product	Yield [%]	*ee* [%] (Config.)
1[a]	**1a** (Ph)	**2a**	96	86 (*R*)
2	**1b** (2-ClC_6H_4)	**2b**	99	75 (*R*)
3	**1c** (3-ClC_6H_4)	**2c**	99	65
4[a]	**1d** (4-ClC_6H_4)	**2d**	95	68 (*R*)
5[b]	**1e** (2-$MeOC_6H_4$)	**2e**	59	32
6	**1f** (3-$MeOC_6H_4$)	**2f**	91	37 (*R*)
7[a]	**1g** (4-$MeOC_6H_4$)	**2g**	94	63 (*R*)
8	**1h** (2-Naph)	**2h**	96	55 (*R*)
9	**1i** ($Ph(CH_2)_2$)	**2i**	38	2 (*R*)

[a] Reaction time was 12 h.
[b] Reaction was examined at 0 °C for 24 h.

(**2b–d**) in high yields with moderate to good enantioselectivities (65–75% *ee*) (entries 2–4). For the relatively less-reactive 2-acetonaphthone and *o*-, *m*-, and *p*-methoxyacetophenone, the products were obtained with up to 63% *ee* (entries 5–8). Unfortunately, aliphatic ketones such as benzylacetone gave almost racemic products in low yields (entry 9).

By taking advantage of the axially chiral binaphthyl skeleton, we also prepared novel (*S*)-2,2′-binaphthyldiamine [(*S*)-BINAM]-derived phosphoric acid **4**. Cyanosilylation of **1a** using 10 mol% of the lithium salt of (*S*)-**4** proceeded in toluene at −40 °C for 6 h, and (*R*)-**2a** was obtained in 83% yield with 68% *ee* [Eq. (2)].



(2)

Finally, we examined the mechanistic aspects. Although further investigation is necessary to obtain a clear understanding, a postulated catalytic cycle is shown in Figure 2 as a working model. An *in situ*-prepared chiral lithium phosphate complex **5** activates TMSCN and then ketone **1** to give Lewis acidic hypervalent silicon intermediates **6** and **7**.[14] An activated cyanide attacks a carbonyl moiety through a six-membered cyclic transition state. In the transition

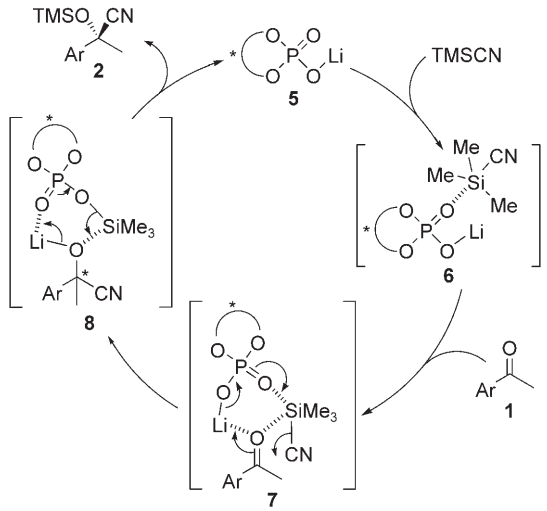


Figure 2. Postulated catalytic cycle with a Lewis acid–base conjugate catalyst.

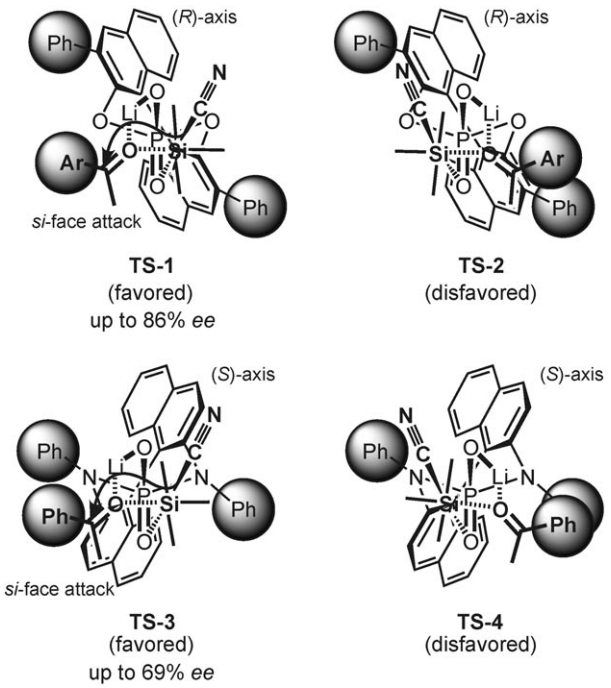


Figure 3. Possible transition states.

states, the *si*-face attack *via* **TS-1**, which leads to (*R*)-products, should be favored exclusively without conspicuous steric repulsion between the substrate and a Ph group of **3d** (Figure 3, **TS-1** *vs.* **TS-2**). Eventually, catalyst **5** would be regenerated *via* intermediate **8** accompanied by the release of product **2**. In the case of a chiral lithium salt of **4**, similar transition states **TS-3** and **TS-4** were assumed (Figure 3). However, steric repulsion would be observed even in the favored **TS-3**, and therefore a slight decrease in enantioselectivity was observed when **4** was used [Eq. (2)].

In summary, we have developed a catalytic enantioselective cyanosilylation of aromatic ketones using chiral lithium salts of (*R*)-BINOL- or (*S*)-BINAM-derived phosphoric acid compounds. In the presence of 10 mol% of chiral lithium catalyst, the corresponding tertiary cyanohydrins were obtained in high yields with moderate to high enantioselectivities (up to 86% *ee*). This is the first successful example of asymmetric catalysis using lithium salts of synthetically useful chiral phosphoric acid compounds. Further studies on detailed mechanistic aspects and the application of this methodology to other catalyses are now underway.

Experimental Section

Representative Procedure for Catalytic Enantioselective Cyanosilylation of Ketones (Table 3, entry 1)

(*R*)-(3,3′-Dipheyl-1,1′-binaphthalen-2,2′-yl)-phosphoric acid (**3d**) (37.2 mg, 0.075 mmol, 10 mol%) was placed in a Schlenk tube under a nitrogen atmosphere and dissolved in dry toluene (0.75 mL). To the solution was added *n*-BuLi (1.60 M in hexane, 46.9 μL, 0.075 mmol, 10 mol%) at −78 °C and the solution was stirred at that temperature for 30 min. Acetophenone (**1a**, 90.1 mg, 0.75 mmol) was added and the mixture was stirred at −78 °C for 30 min. Trimethylsilyl cyanide (0.10 mL, 0.75 mmol) was added dropwise at −78 °C, and then the mixture was stirred at −40 °C for 12 h. The resulting mixture was quenched with water at −40 °C. The organic layer was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by neutral silica gel column chromatography (hexane/AcOEt = 20/1) to give the desired product (**2a**) as a colorless oil; yield: 157.8 mg (96% yield). The enantiomeric purity was determined by chiral GC (γ-TA): 86% *ee*, (*R*).

Acknowledgements

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[25] The reactions could not proceed without *n*-BuLi.
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[27] The unexpected reversal of the absolute enantioselectivity is not fully understood and further examinations are necessary. However, not only steric and electric factors, but also an aggregation structure of lithium salts should be involved.

