CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900210

Facile and Efficient Enantioselective Strecker Reaction of Ketimines by Chiral Sodium Phosphate

Ke Shen, Xiaohua Liu, Yunfei Cai, Lili Lin, and Xiaoming Feng*[a]

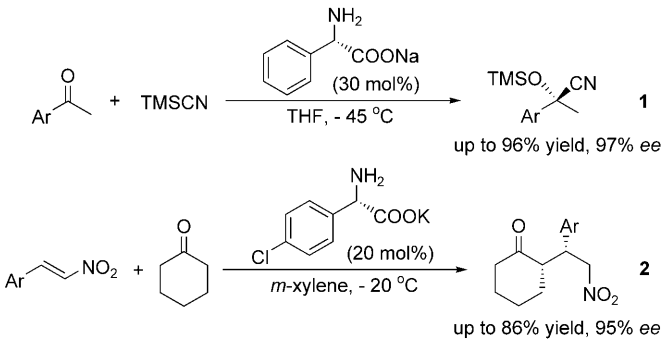
Abstract: A facile and efficient enantioselective Strecker reaction of ketimines catalyzed by a chiral alkali-metal salt has been developed. When 10 mol% BNPNa (BNP = 1,1′-binaphthyl-2,2′-diylphosphate) prepared in situ and 10 mol% *para-tert*-butyl-*ortho*-adamantylphenol (PBAP) were introduced into the reaction, up to 96% yield and up to 95% *ee* (*ee* = enantiomeric excess) were obtained. Both aliphatic and aromatic ketimines, especially sterically bulky cyclic ketimines derived from β-acetonaphthone, α-indanone, and α-tetralone were found suitable for this reaction. On the basis of the experimental results and previous reports, trimethylsilyl cyanide (TMSCN) was indicated to be the real reactive nucleophile despite the existence of PBAP, and a possible working model was proposed to explain the origin of the asymmetric induction. The facile availability of 1,1′-binaphthyl-2,2′-diylphosphoric acid (BNPH) and the simplicity of the procedure are beneficial for practical applications.

Keywords: asymmetric catalysis · enantioselectivity · ketimines · sodium · Strecker reaction

Introduction

The enantioselective Strecker reaction of ketimines is one of the most direct methods to afford the precursors of pharmaceutically important quaternary α-amino acids.[1,2] Since the first effective catalytic system of asymmetric cyanation of ketimines reported in 2000,[2a,b] a number of successful protocols have been disclosed. In general, catalysts involving chiral metal complexes such as Ti[2b,g] and Gd,[2c–f] chiral Brønsted acid organocatalysts,[2a,h,i] and chiral *N*,*N*′-dioxides as neutral Lewis base organocatalysts[2j–l] have been developed for this reaction. However, to the best of our knowledge, a direct catalytic asymmetric Strecker reaction catalyzed by a chiral alkali-metal salt has not yet been described. Recently, a chiral alkali-metal salt,[3,4] a sort of anionic Lewis base,[5,6] has been uncovered as a potential means for catalytic asymmetric reactions. Remarkable progress has been made in the asymmetric additions of trimethylsilyl nucleophiles with such anionic Lewis bases.[6b] Among them, lithium salts were the most-studied catalysts through the understanding of the nature of chiral organolithium aggregates.[3] Meanwhile, there are comparatively few reports about chiral sodium salts and other alkali-metal salts in asymmetric synthesis.[4] In our earlier work in developing chiral alkali-metal salts, bifunctional sodium phenylglycinate was developed for the enantioselective cyanosilylation of ketones (Scheme 1; **1**).[4a] Subsequently, potassium 4-chlorophenylglycinate was applied in the asymmetric Michael addition of ketones to nitroolefins (Scheme 1; **2**).[4c] Herein, our ongoing interest was extended to a Strecker reaction of ketimines catalyzed by a chiral salt.

A possible working model of the salt catalysis was proposed, which was different from that of the hydrocyanation



Scheme 1. Chiral alkali-metal salts developed by our group.

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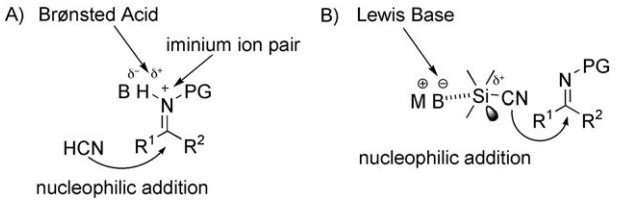
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900210.

of imines catalyzed by Brønsted acids.[2a,h,i,m] (Scheme 2). When HCN was used in most Strecker variants, the imine was activated by Brønsted acids through a hydrogen bond as illustrated in model A. As an alternative strategy, the activation of trimethylsilyl cyanide (TMSCN) by the chiral salt was achieved by means of a reactive hypervalent silicon intermediate (Scheme 2, model B).[6b] Further work has been directed toward a detailed examination of this interesting model of salt activation.



Scheme 2. Different working models of a Strecker reaction (PG = protecting group; $B^{\ominus}$ = chiral anion; $M^{\oplus}$ = metal cation): A) chiral Brønsted acid catalysis; B) chiral alkali-metal-salt catalysis.

Results and Discussion

Our work commenced with a preliminary survey of the reaction conditions using *N*-diphenylphosphinoyl (Dpp)-protected ketimine **1a** and TMSCN as reagents in the presence of sodium salts **3a**–**e**, which were prepared in situ by mixing equimolar amounts of chiral acids with sodium hydroxide in toluene at 35 °C for 1 h (Table 1). Initial catalyst screening revealed that sodium phenylglycine **3a** was active, but exhibited poor asymmetric inducibility (Table 1, entry 1). Similarly, sodium salt prepared from chiral mandelic acid or 1,1′-bi-2-naphthol (BINOL) gave racemic products (Table 1, entries 2 and 4). As binaphthyl phosphate (BNP^{-}) is often used in asymmetric processes,[6e,7–9] sodium phosphate **3e** was prepared and promoted the reaction in good yield and 50 % *ee* (Table 1, entry 5). In contrast, the reaction could not proceed in the presence of BNPH using either HCN or TMSCN as the cyanation nucleophile (Table 1, entry 6),[10] which indicated a different working pathway with a salt catalyst.

Then a series of metal salts of BNPH were examined. The catalyst screening revealed that lithium phosphate gave good reactivity, but afforded a racemic product (Table 2, entries 1 and 2). To our delight, enantioselectivity was improved to 70 % *ee* by the use of sodium phosphate **3e** gener-

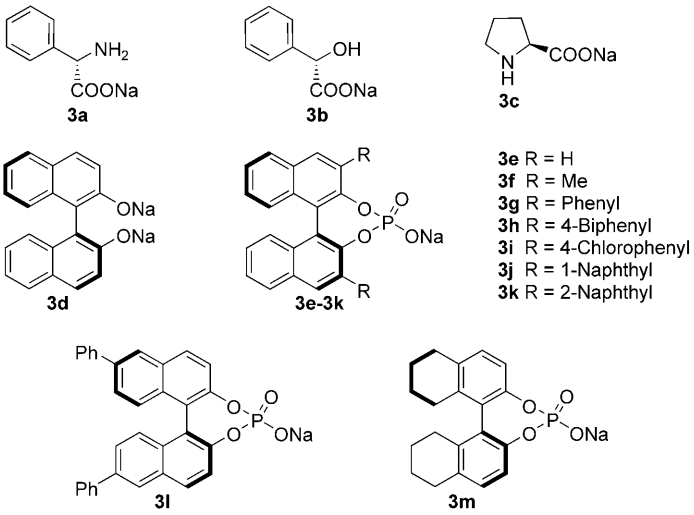
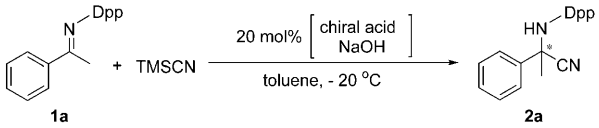


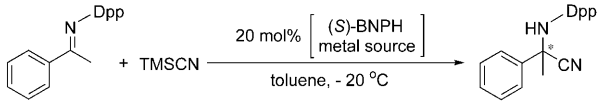
Table 1. Initial screening of typical sodium salts for a Strecker reaction of ketimine **1a**.



Entry[a]	Catalyst	Conversion [%][b]	*ee* [%][c]
1	**3a**	90	8
2	**3b**	80	0
3	**3c**	10	10
4[d]	**3d**	15	0
5	**3e**	100	50
6[e]	(*S*)-BNPH	no reaction	–

[a] Reaction conditions: After stirring a mixture of chiral acid (20 mol %) and NaOH (20 mol %) in toluene (0.3 mL) at 35 °C for 1 h, **1a** (0.125 mmol) in toluene (0.2 mL) was added at room temperature, followed by TMSCN (1.5 equiv) at −20 °C. [b] Determined by chiral HPLC analysis. [c] Determined by HPLC analysis on Chiralcel AD-H. The absolute configuration was determined to be *R* by comparison with literature data.[2c] [d] 20 mol % (*S*)-BINOL and 40 mol % NaOH were used. [e] The reaction was catalyzed by 20 mol % (*S*)-BNPH using either TMSCN or HCN as cyanation reagents.

Table 2. The effect of metal salts on the Strecker reaction of ketimine **1a**.



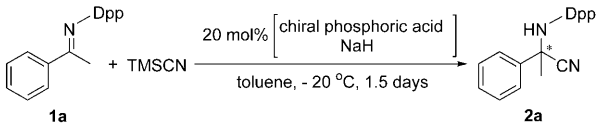
Entry[a]	Metal source	Time [d]	Conversion [%][b]	*ee* [%][c]
1	*n*BuLi	1.0	100	0
2	$LiOH{\cdot}H_2O$	1.5	100	0
3	NaH	1.5	100	70
4	NaOMe	3.0	54	35
5[d]	Na_2CO_3	3.0	15	0
6	KO*t*Bu	1.0	100	12
7	$CsOH{\cdot}H_2O$	1.0	100	17
8	CaH_2	1.5	80	−17[e]

[a] Reaction conditions: After stirring a mixture of (*S*)-BNPH (20 mol %) and metal salt (20 mol %) in toluene (0.3 mL) at 35 °C for 1 h, **1a** (0.125 mmol) in toluene (0.2 mL) was added at room temperature, followed by TMSCN (1.5 equiv) at −20 °C. [b] Determined by chiral HPLC analysis. [c] Determined by HPLC analysis on Chiralcel AD-H. The absolute configuration was determined to be *R* by comparison with literature data.[2c] [d] 20 mol % (*S*)-BNPH and 10 mol % Na_2CO_3 were used. [e] 20 mol % (*S*)-BNPH and 10 mol % CaH_2 were used, and the absolute configuration was determined to be *S*.

ated prior from equimolar amounts of BNPH and NaH (Table 2, entry 3). Other sodium salts only led to inferior outcomes (Table 2, entry 3 vs. 4 or 5).[11] Other alkaline metal salts such as KO*t*Bu and $CsOH{\cdot}H_2O$ were not effective (Table 2, entries 6 and 7). Surprisingly, changing the cation to Ca^{2+} caused a reversion of the absolute configuration of **2a** (Table 2, entry 8). The cation effect shown in Table 2 might be related to the effective size of the metal cation in the solvent.[4f] The lithium cation was prone to form aggregation of the catalyst,[3] while potassium and cesium cations might cause different ion pairs.[4d–f] Hence, NaH was considered as the best metal source.

Subsequently, various BINOL-derived sodium phosphate compounds (**3e**–**m**) prepared by using NaH were investigated (Table 3). Sodium phosphates with sterically congested

Table 3. The influence of the skeleton of chiral phosphates on a Strecker reaction of ketimine **1a**.



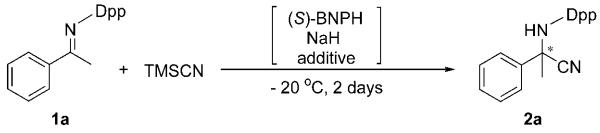
Entry[a]	Sodium phosphate **3e**–**m**	Conversion [%][b]	*ee* [%][c]
1	**3e**	100	70
2	**3f**	100	5
3	**3g**	100	10
4	**3h**	100	30
5	**3i**	100	−40[d]
6	**3j**	85	−35[d]
7	**3k**	80	−18[d]
8	**3l**	100	7
9	**3m**	100	−8[d]

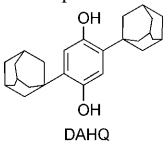
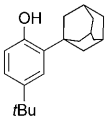
[a] Reaction conditions: After stirring a mixture of phosphoric acid (20 mol%) and NaH (20 mol%) in toluene (0.3 mL) at 35°C for 1 h, **1a** (0.125 mmol) in toluene (0.2 mL) was added at room temperature, followed by TMSCN (1.5 equiv) at −20°C. [b] Determined by chiral HPLC analysis. [c] Determined by HPLC analysis on Chiralcel AD-H. The absolute configuration was determined to be *R* by comparison with literature data.[2c] [d] The absolute configuration was determined to be *S*.

3,3′-disubstituents on the BINOL skeleton, however, gave non-ideal chiral induction in the asymmetric amino nitrile synthesis (Table 3, entries 2–7), despite their excellent performance in other asymmetric transformations.[7–9,12] For example, 3,3′-dibiphenyl-, 3,3′-di-1-naphthyl-, and 3,3′-di-2-naphthyl-BINOL-phosphoric acid combined with NaH all provided much lower *ee* values (Table 3, entries 4, 6, and 7). It was noted that stereochemical inversion of the product occurred when 4-biphenyl was replaced by 4-chlorophenyl (Table 3, entry 5 vs. 4).[13] Inferior asymmetric induction was observed using **3l** (Table 3, entry 8). If the BINOL framework was replaced by H_8-BINOL, poor *ee* value was obtained (Table 3, entry 9), which suggested that a proper dihedral angle be of great importance for chiral induction. Therefore, simple (*S*)-BNPH and NaH were chosen for the following optimization.

Other reaction parameters were optimized. The results showed that the Strecker reaction was significantly influenced by the solvent, temperature, and additives. At −20°C, a routine solvent screening established that toluene was the best choice in terms of the reactivity and enantioselectivity (Table 4, entry 1). The use of CH_2Cl_2 gave trace product

Table 4. Optimization of reaction conditions for the asymmetric Strecker reaction.



Entry[a]	Additives	Solvent	Conversion [%][b]	*ee* [%][c]
1	–	toluene	100	70
2	–	CH_2Cl_2	8	5
3	–	THF	75	0
4	–	Et_2O	39	0
5	–	CH_3CN	25	0
6	3 Å MS	toluene	32	63
7	*i*PrOH	toluene	60	10
8	PhOH	toluene	100	65
9	2-bromophenol	toluene	100	61
10	2-nitrophenol	toluene	100	72
11	 DAHQ	toluene	100	77
12	 PBAP	toluene	100	85
13[d]	PBAP	toluene	100	88

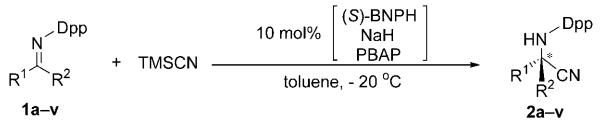
[a] Reaction conditions: After stirring (*S*)-BNPH (20 mol%) and NaH (20 mol%) in toluene (0.3 mL) at 35°C for 1 h, **1a** (0.125 mmol), additive (20 mol%), and toluene (0.2 mL) were added at room temperature, followed by TMSCN (1.5 equiv) at −20°C. [b] Determined by chiral HPLC analysis. [c] Determined by HPLC analysis on Chiralcel AD-H. The absolute configuration was determined to be *R* by comparison with literature data.[2c] [d] 10 mol% (BNPH/NaH/PBAP 1:1:1) were used; see Experimental Section.

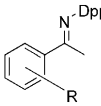
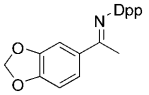
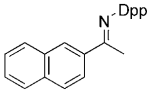
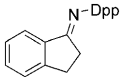
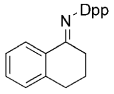
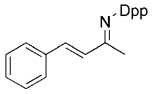
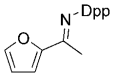
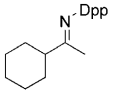
with only 5% *ee* (Table 4, entry 2). Other solvents such as THF, Et_2O, and CH_3CN gave racemic products with low to moderate conversion (Table 4, entries 3–5). Next some additives were investigated. Molecular sieves were not effective in promoting this reaction (Table 4, entry 6). Due to the significant improvement by protic additives in the enantioselective Strecker reaction of ketimines in recent years,[2d–g,j–l,14] *i*PrOH and phenol derivatives were investigated. However, introduction of *i*PrOH sharply diminished enantioselectivity with incompletion of the reaction (Table 4, entry 7). The reaction maintained high reactivity when phenol was employed, but the *ee* decreased to 65% (Table 4, entry 8). Neither 2-bromophenol nor 2-nitrophenol could improve the enantioselectivity (Table 4, entries 9 and 10). The sterically hindered 2,5-di-(1-adamantyl)hydroquinone (DAHQ), an additive in the Strecker reaction of *N*-Ts-protected (Ts = *p*-toluenesulfonyl) ketimines,[2j] slightly in-

creased the *ee* from 70 to 77% (Table 4, entry 11 vs. 1). To our delight, employment of *para*-butyl-*ortho*-adamantyl phenol (PBAP) gave superior results (Table 4, entry 12). Further adjusting the catalyst loading and concentration enhanced the *ee* value up to 88% without any loss of yield (Table 4, entry 13). In addition, the reaction temperature had a significant effect on the yield, but the enantioselectivity of the adduct was not very sensitive to temperature. The amount of TMSCN was tested, but the enantioselectivity could not be further improved (see the Supporting Information). Accordingly, extensive screening showed that the optimized reaction conditions were 0.25 mmol ketimine, 10 mol% catalyst (BNPH/NaH/PBAP 1:1:1), and 1.5 equiv TMSCN in 1.0 mL toluene at −20 °C. It should be noted that the reaction mixture was heterogeneous under the optimized reaction conditions.

Under the optimal reaction conditions, a variety of Dpp-protected ketimines were examined. A wide substrate scope was evidenced with this sodium salt catalyst. Different aryl ketimines proceeded smoothly to produce the corresponding amino nitriles in high yields with good to excellent enantioselectivities (82–95% *ee*) (Table 5, entries 1–16). Ketimines containing electron-withdrawing groups had relatively higher reactivities than those bearing electron-donating groups (Table 5, entries 2–10 vs. 11–15). Notably, the *ortho*-chloro substituent, compared with the *meta* or *para* one on the phenyl ring, afforded excellent *ee* (Table 5, entries 3 and 6 vs. 4, 5, and 7). Most excitingly, the current catalyst system could also be applied to the sterically bulky cyclic ketimines, giving excellent results with 94 and 90% *ee*, respectively (Table 5, entries 17 and 18). In addition, α,β-unsaturated ketimine **1s** could be transformed to the synthetically important product **2s** with 82% *ee* (Table 5, entry 19). In the case of the heterocyclic ketimine of furyl and aliphatic ketimines **1u** and **1v**, good enantioselectivities were observed as well (Table 5, entries 20–22).

Table 5. Substrate generality for the Strecker reaction of ketimine **1**.

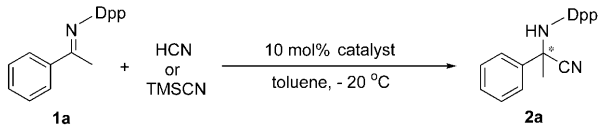


Entry[a]	Ketimine **1**		Time [d]	Product **2**	Yield [%][b]	*ee* [%][c]
1		R = H	2.0	**2a**	93	88 (*R*)
2		R = *p*-F	1.5	**2b**	95	89 (*R*)
3		R = *o*-Cl	1.5	**2c**	94	95
4		R = *m*-Cl	1.5	**2d**	93	87 (*R*)
5		R = *p*-Cl	1.5	**2e**	95	88 (*R*)
6		R = 2,4-Cl_2	1.5	**2f**	93	94
7		R = 3,4-Cl_2	1.5	**2g**	94	85
8		R = *p*-Br	1.5	**2h**	96	88 (*R*)
9		R = *m*-NO_2	1.5	**2i**	94	86 (*R*)
10		R = *p*-NO_2	1.5	**2j**	92	85
11		R = *m*-Me	3.0	**2k**	92	82
12		R = *p*-Me	3.0	**2l**	92	92 (*R*)
13		R = *m*-OMe	3.5	**2m**	88	87
14		R = *p*-OMe	3.5	**2n**	90	91 (*R*)
15			3.5	**2o**	90	90
16			2.0	**2p**	95	90 (*R*)
17			3.0	**2q**	93	94 (*R*)
18			3.0	**2r**	92	90
19			2.0	**2s**	92	82
20			3.5	**2t**	90	79
21			1.5	**2u**	95	80
22			1.5	**2v**	94	82

[a] For reaction conditions, see Experimental Section. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration was determined by comparison with literature data.[2c,k]

Mechanism studies: To shed some light on the possible origin of the remarkable performance of the Strecker reaction catalyzed with sodium phosphate, a series of control experiments were performed (Table 6). To determine whether TMSCN and sodium phosphate took part in the enantioselectivity-determining step, HCN was investigated as another cyanide nucleophile. As expected, the reaction rate was considerably lower and only racemic products were obtained

Table 6. Control experiment for mechanistic study.

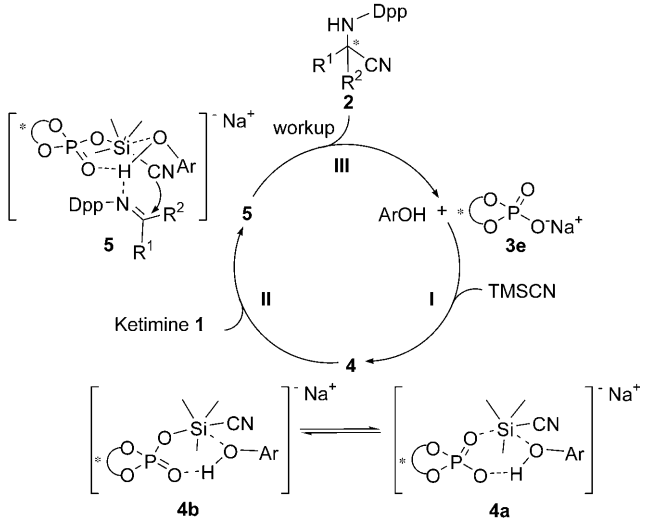


Entry[a]	(*S*)-BNPH	NaH	PBAP	Cyanide source	Time [d]	Conv. [%][b]	*ee* [%][c]
		[mol%]					
1	10	10	–	HCN[d]	4.0	25	0
2	10	10	10	HCN[d]	4.0	29	3
3	10	10	–	TMSCN	1.5	100	72
4	10	10	10	TMSCN	2.0	100	88

[a] Reaction conditions: After stirring the corresponding catalyst in toluene (1.0 mL) at 35 °C for 1 h, **1a** (0.25 mmol) was added, followed by the corresponding cyanide source (1.5 equiv) at −20 °C. [b] Conversion determined by chiral HPLC analysis. [c] Determined by HPLC analysis on Chiralcel AD-H. The absolute configuration was determined to be *R* by comparison with literature data.[2c] [d] HCN solution was generated prior to the reaction from equimolar amounts of TMSCN and methanol.

(Table 6, entries 1 and 2). However, high *ee* values could be obtained when TMSCN was employed (Table 6, entries 3 and 4). So the key role of PBAP was deduced not to generate HCN as it does in most Strecker reactions involving TMSCN.[2e,g] These phenomena also demonstrated that TMSCN was likely to be the real cyanating agent (Table 6, entry 3 vs. 1; entry 4 vs. 2).

In this manner, we speculated that the formation of a reactive hexacoordinate silicon intermediate should be crucial for the asymmetric induction,[6b] and clearly the Strecker reaction catalyzed by the sodium salt was mechanistically distinct from the reaction catalyzed with a chiral Brønsted acid, in which a prochiral ketimine was activated by an acid.[2i] While more detailed investigations of the reaction mechanism are currently underway, a possible asymmetric induction pathway was proposed (Scheme 3). By taking advantage of the detailed studies on hypervalent silicon intermediates[6b] and ion pairs,[15] compound **4** was formed



Scheme 3. Proposed catalytic cycle.

(Scheme 3, step I). PBAP might not only favor the formation of a hydrogen bond with a sodium salt, but might also serve to activate ketimine **1** and participate in the asymmetric induction of the reaction (Scheme 3, step II).[16] The activated nucleophile would attack the highly polarized C=N of ketimine **1** from a less stereohindered direction to give the desired product. Subsequently, elimination of the catalyst furnished the corresponding adduct **2**[17] and regenerated **3e** and PBAP (Scheme 3, step III).

Conclusion

In summary, a successful chiral alkali-metal-salt-catalyzed enantioselective Strecker reaction of ketimines with TMSCN was developed by employing chiral (*S*)-BNPNa (**3e**; 10 mol%) and PBAP. The simplicity and facile availability of the catalyst and high enantioselectivities of the reaction make it potentially applicable in synthesis. Control experiments have suggested that TMSCN is likely the actual nucleophile. Detailed mechanism studies and further investigations into other versions of asymmetric catalysis are currently underway.

Experimental Section

Typical procedure for the enantioselective Strecker reaction of ketimines: (*S*)-1,1′-Binaphthyl-2,2′-diylphosphoric acid (8.7 mg, 0.025 mmol) and sodium hydride (1 mg, 0.025 mmol) were placed in a tube under an argon atmosphere. Toluene (0.5 mL) was added and the mixture was stirred at 30 °C for 1 h. Then PBAP (7.1 mg, 0.025 mmol) and ketimine **1a** (80 mg, 0.25 mmol) were added, followed by additional toluene (0.5 mL) at room temperature. To this mixture trimethylsilyl cyanide (50 μL, 0.375 mmol) was added under −20 °C. The reaction was vigorously stirred at −20 °C and monitored by HPLC. After two days, the residue was purified by flash silica gel chromatography to obtain the corresponding Dpp-protected α-amino nitrile **2a** in 93% yield with 88% *ee*. HPLC (DAICEL CHIRALCEL AD-H, 210 nm, hexane/2-propanol 80:20, 1.0 mL min^{-1}): t_R = 9.01 min (major), t_R = 10.14 min (minor); $[\alpha]_D^{20} = +13.87$ (c = 0.20 in $CHCl_3$), (ref. [2c]: $[\alpha]_D^{23} = -19.1$ (c = 1.00 in $CHCl_3$) (>99% *ee*)); ^{1}H NMR (400 Hz, $CDCl_3$): δ = 8.01–8.07 (m, 2H), 7.81–7.86 (m, 2H), 7.73–7.76 (m, 2H), 7.33–7.60 (m, 9H), 3.68 (d, J = 7.6 Hz, 1H), 2.29 ppm (s, 3H).

Typical procedure for the synthesis of (*S*)-BNPH ((*S*)-1,1′-binaphthyl-2,2′-diylphosphoric acid): (*S*)-BINOL (572 mg, 2 mmol) was dissolved in pyridine (4.5 mL). Phosphorous oxychloride (0.75 mL, 4 mmol) was added dropwise at room temperature with rapid stirring and the resulting solution was stirred at 60 °C for 12 h. Water (4.0 mL) was added and the resulting biphasic suspension was stirred at 50 °C for a further 2 h. The reaction mixture was diluted with CH_2Cl_2 and pyridine was extracted by washing with aqueous 1 N HCl. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude solid was purified by flash silica gel chromatography (5% MeOH in CH_2Cl_2) to yield **7e** as an ivory-white solid (626 mg, 90% yield). ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 8.11 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.8 Hz, 2H), 7.46–7.50 (m, 4H), 7.32–7.36 (m, 2H), 7.22 ppm (d, J = 8.8 Hz, 2H).

Typical procedure for the synthesis of PBAP (*para*-*tert*-butyl-*ortho*-adamantylphenol): To a stirred solution of *para*-*tert*-butylphenol (2.253 g, 15 mmol) and 1-adamantanol (2.283 g, 15 mmol) in CH_2Cl_2 (25 mL), concentrated H_2SO_4 (0.9 mL) was added dropwise at 0 °C over 10 min. The suspension was stirred at room temperature for a further 2 h before 5% aqueous NaOH was added to neutralize H_2SO_4. The resulting biphasic suspension was extracted by CH_2Cl_2 twice. The combined organic phase

was dried over Na_2SO_4 and concentrated. The crude solid was purified by silica gel chromatography using AcOEt/petroleum ether (1:25) as eluent to yield PBAP as a pale white solid (2.773 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 2.4$ Hz, 1H), 7.05–7.08 (m, 1H), 6.58 (d, $J = 8.0$ Hz, 1H), 4.56 (s, 1H), 2.08–2.14 (m, 9H), 1.78–1.79 (t, 6H), 1.29 ppm (s, 9H).

Acknowledgements

We thank the National Natural Science Foundation of China (nos. 20732003 and 20602025) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

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Received: January 23, 2009
Revised: March 30, 2009
Published online: May 5, 2009

