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Metal-Free, Enantioselective Strecker Reactions Catalyzed by Chiral BINOL and TADDOL Catalysts

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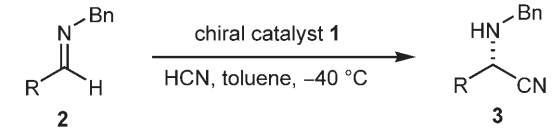
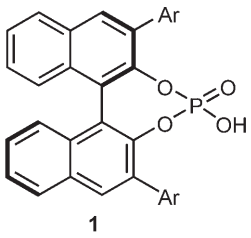
Abstract: An efficient, metal-free Brønsted acid-catalyzed, enantioselective hydrocyanation of ketoimines has been developed. This BINOL phosphate-catalyzed Strecker reaction provides the corresponding amino nitriles, precursors of quaternary amino acids, in good isolated yields and enantioselectivities. Additionally, we demonstrate that chiral diols, such as TADDOL, are effective enantioselective catalysts for the hydrogen-bond activation of aldimines.

Keywords: amino acids; BINOL phosphate; Brønsted acid; hydrocyanation; Strecker reaction; TADDOL





R	*ee* [%]
4-CF_3C_6H4	97
1-Naphthyl	99
1-Thienyl	95
1-Furyl	89
4-$CH_3OC_6H_4$	93

1a Ar = 9-Phenanthryl

Scheme 1. Brønsted acid-catalyzed enantioselective hydrocyanation of aldimines.

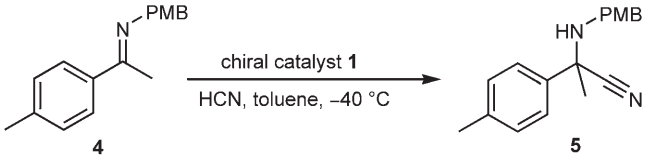
The addition of hydrogen cyanide to imines, the Strecker reaction, constitutes one of the most direct and practical methods for the synthesis of α-amino acids and derivatives.[1] As a result, considerable effort has been devoted towards the development of asymmetric Strecker reactions.[2,3] In addition to various metal-catalyzed hydrocyanations,[4] promising metal-free enantioselective variants[5] have been described. Recently, we reported that chiral Brønsted acids[6,7] are efficient catalysts for highly enantioselective processes, including the hydrogenation of ketoimines,[8a,b] benzoxazines, benzthiazines, benzoxazinones[8c] and quinolines,[9] as well as direct Mannich–Michael reactions,[10] or the hydrocyanation of aldimines (Scheme 1).[11] In this reaction the aldimine is protonated by a chiral BINOL phosphate **1** which leads to the formation of a chiral iminium ion, a chiral ion pair. Subsequent addition of HCN results in formation of the corresponding amino nitrile and the regenerated Brønsted acid catalyst.[11]

Based on our previous results and observations, we herein report the application of yet another metal-free catalyst, the chiral TADDOL, for the hydrocyanation of aldimines. Furthermore, we describe the BINOL phosphate-catalyzed asymmetric Strecker reaction of ketoimines, which is generally not only more difficult to achieve as compared to the hydrocyanation of aldimines,[4h–j,5d] but additionally leads to the formation of valuable quaternary amino acids.

We initially started our investigation with the exploration of various BINOL phosphates **1a–f** in the hydrocyanation of ketoimine **4** (Table 1). The best results with regard to reactivity and selectivity were obtained with catalytic amounts of **1a** (5 mol%) providing amino nitrile **5** in 70% *ee* (Table 1, entry 1). All other tested BINOL phosphate catalysts gave inferior results which is in agreement with our earlier developed Brønsted acid-catalyzed reactions where sterically more congested 3,3′-aryl substituents on the BINOL skeleton gave generally better results. All cyanation reactions were performed in toluene at −40 °C with 1.5 equivs. of *in situ* generated HCN.[12] Other cyanide sources tested, such as trimethylsilyl cyanide or acetone cyanohydrin did not lead to the desired products.

Further examinations concentrated on the solvent employed, as it was previously shown to have an important impact on reactivity and selectivity in Brønsted acid-catalyzed transformations. In accordance with the BINOL phosphate-catalyzed hydrocyanation of

Table 1. Survey of chiral Brønsted acid catalyst **1a–f** for the hydrocyanations of ketoimines.

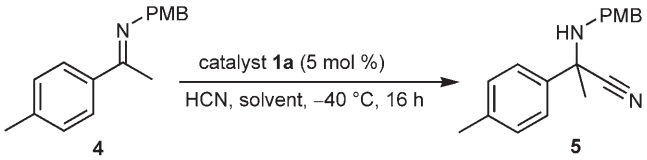


Entry[a]	Catalyst	Ar	*ee* [%][b]
1	**1a**	9-Phenanthryl	70
2	**1b**	Phenyl	*rac*
3	**1c**	1-Naphthyl	32
4	**1d**	2-Naphthyl	30
5	**1e**	3,5-(CF_3)-C_6H_3	*rac*
6	**1f**	4-Biphenyl	*rac*

[a] Reactions were performed with ketoimine **4**, HCN (1.5 equivs.) at 0.15 M concentration using 5 mol % catalyst **1**.
[b] Determined by HPLC analysis using a Chiralcel OD-H column.

aldimines, a non-polar aromatic solvent proved to be the optimal medium for the reaction (70 % *ee*) (Table 2, entry 1). Other solvents such as chloroform and dichloromethane (Table 2, entries 2 and 3) gave inferior results (15 % *ee* and 30 % *ee*).

Table 2. Influence of the solvent on the enantioselectivity of the Strecker reaction.

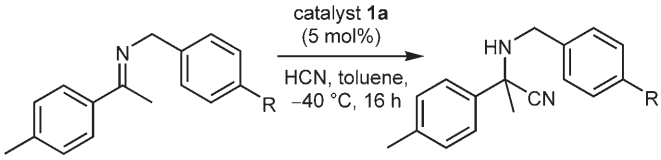


Entry[a]	Solvent	*ee* [%][b]
1	toluene	70
2	chloroform	15
3	dichloromethane	30

[a] Reactions were performed with ketoimine **4** and HCN (1.5 equivs.) using 5 mol % of catalyst **1a** at 0.15 M concentration in toluene.
[b] Determined by HPLC analysis using a Chiralcel OD-H column.

Subsequently, we investigated the influence of the imine protecting group on the reaction enantioselectivity. Several *N*-benzyl-ketoimine derivatives were prepared and tested in the Strecker reaction. The results are summarized in Table 3. The highest enantioselectivities were obtained with *p*-bromobenzyl (80 % *ee*, Table 3, entry 4) and *p*-methoxybenzyl (70 %, Table 3, entry 5) protected ketoimine derivatives, while the reaction with benzyl, *p*-fluorobenzyl and *p*-chlorobenzyl derivatives showed considerably lower

Table 3. Variation of the ketoimine protecting group.



Entry[a]	R	*ee* [%][b]
1	H	56
2	F	54
3	Cl	56
4	Br	80
5	OCH_3	70
6	$CHPh_2$[c]	-

[a] Reactions were performed with the ketoimine and HCN (1.5 equivs.) using 5 mol % of catalyst **1a** at 0.15 M concentration in toluene.
[b] Determined by HPLC analysis using a Chiralcel OD-H column.
[c] No reaction observed.

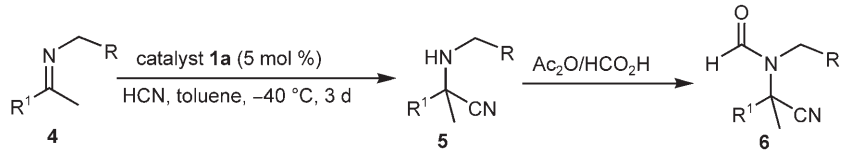
enantioselection (Table 3, entries 1–3). Interestingly, no reaction was observed with *N*-benzhydryl-protected keto imines (Table 3, entry 6).

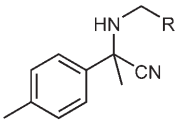
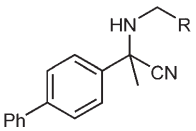
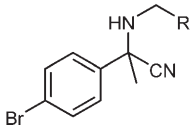
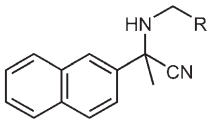
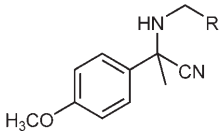
With the optimized catalyst and reaction conditions in hand we explored the scope of the BINOL phosphate-catalyzed Strecker reaction of keto imines (Table 4). In general the hydrocyanation proceeded smoothly and the corresponding adducts were obtained in good isolated yields (69–95 %) and enantioselectivities (56–80 % *ee*).[13]

During the course of our investigation of the Brønsted acid-catalyzed Strecker reactions we also examined various other metal-free catalysts. Surprisingly, we found that not only thiourea derivatives, that have previously been successfully applied as catalysts in asymmetric Strecker reactions and which are able to activate the substrates *via* hydrogen bonds in an enantioselective fashion,[5b–g] but also chiral diols, such as TADDOL **7**,[14] serve as efficient catalysts for this valuable transformation. Herein, we report our first experiments of this TADDOL-catalyzed hydrocyanation of aldimines. Using the reaction conditions established we examined a series of *N*-benzyl-protected aldimine derivatives (Table 5). Best results, were obtained with benzyl (Table 5, entry 1) and *p*-chlorobenzyl (Table 5, entry 5) protected aldimine derivatives using 10 mol % of TADDOL **7** in toluene at −40 °C. The use of other benzyl protecting groups resulted in a loss of selectivity or reactivity.

Following these first observations, we decided to evaluate the scope of the TADDOL-catalyzed Strecker reaction and found that indeed enantioselection could be observed in some cases (Table 6). Although the selectivities obtained are only moderate, the results presented here not only demonstrate the feasibil-

Table 4. Scope of the catalytic enantioselective Strecker reaction of ketoimines.



Entry[a]	4	R	5	Yield [%][b]	*ee* [%][c]
1	**4a**	4-$CH_3OC_6H_4$		89	70
2	**4b**	4-BrC_6H_4		90	76
3	**4c**	4-$CH_3OC_6H_4$		95	72
4	**4d**	4-BrC_6H_4		69	80
5	**4e**	4-$CH_3OC_6H_4$		88	68
6	**4f**	4-$CH_3OC_6H_4$		81	60
7	**4g**	4-$CH_3OC_6H_4$		92	56

[a] Reactions were performed with ketoimines **4** and HCN (1.5 equivs.) using 5 mol % of catalyst **1a** at 0.15 M concentration in toluene.
[b] Yield of the isolated formamide derivatives **6** after formylation of the corresponding amino nitriles **5** and chromatography.
[c] Determined by HPLC analysis of **5** or **6** using a Chiralcel OD-H and Chiralpak AD-H column.

ity of chiral diols, such as TADDOL **7**, as enantioselective catalysts for the Strecker reaction but, more importantly, show that hydrogen-bond activation can be achieved not only for aldehydes[15] but also for the first time for aldimines.

In summary, we have developed an efficient Brønsted acid-catalyzed, enantioselective hydrocyanation of ketoimines using BINOL phosphates as catalyst. This reaction, which generally is more difficult to perform, provides the corresponding amino nitriles, precursors of quaternary amino acids, in good isolated yields and enantioselectivities. Additionally, we here report that chiral diols, such as TADDOL, are promising organocatalysts for the Strecker reaction. Furthermore, the results demonstrate that hydrogen-bond activation through TADDOL derivatives can be achieved not only for aldehydes but also for the corresponding aldimines. Further work will be directed toward a detailed examination of this interesting mode of hydrogen-bond activation, as well as the examination of tailored TADDOL derivatives and further chiral diol catalysts in asymmetric Strecker reactions.

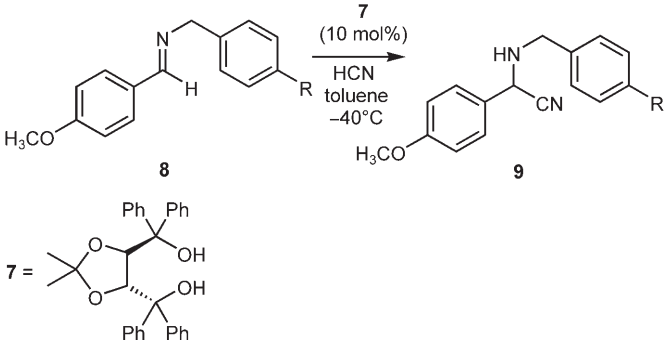
Experimental Section

General Remarks

Unless otherwise stated, all commercially available compounds were used as provided without further purification. Solvents for chromatography were technical grade and distilled prior to use. Analytical thin layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was carried out using silica gel Merck 60 (particle size 0.040–0.063 mm).

^{1}H NMR and ^{13}C NMR were recorded on a Bruker AM 250 spectrometer in $CDCl_3$. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Mass spectra (MS-ESI) were conducted on a Micromass/Waters Qtof Ultima 3 instrument. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer and are reported in terms of frequency

Table 5. Survey of protecting groups in the TADDOL-catalyzed hydrocyanation of aldimines.



Entry[a]	R	*ee* [%][b]
1	H	22
2	OCH_3	8
3	F	16
4	Cl	22
5	Br	14
6	$CHPh_2$[c]	-

[a] Reactions were performed with imine **8** and HCN (1.5 equivs.) using 10 mol% of catalyst at 0.15 M concentration.
[b] Determined by HPLC analysis using a Chiralcel OD-H column.
[c] No reaction observed.

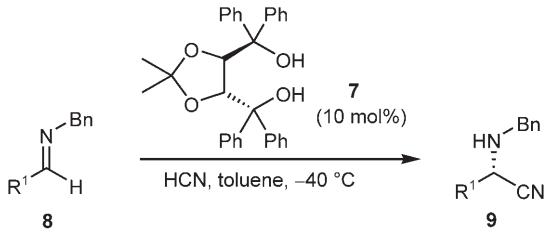
of absorption (cm^{-1}). Spectroscopy data of amides **10a–d** are in agreement with the literature values.[11]

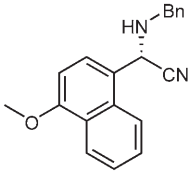
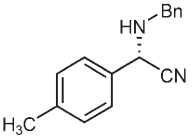
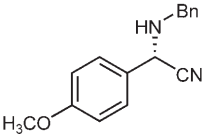
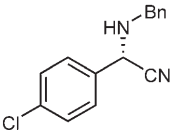
General Procedure for Asymmetric Strecker Reactions

A flame-dried flask equipped with a stir bar was charged with imine, catalyst (0.05 equivs.) and toluene. The reaction mixture was cooled and 1.5 equivs. of HCN solution (generated prior to the reaction from equimolar amounts of TMSCN and methanol) were added. The mixture was allowed to stir at −40 °C for 3 days and was then quenched with *in situ* generated acetic formic anhydride.[16] The resulting mixture was allowed to stir at room temperature for 30 min. The solvents were removed under vacuum and the residue was subjected to column chromatography (hexane: ethyl acetate 5:1) on silica gel to afford the corresponding formamide derivative. (For HPLC analysis of the amino nitrile, before addition of $HCOOH/Ac_2O$, a sample was transferred into a precooled flask *via* a precooled pipette and the solvents were removed under reduced pressure).

***N*-(4-Methoxybenzyl)-*N*-(1-cyano-1-*p*-tolylethyl)formamide (6a):** ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.58$ (s, 1H), 7.30 (d, $J = 8.3$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.14 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.3$ Hz, 2H), 4.57 (dd, $J = 15.8$, 8.3 Hz, 2H), 3.78 (s, 3H), 2.37 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 162.7$, 159.0, 139.8, 134.5, 130.1, 129.3, 128.9, 125.8, 119.4, 113.9, 60.2, 55.3, 45.6, 28.5, 21.1; MS (ESI): *m/z* (%) = 331.17 $[M+Na]^+$ (100), 639.36 $[2M+Na]^+$ (29); IR (neat): $\nu = 2934$, 2838, 1681, 1612, 1585, 1458, 1352, 1300, 1248, 1178, 11127, 1034, 959, 928, 818, 748, 574 cm^{-1}.

Table 6. Scope of the TADDOL-catalyzed enantioselective Strecker reaction.



Entry[a]	Aldimine	Amino nitrile **9**	Yield [%][b]	*ee* [%][c]
1	**8a**		69	56
2	**8b**		68	30
3	**8c**		93	22
4	**8d**		n.d.	32

[a] Reactions were performed with aldimine **8** and HCN (1.5 equivs.) using 10 mol% of catalyst **7** at 0.15 M concentration in toluene.
[b] Yield of the isolated trifluoroacetamides **10** after acetylation of the corresponding amino nitriles **9** and chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD-H column.
[d] Not determined.

***N*-(4-Bromobenzyl)-*N*-(1-cyano-1-*p*-tolylethyl)formamide (6b):** ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.61$ (s, 1H), 7.38 (d, $J = 8.3$ Hz, 2H), 7.28 (d, $J = 8.3$ Hz, 2H), 7.20 (d, $J = 8.3$ Hz, 2H), 7.06 (d, $J = 8.3$ Hz, 2H), 4,55 (dd, $J = 15.8$, 6.3 Hz, 2H), 2.37 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): $\delta = 162.4$, 140.0, 135.9, 134.0, 131.6, 130.2, 129.6, 125.8, 121.5, 119.2, 60.4, 45.8, 28.4, 21.1; MS (ESI): *m/z* (%) = 379.08 $[M+Na]^+$ (Br pattern) (100), 737.18 $[2M+Na]^+$ (Br pattern) (32); IR (neat): $\nu = 3030$, 2995, 2924, 1908, 1677, 1593, 1512, 1488, 1351, 1159, 1072,1013, 963, 937, 818, 746 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[1-(1,1′-biphenyl-4-yl)-1-cyanoethyl]formamide (6c):** ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.68$ (s, 1H), 7.68–7.53 (m, 4H), 7.53–7.35 (m, 5H), 7.14 (d, $J = 8.3$ Hz, 2H), 6.81 (d, $J = 8.3$ Hz, 2H), 4.64 (s, 2H), 3.78 (s,

3H), 2.06 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 162.5, 159.0, 142.5, 139.6, 136.2, 129.3, 128.9, 128.0, 127.1, 126.3, 119.2, 113.9, 60.2, 55.2, 45.7, 28.4; MS-(ESI): *m/z* (%) = 393.19 $[M+Na]^+$ (37), 763.38 $[2M+Na]^+$ (100); IR (neat): ν = 3032, 2999. 2936, 2837, 2251, 1683, 1617, 1515, 1487, 1352, 1249, 1178, 1034, 911, 839, 766, 734, 699 cm^{-1}.

***N*-(4-Bromobenzyl)-*N*-[1-(1,1′-biphenyl-4-yl)-1-cyanoethyl]formamide (6d):** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.55 (s, 1H), 7.37–7.17 (m, 7H), 7.50–7.38 (m, 4H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.44 (s, 2H), 1.92 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 161.1, 141.6, 138.2, 134.5, 130.4, 128.4, 127.7, 126.8, 125.9, 125.0, 120.3, 117.7, 59.3, 44.7, 27.1; MS (ESI): *m/z* (%) = 443.1 $[M+Na]^+$ (Br pattern) (53), 770.6 $[2M+Na]^+$ (Br pattern) (100); IR (neat): ν = 3003, 2937, 1675, 1608, 1585, 1513, 1458, 1352, 1306, 1215, 1184, 1158, 1131, 1077, 1030, 959, 833, 730 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[1-(4-bromophenyl)-1-cyanoethyl]formamide (6e):** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.47 (s, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.15–7.08 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.42 (s, 2H), 3.64 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 162.2, 159.1, 136.7, 132.5, 129.3, 128.5, 127.5, 123.8, 118.7, 114.4, 113.9, 60.0, 55.2, 45.7, 28.4; MS (ESI): *m/z* (%) = 395.0 $[M+Na]^+$ (Br pattern) (100), 671.3 $[2M+Na]^+$ (Br pattern) (63); IR (neat): ν = 2932, 1678, 1618, 1513, 1460, 1439, 1403, 1363, 1299, 1249, 1225, 1178, 1130, 1108, 1073, 1034, 1010, 835 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[1-cyano-1-(naphthalen-3-yl)-ethyl]formamide (6f):** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.66 (s, 1H), 7.98 (s, 1H), 7.80–7.90 (m, 3H), 7.65–7.51 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 4.64 (dd, *J* = 16.0, 6.8 Hz, 2H), 3.77 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 162.5, 159.0, 134.5, 133.2, 132.8, 129.8, 129.4, 128.8, 128.3, 127.6, 127.3, 125.6, 122.4, 119.2, 113.9, 60.6, 55.2, 45.7, 28.4; MS (ESI): *m/z* (%) = 367.19 $[M+Na]^+$ (70), 711.37 $[2M+Na]^+$ (100); IR (neat): ν = 3001, 2936, 1681, 1611, 1512, 1460, 1354, 1301, 1248, 1179, 1133, 1112 1033, 956, 911, 859, 819, 753 cm^{-1}.

***N*-(4-Methoxybenzyl)-*N*-[1-cyano-1-(4-methoxyphenyl)-ethyl]formamide (6g):** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.58 (s, 1H), 7,32 (d, *J* = 9.0 Hz, 2H); 7.12 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8,5 Hz, 2H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.65–4.45 (m, 2H), 3.81 (s, 3H), 3.77 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 162.5, 160.3, 158.9, 129.2, 129.0, 127.4, 119.4, 114.7, 113.9, 59.8, 55.4, 55.2, 45.4, 28.4; MS-(ESI): *m/z* (%) = 347.1 $[M+Na]^+$ (100), 671.3 $[2M+Na]^+$ (88); IR (neat): ν = 3003, 2934, 2838, 1675, 1609, 1512, 1461, 1408, 1363, 1302, 1250, 1177, 1131, 1110, 1070, 1032, 957, 839 cm^{-1}.

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