Brønsted acid-catalyzed efficient Strecker reaction of ketones, amines and trimethylsilyl cyanide†

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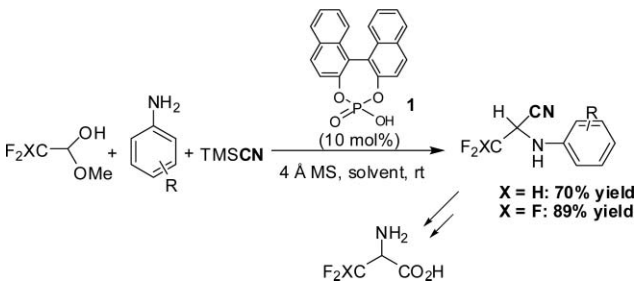
A general method for the one-pot, three-component Strecker reaction of ketones was developed using Brønsted acids as organocatalysts. A series of α-aminonitriles were obtained in good to excellent yields (79–99%). A preliminary extension to a catalytic enantioselective three-component Strecker reaction of ketones (up to 40% ee) is also described.

Introduction

Since Strecker reported the condensation of an aldehyde, ammonia and hydrocyanic acid to afford α-aminonitriles for the synthesis of alanine in 1850 (Strecker reaction),[1] this reaction has been considerably extended by the employment of various catalysts, sources of amino and cyano groups, as well as different solvents.[2] This multicomponent transformation constitutes one of the simplest and most efficient methods for the preparation of α-amino acids.[3,4] Consequently, over the past several decades, many efforts have also been directed to the development of catalytic asymmetric approaches for the production of optically active α-amino acids.[5] A lot of examples of three-component Strecker reactions have been reported; however, in all cases, the use of aldehydes to achieve successful results was necessary. Accordingly, the direct three-component Strecker reaction using ketones is difficult. It is generally based on the use of preformed ketimines and subsequent cyanide addition in the presence of catalysts.[6] Therefore, the development of efficient processes for the direct Strecker reaction of ketones has become a much attempted research endeavor. Recently Matsumoto *et al.* developed the three-component Strecker reaction of ketones under high pressure conditions,[7] while Olah's and Khan's groups reported results of the synthesis of α-aminonitriles from the corresponding ketones and amines with trimethylsilyl cyanide (TMSCN) using $Ga(OTf)_3$[8] or $Fe(Cp)_2PF_6$[9] as a catalyst, respectively. Suginome and co-workers have demonstrated that bis(dialkylamino)cyanoboranes as a new cyanide source reacted with non-aromatic acyclic and cyclic aliphatic ketones.[10] In addition, a solvent-free process for the three-component Strecker reaction of ketones has been reported; however, it only contained a limited amount of ketone substrates.[11] Therefore, the development of new catalytic systems for the direct three-component Strecker condensation of ketones is still needed.

Organocatalysis, the use of small organic molecules as catalysts, has been a fruitful area of research over the past decade.[12] Indeed, numerous successful examples of the organocatalytic Strecker reaction have been developed.[13] However, an organocatalytic three-component Strecker condensation using ketones remains a significant challenge. BINOL-derived phosphoric acids (independently reported by Akiyama *et al.*,[14a] and Uraguchi and Terada[14b] in 2004) have become one of the most privileged groups of organocatalysts. By using these Brønsted acid catalysts, a variety of new reactions have been developed in organic synthesis.[14] Recently, we have demonstrated that BINOL-derived phosphoric acids can catalyze asymmetric arylation reactions of trifluoroacetaldimines (generated *in situ*) and simple trifluoromethyl ketones with high stereoselectivities.[15] Subsequently, we have also found that the one-pot, three-component Strecker reactions of tri- and difluoroacetaldehyde hemiacetal proceeded well by employing phosphoric acids as efficient catalysts. The corresponding fluorine-containing amino acids could be obtained (Scheme 1).[16,17] As a part of our ongoing studies, herein, we would like report our preliminary results on the Brønsted acid-catalyzed three-component Strecker reaction of ketones.



Scheme 1 Brønsted acid-catalyzed three-component Strecker reactions of tri- and difluoroacetaldehyde hemiacetal.

Results and discussion

Initially, the condensation of acetophenone, aniline and TMSCN as a model reaction was explored. The results are listed in Table 1. The reaction did not proceed in the absence of Brønsted acid (entry 1). The use of BINOL-derived phosphoric acid gave the desired α-aminonitrile in 63% yield (entry 2). Accordingly, a yield of 78% was obtained when the reaction was run at 40 °C (entry 3). However, at a higher temperature (80 °C) the trimethylsilyl protected cyanohydrin derivative was observed (entry 4). Subsequently, the three-component Strecker reaction was conducted in different solvents (Table 1, entries 5–12). Toluene was found to be the best with respect to catalytic activity. It is

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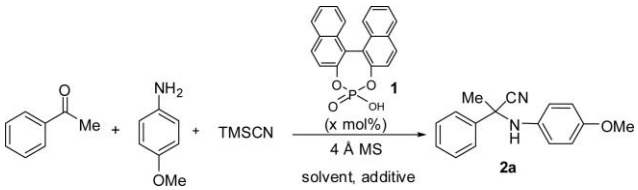
Table 1 Optimization of the reaction conditions for the three-component condensation[a]



Entry	Catalyst (mol%)	Solvent	T/°C	Additive	Yield (%)[b]
1	0	Toluene	25	None	NR
2	10	Toluene	25	None	63
3	10	Toluene	40	None	78
4	10	Toluene	80	None	51
5	10	$Cl(CH_2)_2Cl$	40	None	73
6	10	CCl_4	40	None	70
7	10	THF	40	None	55
8	10	MTBE	40	None	49
9	10	1,4-dioxane	40	None	30
10	10	CH_3CN	40	None	47
11	10	$EtNO_2$	40	None	75
12	5	Toluene	40	None	65
13	10	Toluene	40	*i*-PrOH (1.0 eq.)	82
14	10	Toluene	40	PhOH (1.0 eq.)	87
15	0	Toluene	40	*i*-PrOH (1.0 eq.)	NR
16	0	Toluene	40	PhOH (1.0 eq.)	NR

[a] A mixture of acetophenone (1.1 equiv.), aniline (1.0 equiv.), TMSCN (1.5 equiv.) and 4 Å MS (50 mg) in solvent (0.5 mL) in the presence of catalyst was stirred for 24–48 h. [b] Isolated yield.

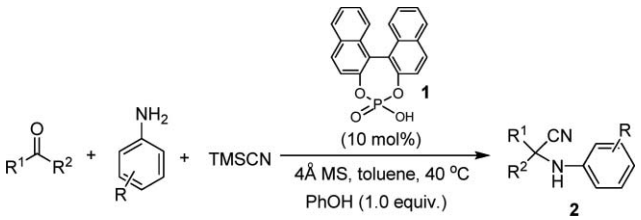
interesting to note that with additives of *i*-PrOH and PhOH the yields were further improved, to 82% and 87%, respectively (entries 13 and 14). Under control conditions, no condensation reaction occurred (entries 15 and 16).

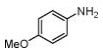
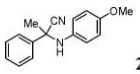
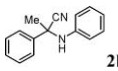
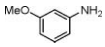
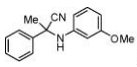
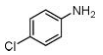
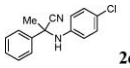
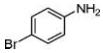
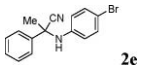
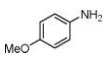
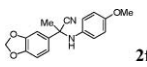
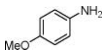
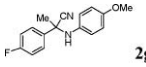
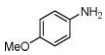
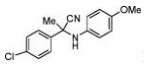
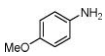
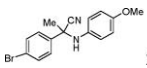
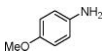
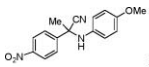
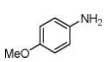
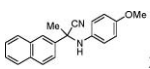
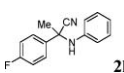
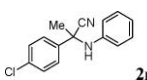
Encouraged by these promising results, we extended our studies using a variety of aromatic and aliphatic ketones, and different amines in the presence of phosphoric acid (10 mol%). As highlighted in Table 2, a series of aromatic amines gave significant amounts of the Strecker products (entries 1–5). However, these conditions are not suitable for the phosphoric acid-catalyzed direct Strecker reaction of aliphatic amines and benzylamine due to their interaction with the catalyst (the ammonium salt of the phosphoric acid was detected by TLC). Both electron-donating and electron-withdrawing substituents on the phenyl groups of aromatic ketones had little effect on the reactions. The desired α-aminonitriles were obtained in 79–99% yields (entries 6–16). Moreover, heteroaromatic ketones also worked well in the three-component reactions (entries 17–19). By contrast, the ketone substrates with bulky groups showed relatively low reactivity. For example, the condensation of benzophenone required a higher temperature and prolonged reaction time to afford the expected three-component product (entry 20). Furthermore, we found that acyclic and cyclic aliphatic ketones react smoothly with the aniline under the same reaction conditions to provide the corresponding α-aminonitriles in high yields (entries 21–26). In addition, in all cases the organocatalysts can be recovered by flash column chromatography in almost quantitative yields, then washed with 4 N HCl and water prior to reuse, without loss of the activity.

In the control experiment, the imine intermediate, derived from the ketone and amine, was detected by ^{1}H NMR (Fig. 1A). With the formation of the Strecker product, the imine would completely disappear from the catalytic system (Fig. 1B). The existence of the imine intermediate was also confirmed by ESI-MS (Fig. 2). In addition, no cyanohydrin trimethylsilyl ether was detected in the reaction mixture. Therefore, it is probable that the rate of hemiaminal and/or imine formation is fast compared with the rate of the cyanohydrin adduct formation. Regarding the mechanism of this one-pot three-component condensation, we assume that two pathways could be involved in the catalytic cycle. In the first step, the reaction of ketone with aniline readily provides the corresponding hemiaminal and/or imine in the presence of phosphoric acid and molecular sieves. Subsequently, the hemiaminal was protonated by the Brønsted acid to undergo an S_N2 displacement by cyanide (S_N2 substitution). In another pathway, the imine could be protonated by the Brønsted acid to produce an iminium ion as a more electrophilic intermediate, and TMSCN interacts with the alcohol or water to liberate HCN as a nucleophile to attack the activated iminium ion (nucleophilic addition).[2j,w] Finally, elimination of the catalyst furnished the corresponding α-aminonitriles and regenerated the phosphoric acid (Fig. 3).

The described three-component Strecker condensation of ketones could, in principle, be extended to a catalytic enantioselective reaction.[18] Unfortunately, only racemic products were obtained under the above reaction conditions. When there is no additive of PhOH (or *i*-PrOH), screening of a series of available BINOL-derived phosphoric acids indicated that the most promising chiral catalyst is the phenanthr-9-yl-substituted acid at the 3,3′-positions of the binaphthyl scaffold (**3**) (Scheme 2). TMSCN was likely to be the real cyanating agent in this catalytic asymmetric process. Detailed investigations of the reaction mechanism are currently underway. Although enantioselectivity is low (20–40% ee) at this stage, this catalytic enantioselective one-pot, three-component process is a new entry for the direct construction of chiral quaternary α-amino acids.

Table 2 The scope of the three-component Strecker reaction[a]



Entry	Ketone	Amine	Product	Yield (%)[b]
1			 **2a**	87
2			 **2b**	98
3			 **2c**	99
4			 **2d**	90
5			 **2e**	98
6			 **2f**	82
7			 **2g**	79
8			 **2h**	99
9			 **2i**	82
10			 **2j**	91
11			 **2k**	80
12			 **2l**	97
13			 **2m**	98
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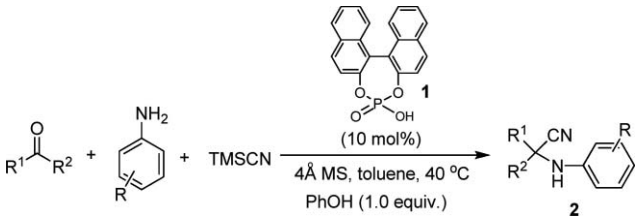
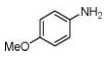
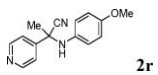
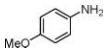
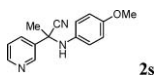
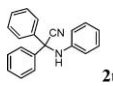
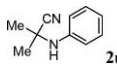
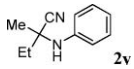
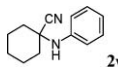
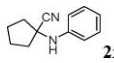
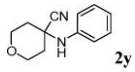
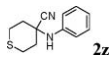
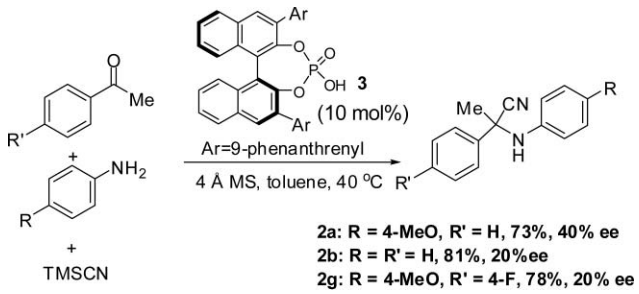


Entry	Ketone	Amine	Product	Yield (%)[b]
18			 2r	99
19			 2s	90
20			 2t	80[c]
21			 2u	99
22			 2v	85
23			 2w	99
24			 2x	99
25			 2y	82
26			 2z	88

[a] A mixture of acetophenone (1.1 equiv.), aniline (1.0 equiv.), TMSCN (1.5 equiv.), PhOH (1.0 equiv.) and 4 Å MS (50 mg) in toluene (0.5 mL) in the presence of catalyst (10 mol%) was stirred at 40 °C for 24–48 h. [b] Isolated yield. [c] At 60 °C for 96 h.



Scheme 2 Chiral phosphoric acid-catalyzed three-component Strecker reaction of ketones.

In summary, we have developed a convenient and efficient one-pot, three-component Strecker reaction of ketones, amines and trimethylsilyl cyanide in the presence of Brønsted acid. A series of α-aminonitriles were obtained in good to excellent yields. Our method also provides an efficient alternative route for the existing stepwise methodologies for the Strecker reaction of ketones. The methodology can be a platform for catalytic enantioselective three-component Strecker reaction of ketones. Further studies focusing on improving the enantioselectivity are ongoing.

Experimental section

General details

Unless otherwise noted, all commercially available compounds and solvents were used as provided without further purification. The phosphoric acids were synthesized according to the literature.[14]

^{1}H and ^{13}C were recorded on Varian Mercury Plus 500 instruments at 500 MHz (^{1}H NMR) or 125 MHz (^{13}C NMR). Chemical shifts were reported in ppm from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). MS were recorded on a VG-7070E or HP 5988A spectrometer using the ESI method. HPLC analyses were carried out on a Hewlett Packard Model HP 1200 instrument. All of the reactions were carried out under an argon atmosphere with the exclusion of moisture.

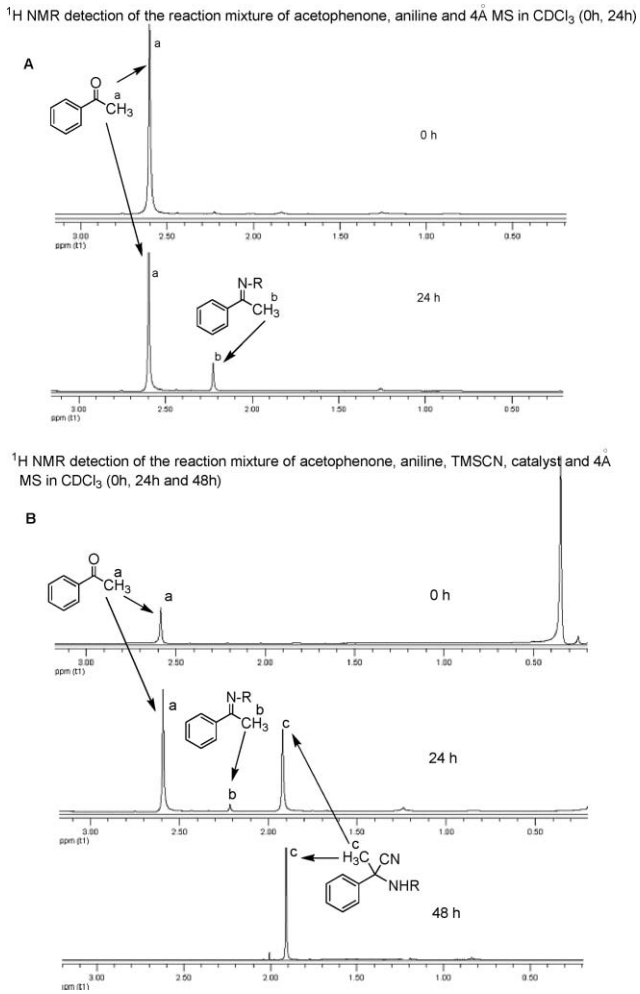


Fig. 1 The detection of the reaction processes by ^{1}H NMR.

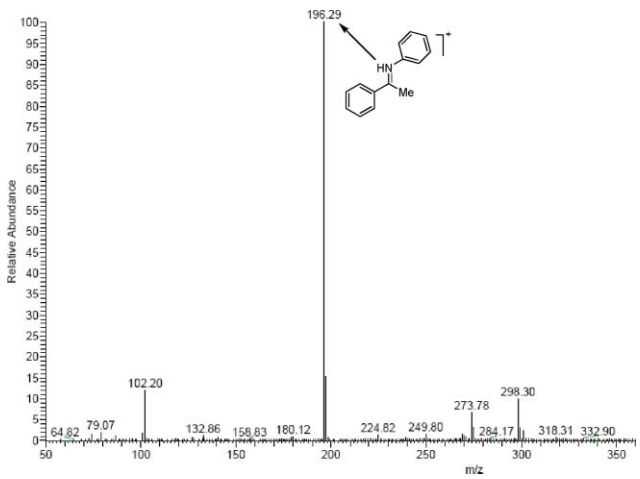


Fig. 2 ESI-MS (+) spectra of the imine intermediate in the reaction system.

Representative procedure for three-component Strecker reaction of ketone

2-(4-methoxyphenylamino)-2-phenylpropanenitrile (2a). Brønsted acid catalyst (8.7 mg, 0.025 mmol) was added to a mixture of acetophenone (33.0 mg, 0.275 mmol), 4-methoxylaniline (30.8 mg, 0.25 mmol), TMSCN (37.2 mg, 0.375 mmol), phenol (23.5 mg, 0.25 mmol), and powdered 4 Å molecular sieves (50 mg) in toluene (0.5 mL). The resulting mixture was stirred at 40 °C until completion of the reaction with monitoring by TLC. Then, the reaction solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (petroleum ether–AcOEt: 20 : 1) to give the desired product as a white solid, 54.8 mg. The Brønsted acid was recovered (eluent: methanol) in 95% yield (8.3 mg).

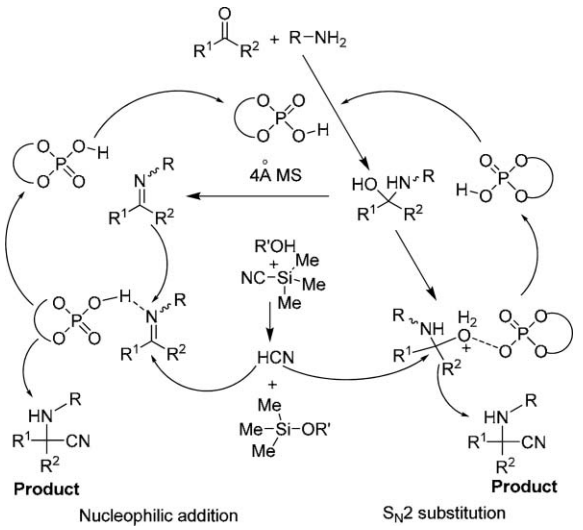


Fig. 3 Proposed mechanisms for the three-component Strecker reaction of ketone, amine and TMSCN.

87% yield, mp: 101–102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 7.65-7.36 (m, 5H), 6.71-6.55 (m, 4H), 3.70 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm] 154.2, 140.3, 137.4, 129.4, 128.8, 125.3, 121.2, 118.5, 114.6, 58.4, 55.7, 33.2; IR (KBr) ν/cm^{-1}: 3379, 1517, 1454, 1351, 1249, 1031, 822, 755, 692; MS (EI) m/z: 254.11 $[M + H]^+$, 226.31 $[M - CN]^+$.

2-(3-methoxyphenylamino)-2-phenylpropanenitrile (2c). 99% yield, mp: 102–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.63 (d, J = 7.0 Hz, 2H), 7.42-7.34 (m, 3H), 7.04-7.01 (m, 1H), 6.38-6.16 (m, 2H), 6.10 (s, 1H), 3.63 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 160.4, 145.1, 140.2, 130.0, 129.5, 128.8, 125.0, 120.9, 108.7, 105.5, 102.0, 57.3, 55.2, 33.5; IR (KBr) ν/cm^{-1}: 3398, 1617, 1596, 1496, 1227, 1170, 1049, 857, 749, 705; MS (ESI) m/z: 226.31 $[M - CN]^+$, 227.33 $[M - CN + H]^+$, 253.04 $[M + H]^+$.

2-(4-methoxyphenylamino)-2-(benzo[d]-[1,3]-dioxol-6-yl)propanenitrile (2f). 82% yield, mp: 127–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.16-7.09 (m, 2H), 6.82 (d, J = 8.0 Hz, 1H), 6.73-6.57 (m, 4H), 5.99 (d, J = 2.0 Hz, 2H), 3.71 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.3, 148.6, 148.0, 137.4, 134.3, 121.2, 118.9, 114.6, 108.7, 105.8, 101.7, 58.1, 55.7, 33.3; IR (KBr) ν/cm^{-1}: 3392, 1521, 1492, 1450, 1245, 1027, 922, 809, 759; MS (EI) m/z: 270.23 $[M - CN]^+$, 271.24 $[M - CN + H]^+$.

2-(4-methoxyphenylamino)-2-(4-fluorophenyl)propanenitrile (2g). 79% yield, mp: 103–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.19 (br, 1H), 7.39 (1H), 7.31-7.28 (m, 2H), 7.08 (d, J = 8.4 Hz, 1H), 5.98 (s, 2H), 5.14 (d, J = 2.4, 1H), 3.77 (s, 9H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 162.8 (d, J = 246.5 Hz),

154.4, 137.2, 136.1, 127.2 (d, $J = 8.2$ Hz), 121.0 (d, $J = 2.5$ Hz), 118.6, 116.3 (d, $J = 21.7$ Hz), 114.7, 57.9, 55.7, 33.2; IR (KBr) ν/cm^{-1}: 3383, 1504, 1437, 1257, 1219, 1044, 998, 826, 763; MS (EI) m/z: 244.29 [M – CN]$^+$, 245.28 [M – CN + H]$^+$.

2-(4-methoxyphenylamino)-2-(4-chlorophenyl)propanenitrile (2h). 99% yield, mp: 97–99 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.59-7.37 (m, 4H), 6.72-6.52 (m, 4H), 3.71 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.4, 139.0, 137.1, 134.7, 129.6, 126.8, 120.8, 118.5, 114.7, 57.9, 55.7, 33.1; IR (KBr) ν/cm^{-1}: 3383, 1512, 1487, 1245, 1219, 1182, 1098, 1035, 809, 742; MS (ESI) m/z: 260.26 [M – CN]$^+$.

2-(4-methoxyphenylamino)-2-(4-bromophenyl)propanenitrile (2i). 82% yield, mp: 95–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.55-7.50 (m, 4H), 6.72-6.52 (m, 4H), 3.71 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.4, 139.5, 137.0, 132.5, 127.1, 122.8, 120.8, 118.5, 114.7, 58.0, 55.7, 33.1; IR (KBr) ν/cm^{-1}: 3379, 1512, 1487, 1249, 1186, 1035, 1010, 822, 772; MS (ESI) m/z: 304.23 [M – CN – H]$^+$.

2-(4-methoxyphenylamino)-2-(4-nitrophenyl)propanenitrile (4j). 91% yield, mp: 107–109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.28-7.84 (m, 4H), 6.72-6.49 (m, 4H), 4.12 (br, 1H), 3.71 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.5, 148.2, 147.7 (d, $J = 1.7$ Hz, 1H), 136.6, 126.6, 124.7, 120.3 (d, $J = 1.6$ Hz), 118.3, 114.8, 58.0, 55.7, 32.9; IR (KBr) ν/cm^{-1}: 3372, 1531, 1504, 1339, 1248, 1031, 853, 827; MS (ESI) m/z: 271.26 [M – CN]$^+$, 272.33 [M – CN + H]$^+$.

2-(4-methoxyphenylamino)-2-(naphthalen-2-yl)propanenitrile (4k). 80% yield, mp: 122–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.15 (d, $J = 2.0$ Hz, 1H), 7.90-7.85 (m, 3H), 7.73-7.71 (m, 1H), 7.54-7.52 (m, 2H), 6.68-6.58 (m, 4H), 3.68 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.3, 137.8, 137.5, 133.4 (2C), 129.5, 128.5, 127.9, 126.9 (2C), 124.8, 122.6, 121.3, 118.6, 114.7, 58.6, 55.7, 33.1; IR (KBr) ν/cm^{-1}: 3367, 1521, 1450, 1236, 1178, 1044, 811, 747, 721; MS (ESI) m/z: 276.27 [M – CN]$^+$, 277.26 [M – CN + H]$^+$.

2-(4-fluorophenyl)-2-(phenylamino)propanenitrile (2l). 97% yield, mp: 141–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.62-7.59 (m, 2H), 7.15-7.07 (m, 4H), 6.84-6.81 (m, 1H), 6.54 (d, $J = 8.0$ Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 162.8 (d, $J = 246.5$ Hz), 143.4, 135.8 (d, $J = 3.3$ Hz), 129.3, 127.0 (d, $J = 8.2$ Hz), 120.7, 120.4, 116.4 (d, $J = 21.7$ Hz), 116.0, 56.8, 33.6; IR (KBr) ν/cm^{-1}: 3387, 1596, 1500, 1320, 1228, 1173, 831, 747, 688; MS (ESI) m/z: 214.32 [M – CN]$^+$.

2-(4-chlorophenyl)-2-(phenylamino)propanenitrile (2m). 98% yield, mp: 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.57 (d, $J = 8.5$ Hz, 2H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.15-7.12 (m, 2H), 6.85-6.82 (m, 2H), 6.54 (d, $J = 8.5$ Hz, 2H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 143.4, 138.7, 134.7, 129.7, 129.3, 126.6, 120.6, 120.4, 115.9, 56.9, 33.5; IR (KBr) ν/cm^{-1}: 3379, 1600, 1517, 1483, 1312, 1261, 1094, 1014, 824, 747, 696; MS(ESI)m/z: 230.71 [M – CN]$^+$.

2-(3-methoxyphenylamino)-2-(4-fluorophenyl)propanenitrile (2n). 93% yield, mp 77–80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.62-7.59 (m, 2H), 7.11-7.02 (m, 3H), 6.39-6.37 (m, 1H), 6.15-6.13 (m, 1H), 6.07 (s, 1H), 3.65 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 162.8 (d, $J = 246.5$ Hz), 160.5, 144.8, 135.9 (d, $J = 3.1$ Hz), 130.1, 127.0 (d, $J = 8.2$ Hz), 120.7, 116.4 (d, $J = 21.8$ Hz), 108.7, 105.5, 102.2, 56.8, 55.2, 33.6; IR (KBr) ν/cm^{-1}: 3341, 1613, 1535, 1513, 1209, 1157, 1053, 844, 771; MS (ESI) m/z: 244.38 [M – CN]$^+$, 245.45 [M – CN + H]$^+$.

2-(3-methoxyphenylamino)-2-(4-chlorophenyl)propanenitrile (2o). 99% yield, mp: 129–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 7.57 (d, $J = 8.5$ Hz, 2H), 7.38 (d, $J = 8.5$ Hz, 2H), 7.05-7.02 (m, 1H), 6.39 (d, $J = 8.0$ Hz, 1H), 6.14 (d, $J = 8.0$ Hz, 1H), 6.08 (s, 1H), 3.66 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 160.5, 144.7, 138.8, 134.7, 130.1, 129.7, 126.6, 120.5, 108.7, 105.6, 102.2, 56.8, 55.2, 33.5; IR (KBr) ν/cm^{-1}: 3398, 1613, 1591, 1491, 1287, 1170, 1049, 836, 753, 692; MS (ESI) m/z: 260.33 [M – CN]$^+$, 262.33 [M – CN + 2H]$^+$.

2-(3-methoxyphenylamino)-2-(naphthalen-2-yl)propanenitrile (2p). 86% yield, mp: 130–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.15 (d, $J = 1.5$ Hz, 1H), 7.89-7.84 (m, 3H), 7.70-7.67 (m, 1H), 7.54-7.52 (m, 2H), 7.01-6.98 (m, 1H), 6.36-6.34 (m, 1H), 6.20-6.18 (m, 1H), 6.15 (s, 1H), 3.61 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 160.5, 145.2, 137.7, 133.5, 133.4, 130.1, 129.7, 128.5, 127.9, 126.9 (2C), 124.5, 122.3, 121.0, 108.7, 105.5, 57.6, 55.2, 33.5; IR (KBr) ν/cm^{-1}: 3402, 1596, 1496, 1222, 1170, 1161, 1049, 818; MS (ESI) m/z: 276.34 [M – CN]$^+$, 303.28 [M + H]$^+$.

2-(4-methoxyphenylamino)-2-(pyridin-2-yl)propanenitrile (2q). 83% yield, mp: 93–95 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.69-8.68 (m, 1H), 7.74-7.71 (m, 1H), 7.60-7.59 (m, 1H), 7.31-7.29 (m, 1H), 6.73-6.62 (m, 4H), 3.71 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 158.2, 154.3, 149.7, 137.8, 137.3, 123.7, 121.1, 120.0, 118.7, 114.7, 60.0, 55.7, 30.6; IR (KBr) ν/cm^{-1}: 3380, 1526, 1509, 1465, 1244, 1174, 1031, 818, 736; MS (ESI) m/z: 227.23 [M – CN]$^+$, 254.06 [M + H]$^+$.

2-(4-methoxyphenylamino)-2-(pyridin-4-yl)propanenitrile (2r). 99% yield, mp: 132–135 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.67-8.66 (m, 2H), 7.60-7.58 (m, 2H), 6.72-6.48 (m, 4H), 3.71 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.3, 150.8, 149.9, 136.8, 120.4, 118.2, 118.7, 114.7, 57.6, 55.7, 32.4; IR (KBr) ν/cm^{-1}: 3253, 1592, 1508, 1408, 1249, 1035, 818, 730; MS (ESI) m/z: 227.29 [M – CN]$^+$, 254.09 [M + H]$^+$.

2-(4-methoxyphenylamino)-2-(pyridin-3-yl)propanenitrile (2s). 90% yield, oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm]: 8.91 (s, 1H), 8.63 (d, $J = 1.1$ Hz, 1H), 7.95 (d, $J = 2.0$ Hz, 1H), 7.37-7.35 (m, 1H), 6.72-6.55 (m, 4H), 4.08 (br, 1H), 3.71 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 154.4, 153.7, 150.1, 147.3, 136.9, 133.4, 124.0, 120.3, 118.8, 114.7, 56.7, 55.7, 32.8; IR (KBr) ν/cm^{-1}: 3350, 3258, 1688, 1508, 1420, 1245, 1173, 1105, 1031, 822, 709; MS (ESI) m/z: 227.34 [M – CN]$^+$.

4-(phenylamino)tetrahydro-2*H*-pyran-4-carbonitrile (2y). 82% yield, mp: 112–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.29-7.25 (m, 2H), 6.97-6.93 (m, 3H), 4.02-3.97 (m, 2H), 3.80-3.74 (m, 2H), 2.34-2.30 (m, 2H), 1.95-1.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ [ppm]: 143.0, 129.6, 121.6, 120.5, 110.3, 64.0, 52.6, 36.8; IR (KBr) ν/cm^{-1} 3308, 1603, 1495, 1347, 1255, 1096, 1034, 845, 748; MS (ESI) m/z: 176.23 [M – CN]$^+$.

Representative asymmetric version of the three-component procedure

2-(4-methoxyphenylamino)-2-phenylpropanenitrile (2a). Brønsted acid catalyst (17.5 mg, 0.025 mmol) was added to a mixture of acetophenone (31.5 mg, 0.262 mmol), 4-methoxylaniline (30.8 mg, 0.25 mmol), TMSCN (37.2 mg, 0.375 mmol) and powdered 4 Å molecular sieves (50 mg) in toluene (0.5 mL). The resulting mixture was stirred at 40 °C for 48 h. Then, the reaction solution was concentrated under vacuum, and the residue was purified by silica gel flash column chromatography (petroleum ether–AcOEt: 20 : 1) to give the desired product as a white solid: 45.9 mg (73% yield, 40% ee).

73% yield, 40% ee [Daicel Chiralcel AD-H, hexanes–^{i}PrOH = 80 : 20, 0.5 mL min^{-1}, λ = 254 nm, t_R (minor) = 14.163 min, t_R (major) = 17.404 min].

2-phenyl-2-(phenylamino)propanenitrile (2b). 81% yield, 21% ee [Daicel Chiralcel AD-H, hexanes–^{i}PrOH = 80 : 20, 0.5 mL min^{-1}, λ = 254 nm, t_R (minor) = 12.120 min, t_R (major) = 12.995 min].

2-(4-methoxyphenylamino)-2-(4-fluorophenyl)propanenitrile (2g). 78% yield, 20% ee [Daicel Chiralcel AD-H, hexanes–^{i}PrOH = 80 : 20, 0.5 mL min^{-1}, λ = 254 nm, t_R (minor) = 12.395 min, t_R (major) = 14.936 min].

Acknowledgements

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References

1 A. Strecker, *Liebigs Ann. Chem.*, 1850, **75**, 27.
2 (*a*) H. Kunz, in *Stereoselective Synthesis*, ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Georg Thieme, Stuttgart, 1995, Vol. E21b, 1931; (*b*) D. Enders and J. P. Shilvock, *Chem. Soc. Rev.*, 2000, **29**, 359.
3 For reviews on the synthesis of α-amino acids, see: (*a*) R. W. Williams and J. A. Hendrix, *Chem. Rev.*, 1992, **92**, 889; (*b*) R. O. Duthaler, *Tetrahedron*, 1994, **50**, 1539; (*c*) J.-A. Ma, *Angew. Chem., Int. Ed.*, 2003, **42**, 4290; (*d*) A. Perdih and M. S. Dolenc, *Curr. Org. Chem.*, 2007, **11**, 801; (*e*) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584.
4 For recent reviews on the multicomponent reactions, see: (*a*) *Multicomponent Reactions*, ed. J. Zhu and H. Bienaymé, Wiley-VCH, Weinheim, 2005; (*b*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; (*c*) A. Dondoni and A. Massi, *Acc. Chem. Res.*, 2006, **39**, 451; (*d*) G. Guillena, D. J. Ramón and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693, and references therein.
5 (*a*) H. Gröger, *Chem. Rev.*, 2003, **103**, 2795; (*b*) T. Vilaivan, W. Bhanthumnavin and Y. Sritana-Anant, *Curr. Org. Chem.*, 2005, **9**, 1315.
6 (*a*) C. Spino, *Angew. Chem., Int. Ed.*, 2004, **43**, 1764; (*b*) S. J. Connon, *Angew. Chem., Int. Ed.*, 2008, **47**, 1176.
7 (*a*) K. Matsumoto, J. C. Kim, N. Hayashi and G. Jenner, *Tetrahedron Lett.*, 2002, **43**, 9167; (*b*) G. Jenner, R. B. Salen, J. C. Kim and K. Matsumoto, *Tetrahedron Lett.*, 2003, **44**, 447; (*c*) K. Matsumoto, J. C. Kim, H. Iida, H. Hamana, K. Kumamoto, H. Kotsuki and G. Jenner, *Helv. Chim. Acta*, 2005, **88**, 1734.
8 G. K. S. Prakash, T. Mathew, C. Panja, S. Alconcel, H. Vaghoo, C. Do and G. A. Olah, *Proc. Natl. Acad. Sci. U. S. A.*, 2007, **104**, 3703.
9 N. H. Khan, S. Agrawal, R. I. Kureshy, S. H. R. Abdi, S. Singh, E. Suresh and R. V. Jasra, *Tetrahedron Lett.*, 2008, **49**, 640.
10 M. Suginome, A. Yamamoto and Y. Ito, *Chem. Commun.*, 2002, 1392.
11 A. Baeza, C. Nájera and J. M. Sansano, *Synthesis*, 2007, 1230.
12 Selected reviews: (*a*) B. List, *Tetrahedron*, 2002, **58**, 5573; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*c*) W. Notz, F. Tanaka and C. F. Barbas III, *Acc. Chem. Res.*, 2004, **37**, 580; (*d*) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, Germany, 2007.
13 For a review, see: (*a*) P. Merino, E. Marqués-López, T. Tejero and R. P. Herrera, *Tetrahedron*, 2009, **65**, 1219. Selected recent examples: (*b*) M. J. Sigman, P. Vachal and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 1279; (*c*) P. Vachal and E. N. Jacobsen, *Org. Lett.*, 2000, **2**, 867; (*d*) D. Seebach, A. K. Beck and A. Heckel, *Angew. Chem., Int. Ed.*, 2001, **40**, 92; (*e*) B. Liu, X. Feng, F. Chen, G. Zhang, X. Cui and Y. Jiang, *Synlett*, 2001, 1551; (*f*) P. Vachal and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 10012; (*g*) A. G. Wenzel, M. P. Lalonde and E. N. Jacobsen, *Synlett*, 2003, 1919; (*h*) Z. Jiao, X. Feng, B. Liu, F. Chen, G. Zhang and Y. Jiang, *Eur. J. Org. Chem.*, 2003, 3818; (*i*) J. Huang and E. J. Corey, *Org. Lett.*, 2004, **6**, 5027; (*j*) N. Kato, M. Suzuki, M. Kanai and M. Shibasaki, *Tetrahedron Lett.*, 2004, **45**, 3147; (*k*) S. C. Pan, J. Zhou and B. List, *Synlett*, 2006, 3275; (*l*) X. Huang, J. Huang, Y. Wen and X. Feng, *Adv. Synth. Catal.*, 2006, **348**, 2579; (*m*) Y. Fukuda, K. Kondo and T. Aoyama, *Synthesis*, 2006, 2649; (*n*) R. P. Herrera, V. Sgarzani, L. Bernardi, F. Fini, D. Pettersen and A. Ricci, *J. Org. Chem.*, 2006, **71**, 9869; (*o*) T. Ooi, Y. Uematsu and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 2548; (*p*) M. Rueping, E. Sugiono and C. Azap, *Angew. Chem., Int. Ed.*, 2006, **45**, 2617; (*q*) S. C. Pan and B. List, *Synlett*, 2007, 318; (*r*) S. C. Pan and B. List, *Org. Lett.*, 2007, **9**, 1149; (*s*) Y. Wen, Y. Xiong, L. Chang, J. Huang, X. Liu and X. Feng, *J. Org. Chem.*, 2007, **72**, 7715; (*t*) J. Huang, X. Liu, Y. Wen, B. Qiu and X. Feng, *J. Org. Chem.*, 2007, **72**, 204; (*u*) M. Negru, D. Schollmeyer and H. Kunz, *Angew. Chem., Int. Ed.*, 2007, **46**, 9339; (*v*) I. V. P. Raj, G. Suryavanshi and A. Sudalai, *Tetrahedron Lett.*, 2007, **48**, 7211; (*w*) J. Wang, X. L. Hu, J. Jiang, S. H. Gou, X. Huang, X. H. Liu and X. M. Feng, *Angew. Chem., Int. Ed.*, 2007, **46**, 8468.
14 (*a*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566; (*b*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356For reviews: (*c*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (*d*) S.-L. You, *Chem.–Asian J.*, 2007, **2**, 820; (*e*) M. Terada, *Chem. Commun.*, 2008, 4097; (*f*) G. Adair, S. Mukherjee and B. List, *Aldrichimica Acta*, 2008, **41**, 31. For some selected examples of phosphoricacid catalyzed multicomponent reactions, see: (*g*) R. I. Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84; (*h*) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun and L.-Z. Gong, *J. Am. Chem. Soc.*, 2006, **128**, 14802; (*i*) Q.-X. Guo, H. Liu, C. Guo, S.-W. Luo, Y. Gu and L.-Z. Gong, *J. Am. Chem. Soc.*, 2007, **129**, 3790; (*j*) J. Zhou and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 7498; (*k*) J. Jiang, J. Yu, X.-X. Sun, Q.-Q. Rao and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2008, **47**, 2458; (*l*) X. Cheng, R. Goddard and B. List, *Angew. Chem., Int. Ed.*, 2008, **47**, 5079; (*m*) H. Liu, G. Dagousset, G. Masson, P. Retailleau and J. Zhu, *J. Am. Chem. Soc.*, 2009, **131**, 4598.
15 (*a*) G.-W. Zhang, L. Wang, J. Nie and J.-A. Ma, *Adv. Synth. Catal.*, 2008, **350**, 1457; (*b*) J. Nie, G.-W. Zhang, L. Wang, A. Fu, Y. Zheng and J.-A. Ma, *Chem. Commun.*, 2009, 2356.
16 G.-W. Zhang and J.-A. Ma, unpublished results. When using BINOL-derived chiral phosphoric acids, racemic fluorinated α-aminonitriles were obtained.
17 For fluorine-containing amino acids, see review: (*a*) V. P. Kukhar and V. A. Soloshonok, *Fluorine-Containing Amino Acids: Synthesis and Properties*, Wiley, New York, 1995. For recent examples, see: (*b*) A. Sutherland and C. L. Willis, *Nat. Prod. Rep.*, 2000, **17**, 621; (*c*) X. Qiu and F. Qing, *J. Chem. Soc., Perkin Trans. 1*, 2002, 2052; (*d*) X. L. Qiu and F. L. Qing, *J. Org. Chem.*, 2002, **67**, 7162; (*e*) J. R. Del Valle and M. Goodman, *Angew. Chem. Int. Ed.*, 2002, **41**, 1600; (*f*) R. Dave, B. Badet and P. Meffre, *Amino Acids*, 2003, **24**, 245; (*g*) X.-L. Qiu, W.-D. Meng and F.-L. Qing, *Tetrahedron*, 2004, **60**, 6711; (*h*) G. Chaume, M. C. Van Severen, S. Marinkovic and T. Brigaud, *Org. Lett.*, 2006, **8**, 6123; (*i*) P. K. Mykhailiuk, S. Afonin, G. V. Palamarchuk, O. V. Shishkin, A. S. Ulrich and I. V. Komarov, *Angew. Chem., Int. Ed.*, 2008, **47**, 5765.
18 The catalytic enantioselective Strecker reactions of ketoimines, see recent excellent examples: (*a*) M. Rueping, E. Sugiono and S. A. Moreth, *Adv. Synth. Catal.*, 2007, **349**, 759; (*b*) K. Shen, X. Liu, Y. Cai, L. Lin and X. Feng, *Chem.–Eur. J.*, 2009, **15**, 6008; (*c*) J. Wang, W. Wang, W. Li, X. Hu, K. Shen, C. Tan, X. Liu and X. Feng, *Chem.–Eur. J.*, 2009, **15**, 11642.