Chiral Sodium Phosphate Catalyzed Enantioselective 1,4-Addition of TMSCN to Aromatic Enones

Jingya Yang,[a,b] Shaoxiang Wu,[a] Fu-Xue Chen*[a]

[a] Department of Applied Chemistry, School of Chemical Engineering & the Environment, Beijing Institute of Technology, No. 5 South Zhongguancun Street, Haidian District, Beijing 100081, P. R. of China
Fax +86(10)68918296; E-mail: fuxue.chen@bit.edu.cn

[b] College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. of China

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Abstract: A facile enantioselective 1,4-addition of TMSCN to aromatic enones has been developed using chiral sodium phosphate. Thus, in the presence of 20 mol% of sodium salt generated in situ from (*R*)-3,3′-di(1-adamantyl)-1,1′-binaphthyl-2,2′-diylphosphoric acid and NaOH, β-cyano ketones were obtained in high yield (86–96%) and up to 72% ee within three hours at 80 °C in toluene.

Key words: asymmetric catalysis, enones, 1,4-addition, nitriles, phosphates

The catalytic asymmetric conjugate addition of α,β-unsaturated carbonyl compounds is one of the most powerful carbon–carbon bond-forming reactions.[1] Recently, significant achievements have been made in the catalytic asymmetric 1,4-addition of cyanide to α,β-unsaturated carboxylic acid derivatives.[2] However, the asymmetric 1,4-addition of cyanide to enones is limited.[3] The pioneering work of the enantioselective reaction was reported by Shibasaki and co-workers in 2008.[3] To develop a new practical methodology for this useful transformation of aromatic enones is still highly demanding.[4]

Previously, we reported CsF- and Cs_2CO_3-catalyzed 1,4-addition of trimethylsilyl cyanide (TMSCN) to enones to prepare racemic β-cyano ketones in excellent yield and perfect regioselectivity.[5,6] Inspired by this work, we speculated that an asymmetric variant might be achieved using metal salts of chiral acids as catalysts. Recently, metal salts,[7–9] a kind of chiral anionic Lewis base,[10,11] have been employed as potential catalysts in asymmetric reactions. Among them, alkali-metal salts of chiral amino acid catalyzed asymmetric Michael reactions have been disclosed.[7a–h] However, chiral-salt-catalyzed 1,4-addition of cyanide to enones, to the best of our knowledge, has not been reported. Herein, we report a chiral sodium phosphate catalyzed enantioselective 1,4-addition of TMSCN to aromatic enones.

To optimize the reaction parameters, model reaction was conducted with chalcone (**1a**) and TMSCN (Table 1). Initially, various chiral acids (20 mol%) were screened (Figure 1), which reacted with sodium hydroxide in situ to give the corresponding chiral sodium salts as the catalysts (entries 1–6). Sodium salt of L-proline (**3**) exhibited certain catalytic activity but giving racemic β-cyano ketone (**2a**) (entry 1).[7] Similarly, the salt of D-camphor sulfonic acid (**4**) also afforded a racemic product (entry 2). However, the bissodium salt of L-tartaric acid (**5**) bearing two chiral centers yielded the product **2a** in low yield and 20% ee (entry 3). The bissodium salt of (*R*)-BINOL (BINOL = 1,1′-binaphthyl-2,2′-diol, **6a**) showed poor chiral inductive capability (entry 4).[8] To our delight, sodium salt of (*R*)-BNPH (BNPH = 1,1′-binaphthyl-2,2′-diylphosphoric acid, **7a**) gave the product **2a** with 31%

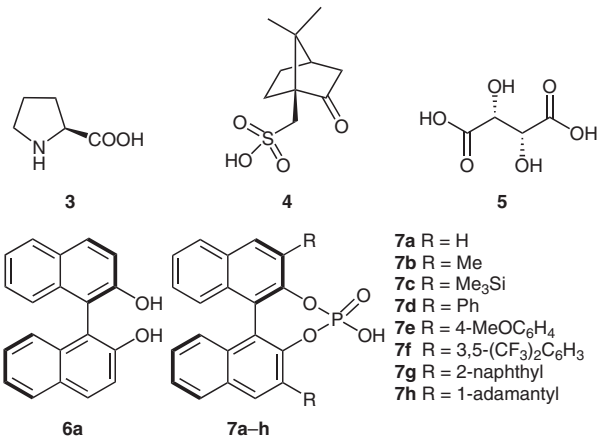
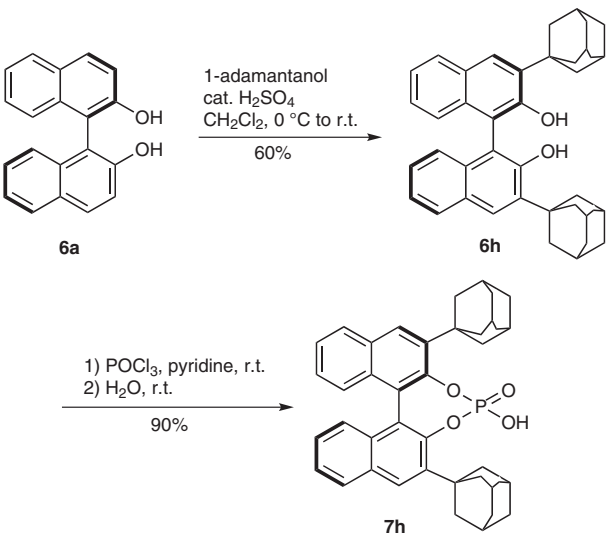


Figure 1 Chiral acids evaluated in catalyst screening



Scheme 1 Synthesis of phosphoric acid **7h** from (*R*)-BINOL

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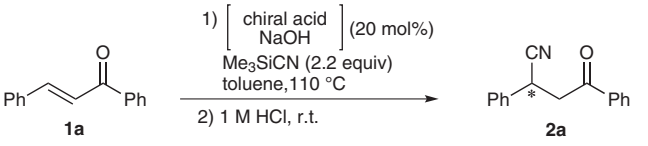
yield and 53% ee (entry 5) comparing with no reaction when using (*R*)-BNPH alone (entry 6).[9]

Subsequently, several sodium salts of 3,3′-disubstituted BINOL-derived phosphoric acids **7a**–**h**[12] were evaluated in terms of enantioselectivity and catalytic activity (Table 1, entries 7–13). Thus, with sodium salt of **7b**, poor enantioselectivity (4% ee) and yield (5%) were obtained (entry 7). Sodium salt of **7c** gave 15% ee with the other enantioisomer as major product (entry 8). Other candidates (**7d**–**g**) with aromatic substituents at 3,3′-positions showed good catalytic activity but poor enantioselectivity ranging 0–37% ee (entries 9–12). However, the sodium salt of phosphoric acid **7h**, synthesized from (*R*)-BINOL with the bulky 1-adamantyl substituent (Scheme 1),[13] exhibited much better catalytic activity than **7a**, giving **2a** 88% in yield and 49% ee in enantioselectivity (entry 13 vs. entry 5). Considering significant improvement on other reactions could be realized by the addition of proton additives,[2,5b] 20 mol% of 2-*t*-BuC_6H_4OH was introduced into the reaction mixture. To our delight, higher enantioselectivity (63% ee) and better yield (92%) were obtained in a short reaction time (entry 14 vs. entry 13). Furthermore, decreasing the reaction temperature from 110 °C to 80 °C, the enantioselectivity was improved to 71% ee (entry 15). Other reaction parameters including solvents, the nature of metal salts, and other additives were also examined but generally inferior results were obtained.

Under the optimized reaction conditions, the substrate generality of the chiral sodium phosphate-catalyzed 1,4-addition of TMSCN to enones was investigated (Table 2).[14] In general, chalcone derivatives gave excellent yields (86–99%) and moderate enantioselectivities (53–72% ee) at varying reaction rate (entries 1–10). The reactions with electron-donating substituents proceeded

Table 1 Optimization of Reaction Conditions

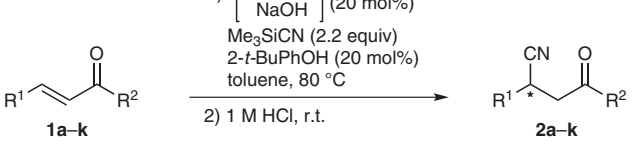


1a 2a

Entry[a]	Chiral acid	Time (h)	Yield (%)[b]	ee (%)[c]
1	**3**	4.5	34	0
2	**4**	4.5	75	0
3[d]	**5**	4.5	7	–20
4[d]	**6a**	4.5	21	4
5	**7a**	4.5	31	53
6[e]	**7a**	4.5	n.r.	–
7	**7b**	4.5	5	4
8	**7c**	4.5	84	–15
9	**7d**	4.5	71	2
10	**7e**	4.5	84	37
11	**7f**	4.5	94	0
12	**7g**	4.5	87	2
13	**7h**	4.5	88	49
14[f]	**7h**	2	92	63
15[g]	**7h**	2	94	71

[a] Reaction conditions: After stirring 1 h at 30 °C under argon the solution of chiral acid (20 mol%) and NaOH (20 mol%) in toluene (0.5 mL) was sequentially added **1a** (0.15 mmol), toluene (0.5 mL) and TMSCN (0.33 mmol, 2.2 equiv) at r.t. followed by stirring for indicated reaction time at 110 °C or otherwise noted reaction temperature.
[b] Isolated yield; n.r. = no reaction.
[c] Determined by chiral HPLC analysis on Chiralpak AS-H.
[d] Conditions: 20 mol% of chiral acid and 40 mol% of NaOH were loaded.
[e] In the absence of NaOH.
[f] In the presence of 2-*t*-BuC_6H_4OH (20 mol%).
[g] The reaction was performed in the presence of 2-*t*-BuPhOH (20 mol%) at 80 °C.

Table 2 Substrate Scope



1a–k 2a–k

Entry[a]	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a** R^1 = Ph, R^2 = Ph	2	94	71
2	**2b** R^1 = 2-MeOC_6H_4, R^2 = Ph	3	96	63
3	**2c** R^1 = 3-MeOC_6H_4, R^2 = Ph	2	91	67
4	**2d** R^1 = 4-MeOC_6H_4, R^2 = Ph	2	97	70[d]
5	**2e** R^1 = 4-MeC_6H_4, R^2 = Ph	2	93	72
6	**2f** R^1 = 4-MeOC_6H_4, R^2 = 3-BrC_6H_4	2	97	66 (100, *S*)[e]
7	**2g** R^1 = 2-ClC_6H_4, R^2 = Ph	1	99	53[f]
8	**2h** R^1 = 2,4-$Cl_2C_6H_3$, R^2 = Ph	1	99	64
9	**2i** R^1 = 3-$O_2NC_6H_4$, R^2 = Ph	1	99	65
10	**2j** R^1 = 2-ClC_6H_4, R^2 = 4-$O_2NC_6H_4$	0.5	86	62
11	**2k** R^1 = Me, R^2 = Ph	1	94	50

[a] Reaction conditions: After stirring 1 h at 30 °C under argon, the solution of **7h** (0.03 mmol, 20 mol%) and NaOH (0.03 mmol, 20 mol%) in toluene (0.5 mL) was added enones (0.15 mmol), 2-*t*-BuPhOH (0.03 mmol, 20 mol%), toluene (0.5 mL), and TMSCN (0.33 mmol, 2.2 equiv) at r.t. followed by stirring for indicated reaction time at 80 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis on Chiralpak AS-H or otherwise noted.
[d] Determined by chiral HPLC analysis on Chiralcel OD-H.
[e] In parentheses, enantiopure **2f** was obtained after recrystallization from EtOAc and PE with the absolute configuration of **2f** determined by X-ray crystal structure analysis.
[f] Determined by chiral HPLC analysis on Chiralpak AD-H.

slower than or comparable to that of chalcone (entries 2–6 vs. entry 1). On the other hand, electron-deficient enones were converted into β-cyano ketones much quickly with slightly lower enantioselectivity (entries 7–10 vs. entry 1). Therefore, 4-methyl- and 4-methoxy-substituted chalcone derivatives had higher enantioselectivity (66–72% ee, entries 3–6) than electron-deficient ones (53-65% ee, entries 7–10). β-Alkyl-substituted enone **1k** also gave excellent yield and 50% ee under the same reaction conditions (entry 11). Enantiopure **2f** was easily obtained after simple recrystallization of a 66% ee product sample (entry 6). Its absolute configuration was established to be *S* by X-ray crystal structure analysis (Figure 2).[15]

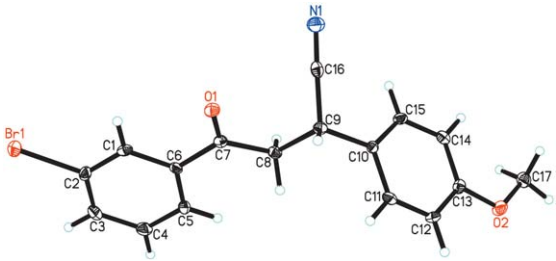


Figure 2 X-ray crystallographic structure of (*S*)-**2f**

In summary, a catalytic enantioselective 1,4-addition of TMSCN to aromatic enones have been developed using chiral sodium (*R*)-BINOL-derived phosphate. In the presence of 20 mol% of sodium salt of **7h**, the corresponding β-cyano ketones were obtained in high yields (86–99%) and moderate enantioselectivities (up to 72% ee). This protocol provides a complementary substrate scope to Shibasaki's methodology.[3] Further optimization and mechanism elucidation are currently under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **Preparation of 6h**
To a stirred solution of (*R*)-BINOL (**6a**; 1.431 g, 5.0 mmol) and 1-adamantanol (1.522 g, 10.0 mmol) in CH_2Cl_2 (25 mL),

concd H_2SO_4 (0.8 mL) was added dropwise at 0 °C over 5 min. After stirring at 0 °C for 30 min the ice bath was removed. The suspension was stirred at r.t. for an additional 6 h before aq NaOH (5%) was added to neutralize H_2SO_4 thus to quench the reaction. The resulting mixture was extracted by CH_2Cl_2 twice. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude solid was purified by silica gel chromatography using PE–EtOAc (10:1, v/v) as the eluent to yield (*R*)-3,3′-di(1-adamantyl)-1,1′-binaphthyl-2,2′-diol (**6h**) as a white solid (1.670 g, 3.01 mmol); 60% yield, mp 207–209 °C; $[\alpha]_D^{17}$ –82.5 (*c* 0.114, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79–1.85 (dd, *J* = 21.0, 12.0 Hz, 12 H, CHC*H*$_2$CH), 2.00 (s, 12 H, CC*H*$_2$CH), 2.15 [s, 6 H, C*H*(CH_2)$_3$], 7.17 (d, *J* = 9.0 Hz, 2 H, ArH), 7.37–7.43 (m, 4 H, ArH), 7.80 (s, 2 H, ArH), 7.97 (d, *J* = 9.0 Hz, 2 H, ArH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.0, 36.1, 36.8, 43.1, 110.7, 117.5, 123.5, 124.0, 125.7, 129.5, 131.4, 131.6, 147.0, 152.3 ppm.

Preparation of 7h

(*R*)-3,3′-Di(1-adamantyl)-1,1′-binaphthyl-2,2′-diol (**6h**; 555 mg, 1 mmol) was dissolved in pyridine (3 mL) in a 50 mL Schlenk tube. Phosphorous oxychloride (185 μL, 2 mmol) was added dropwise at r.t. After stirring for 10 h at r.t., H_2O (3 mL) was added. The resulting mixture was stirred for additional 6 h at r.t. followed by addition of CH_2Cl_2. All pyridine was removed by reverse extraction with 1 M HCl. The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude solid was purified by flash silica gel chromatography CH_2Cl_2–MeOH (5:1, v/v) as the eluent to yield (*R*)-3,3′-di(1-adamantyl)-1,1′-binaphthyl-2,2′-diylphosphoric acid (**7h**) as a white solid (555 mg, 0.9 mmol); 90% yield; mp >300 °C; $[\alpha]_D^{21}$ –283.3 (*c* 0.240, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.75 (s, 12 H, CHC*H*$_2$CH), 1.95 (s, 12 H, CC*H*$_2$CH), 2.07 [s, 6 H, C*H*(CH_2)$_3$], 7.21–7.23 (m, 2 H, ArH), 7.41–7.42 (m, 4 H, ArH), 7.87 (s, 2 H, ArH), 8.01 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.5, 35.9, 36.4, 42.7, 121.6, 122.4, 123.4, 124.3, 126.0, 130.0, 130.3, 130.8, 147.1, 149.3 ppm. ^{31}P NMR (162 MHz, DMSO-d_6): δ = 3.5 (s) ppm.

(14) **Typical Procedure for the Asymmetric 1,4-Addition of TMSCN to Enones**

After (*R*)-3,3′-di(1-adamantyl)-1,1′-binaphthyl-2,2′-diyl phosphoric acid (**7h**, 18.5 mg, 0.03 mmol, 20 mol%) and NaOH (1.2 mg, 0.03 mmol, 20 mol%) were placed in a dry Schlenk tube under argon. Toluene (0.5 mL) was added, and the mixture was stirred at 30 °C for 1 h. Then, chalcone (**1a**, 31.2 mg, 0.15 mmol), 2-*t*-BuPhOH (0.03 mmol, 20 mol%), additional toluene (0.5 mL), and TMSCN (0.33 mmol, 2.2 equiv) were added at r.t. Equipped with cold finger, the reaction mixture was stirred at 80 °C until the reaction was completed (monitored by TLC). The reaction was quenched with 1 M HCl (0.3 mL) followed by diluting with dioxane (2 mL) and stirring for additional 30 min at r.t. To work it up, H_2O (2 mL) was added, and the resulting mixture was extracted with EtOAc (5 mL) (Caution! HCN possibly generated in the reaction mixture is highly toxic. Those operations should be conducted in a well-ventilated hood). The extract was washed with H_2O (2 mL), brine (3 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (PE–EtOAc, 20:1, v/v) to afford pure product **2a** as a white solid in 94% yield and 71% ee.

4-Oxo-2,4-diphenylbutanenitrile (2a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, *J* = 18.0, 6.0 Hz, 1 H, NCCHC*H*$_A$H$_B$CO), 3.74 (dd, *J* = 18.0, 8.0 Hz, 1 H, NCCHCH$_A$*H*$_B$CO), 4.57 (dd, *J* = 8.0, 6.0 Hz, 1 H, NCC*H*CH$_A$H$_B$CO), 7.34–7.49 (m, 7 H, ArH), 7.58–7.62 (m, 1 H, ArH), 7.92–7.94 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.9, 44.5, 120.6, 127.5, 128.1, 128.4, 128.8, 129.3, 133.9, 135.3, 135.8, 194.6 ppm. IR (KBr): ν = 1681, 2236 cm^{-1}. HPLC [Chiralpak AS-H, 254 nm, *n*-hexane–2-PrOH (70:30), 1.0 mL/min]: t_R(major) = 13.3 min, t_R(minor) = 21.4 min; $[\alpha]_D^{17}$ –20.0 (*c* 0.100, CH_2Cl_2, 71% ee).

(15) CCDC-787260 contains the supplementary crystallographic data of **2f** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.