Strecker-Type Reaction Catalyzed by Carboxylic Acids in Aqueous Media

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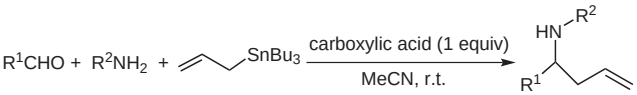
Abstract: Carboxylic acid catalyzed Strecker-type reactions were successfully carried out by simply mixing aldehydes, amines, tributyltin cyanide and carboxylic acid in aqueous media at room temperature, to afford α-aminonitriles in high yields.

Key words: Strecker reaction, α-aminonitriles, tributyltin cyanide, carboxylic acid, aqueous media

The Strecker reaction is one of the most efficient and straightforward methods for the synthesis of α-aminonitriles,[1] which are very important intermediates for the synthesis of α-amino acids and various nitrogen-containing heterocycles, such as thiadiazoles, imidazoles, etc.[2] Generally, the classical Strecker reaction takes place through nucleophilic addition of cyanide anions on imines, using various kinds of catalysts or promoters, such as polymeric scandium triflamide, $BiCl_3$, $NiCl_2$, $RuCl_3$, $Pr(OTf)_3$, $Yb(OTf)_3$, silica sulfuric acid, $[HP(HNCH_2CH_2)_3N]NO_3$,[2c,3] Lanthanide-PYBOX complexes, chiral *N*,*N*′-dioxide, Al(salen)/triphenylphosphine oxide, iodine, and Montmorillonite KSF clay, [4] etc. The Strecker reaction in ionic liquids has also been reported.[5] Additionally, several modifications of the Strecker reaction have been reported, which use a variety of cyanating agents such as α-trimethylsiloxynitriles, tributyltin cyanide or diethyl phosphorocyanidate, under a variety of reaction conditions.[6] Amongst these, tributyltin cyanide has been successfully used by S. Kobayashi et al. as a safe cyanide source for the Strecker reaction – the reagent is stable, easily handled and more effective in the nucleophilic addition reactions under mild conditions than hydrogen, sodium or potassium cyanides.

Recently, it was found that carboxylic acids are efficient promoters for the allylation of aldehydes and imines with tributylallyltin under mild reaction conditions.[7] In all of these reactions at least one equivalent of carboxylic acid is necessary due to the production of the corresponding tin ester of the carboxylic acid (Scheme 1). In our subsequent studies to develop carboxylic acid-catalyzed reactions, we considered that in the presence of the acid HCN, generated from carboxylic acid and tributyltin cyanide (Bu_3SnCN) in water, the carboxylic acid might be regenerated, thus the Strecker-type reaction catalyzed by carboxylic acid could be achieved (Scheme 2). Herein, we would like to describe the Strecker reaction catalyzed by carboxylic acids in an aqueous media.



Scheme 1

In an initial experiment using pure water as solvent and benzoic acid (20 mol%) as catalyst, the Strecker-type reaction of benzaldehyde (0.2 mmol), aniline (0.2 mmol), and tributyltin cyanide (0.22 mmol) was studied (Table 1). To our delight, a moderate yield (67%) of the desired α-amino nitrile **4a** was produced (entry 1). Therefore, several other carboxylic acids were then investigated for this reaction. A number of dicarboxylic acids were found to be highly efficient for promoting the Strecker reaction (entries 5–7). For example, the acid **A6** provided **4a** in a yield of 93% (entry 6). When 2,2′-(4-methylbenzenesulfonamido)diacetic acid (**A7**) was utilized as a catalyst, a quantitative yield was obtained. This is presumably due to the fact that this dicarboxylic acid is more soluble in water and thus functions not only as a catalyst but probably also as a surface-active agent. Decreasing the amount of the catalyst **A7** to 15 mol% resulted in a lower yield (81%, entry 8). Compared with the results obtained using water as solvent, similar Strecker reactions performed in acetonitrile were also conducted. As shown in Table 1, a yield of only 29% of **4a** was obtained when the solvent water was replaced with acetonitrile (entry 9). It is apparent that at least one equivalent of acid **A7** was needed in order to promote the Strecker reaction and provide comparably good results in acetonitrile (99% yield, entry 11).

However, we did not achieve satisfactory results (Table 2, entries 1–8) when using other aldehydes and amines as substrates; for example, *p*-anisaldehyde (37%, entry 1), *m*-anisaldehyde (17%, entry 3), *p*-chlorobenzaldehyde (39%, entry 5) and *p*-anisidine (13%, entry 7), all provided low yields. These results could be understood by the fact that, except for catalyst **A7**, the starting materials and products (generally, all are solid) are all insoluble in water. Therefore, as we observed, the reaction took place

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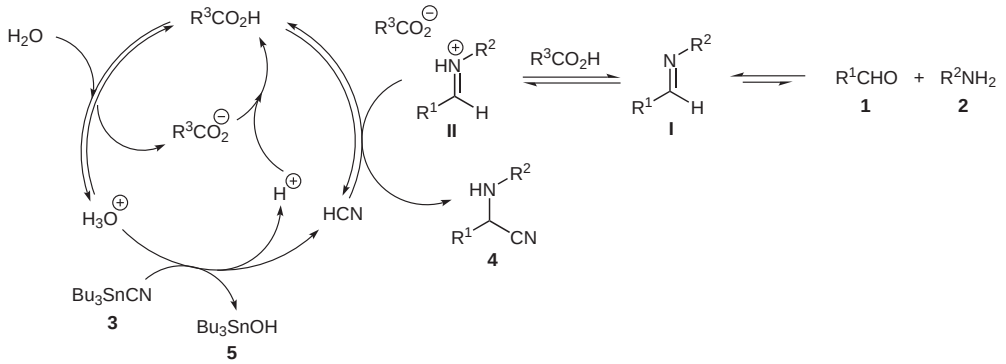


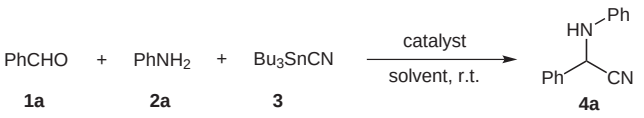
Scheme 2

completely heterogeneously in pure water. Good to high yields were obtained when a mixed solvent system (H_2O–MeCN, 9:1) was used. Compared with the results obtained using water as a solvent, the yields obtained by using mixed solvent were greatly increased (57%, entry 2; 67%, entry 4; 86%, entry 6; 92%, entry 8).

With the optimal reaction conditions established (**A7** as catalyst and H_2O–MeCN, 9:1 as solvent), the scope of the reaction was explored (Table 3). It is obvious that the carboxylic acid **A7** is an efficient catalyst for the Strecker-type reaction. For example, moderate to excellent yields were obtained in the cases of aromatic aldehydes (entries 1–7, 11 and 13). α-Furaldehyde also gave the desired α-amino nitrile **4l** in a moderate yield (65%, entry 12). In the case of aliphatic aldehydes, such as butyraldehyde (78%, entry 8), isobutyraldehyde (84%, entry 9), and cyclohexanecarbaldehyde (86%, entry 10), the Strecker-type reaction catalyzed by carboxylic acid **A7** in aqueous media was also efficient. When aromatic amines were used as substrates, the Strecker-type reaction also proceeded smoothly and provided moderate to very high yields of the corresponding α-amino nitriles (entries 5, 14 and 15). Unfortunately, when the aliphatic amine of benzylamine was used as a substrate, none of the desired α-amino nitrile was observed (entry 20).

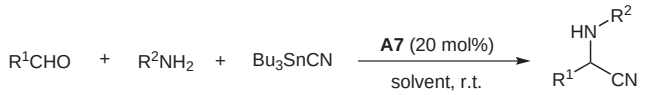
While the exact mechanism of the carboxylic acid-catalyzed Strecker-type reaction is not currently clear, a possible mechanism was proposed (Scheme 2). It is known that the ability of water to dissociate an oxygen acid and to solvate the proton is much stronger than that of acetonitrile.[8] Here, the carboxylic acid was hydrolyzed by water to produce a carboxylate anion and a hydronium ion, which would react with tributyltin cyanide to give the tributyltin hydroxide, HCN and regenerate carboxylic acid at the same time. On the other hand, the carboxylic acid could activate imine **I** by forming iminium **II**, which can then be subjected nucleophilic attack by CN^- to provide the α-amino nitrile **4**. Therefore, in the presence of

Table 1 Development of the Strecker Reaction Catalyzed by Carboxylic Acids



Entry	Catalyst	Catalyst loading (mol%)	Solvent	Yield (%)
1	$PhCO_2H$ (**A1**)	20	H_2O	67
2	*p*-$NO_2C_6H_4CO_2H$ (**A2**)	20	H_2O	82
3	*p*-$MeC_6H_4SO_2NHCH_2CO_2H$ (**A3**)	20	H_2O	72
4	*p*-$MeC_6H_4SO_3H$ (**A4**)	20	H_2O	72
5	maleic acid (**A5**)	20	H_2O	82
6	$BnN(CH_2CO_2H)_2$ (**A6**)	20	H_2O	93
7	*p*-$MeC_6H_4SO_2N(CH_2CO_2H)_2$ (**A7**)	20	H_2O	100
8	*p*-$MeC_6H_4SO_2N(CH_2CO_2H)_2$ (**A7**)	15	H_2O	81
9	*p*-$MeC_6H_4SO_2N(CH_2CO_2H)_2$ (**A7**)	20	MeCN	29
10	*p*-$MeC_6H_4SO_2N(CH_2CO_2H)_2$ (**A7**)	40	MeCN	48
11	*p*-$MeC_6H_4SO_2N(CH_2CO_2H)_2$ (**A7**)	100	MeCN	99

Table 2 Effect of Solvents on the Strecker-Type Reaction Catalyzed by Carboxylic Acid **A7**



1 2 3 **4b–e**

Entry	R^1	R^2	Solvent	Product	Yield (%)
1	*p*-$MeOC_6H_4$	Ph	H_2O	**4b**	37
2	*p*-$MeOC_6H_4$	Ph	H_2O–MeCN[a]	**4b**	57
3	*m*-$MeOC_6H_4$	Ph	H_2O	**4c**	17
4	*m*-$MeOC_6H_4$	Ph	H_2O–MeCN[a]	**4c**	67
5	*p*-ClC_6H_4	Ph	H_2O	**4d**	39
6	*p*-ClC_6H_4	Ph	H_2O–MeCN[a]	**4d**	86
7	Ph	*p*-$MeOC_6H_4$	H_2O	**4e**	13
8	Ph	*p*-$MeOC_6H_4$	H_2O–MeCN[a]	**4e**	92

[a] Solvent ratio: H_2O–MeCN, 9:1.

H_3O^+ in the aqueous media, as shown in Table 2, the equilibrium between carboxylic acid, H_3O^+, and HCN, might keep the catalytic cycle working. As supporting evidence for this mechanism, we isolated the side-product Bu_3SnOH from the reaction mixture after workup using silica gel chromatography. In conclusion, a carboxylic acid-catalyzed Strecker-type reaction has been successfully developed. As expected, the reaction proceeded smoothly in aqueous media to afford the corresponding α-amino nitriles in moderate to quantitative yields under mild reaction conditions.

Solvents and reagents were purified using standard methods. Petroleum ether (PE) refers to the fraction boiling in the range 60–90 °C. Flash column chromatography was performed on silica gel (300–400 mesh, Qingdao, China). Melting points were measured on a Mettler FP62 or WRS-1A apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on EM-360A or Bruker AM-300 300 MHz spectrometers with TMS as an internal standard (δ = 0.00 ppm). LRMS were obtained on a HP-5989A mass spectrometer. HRMS were performed on Finigan MAT8403 mass spectrometer.

(Toluene-4-sulfonylimino)diacetic Acid (A7)

Diethyl iminodiacetate[9] (1.17 g, 6.19 mmol) and Et_3N (0.71 g, 7.03 mmol) were dissolved in $CHCl_3$, and TsCl (1.18 g, 6.20 mmol) was added under cooling with an ice bath. The mixture was stirred at r.t. for 24 h, then the organic layer was washed with H_2O (3 × 5 mL), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography over silica gel (PE–EtOAc, 95:5) to give pure ester.

Yield: 1.66 g (80%).

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.14 (t, *J* = 7.2 Hz, 6 H), 2.35 (s, 3 H), 4.05 (q, *J* = 7.2 Hz, 4 H), 4.13 (s, 4 H), 7.21 (d, *J* = 8.4 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H).

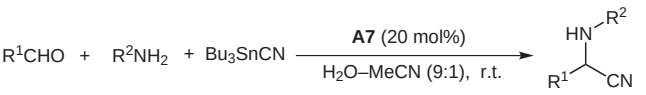
The ester (1.66 g, 4.83 mmol) and NaOH (0.58 g, 14.50 mmol) in H_2O (10 mL) were refluxed until hydrolysis was complete (indicated by TLC). The mixture was cooled to r.t. and acidified to pH 3.0 with 1 M HCl. The white precipitate was filtered and washed with ice-water (5 mL) to afford the product **A7**.

Yield: 1.18 g (87%); white solid; mp 191–193 °C (Lit.[10] yield 61%, mp 193–194 °C).

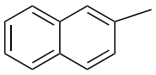
IR (KBr): 3415, 2948, 2552, 1720, 1660, 1367, 1255, 1157, 1093, 816, 777 cm^{-1}.

^1H NMR (D_2O, 300 MHz): δ = 2.23 (s, 3 H), 3.97 (s, 4 H), 7.24 (d, *J* = 8.4 Hz, 2 H), 7.56 (d, *J* = 8.4 Hz, 2 H).

Table 3 The Strecker-Type Reaction Catalyzed by Carboxylic Acid **A7**



1 2 3 **4a–s**

Entry	R^1	R^2	Product	Yield (%)
1	Ph	Ph	**4a**	99
2	*p*-$MeOC_6H_4$	Ph	**4b**	57
3	*m*-$MeOC_6H_4$	Ph	**4c**	67
4	*p*-ClC_6H_4	Ph	**4d**	86
5	Ph	*p*-$MeOC_6H_4$	**4e**	92
6	*p*-BrC_6H_4	Ph	**4f**	92
7	2,4-$Cl_2C_6H_3$	Ph	**4g**	58
8	$MeCH_2CH_2$	Ph	**4h**	78
9	Me_2CH	Ph	**4i**	84
10	*c*-C_6H_{11}	Ph	**4j**	86
11		Ph	**4k**	81
12		Ph	**4l**	65
13	*p*-MeC_6H_4	Ph	**4m**	69
14	Ph	*p*-ClC_6H_4	**4n**	54
15	Me_2CH	*p*-$MeOC_6H_4$	**4o**	100
16	Ph	*p*-FC_6H_4	**4p**	82
17	Ph	*p*-BrC_6H_4	**4q**	77
18	Ph	*p*-MeC_6H_4	**4r**	81
19	*p*-$MeOC_6H_4$	*p*-$MeOC_6H_4$	**4s**	39
20	Ph	$PhCH_2$	–	–

Strecker-Type Reaction; Typical Procedure

A mixture of benzaldehyde (21.2 mg, 0.2 mmol), aniline (18.6 mg, 0.2 mmol), Bu_3SnCN (69.5 mg, 0.22 mmol) and (toluene-4-sulfonylimino)diacetic acid (**A7**; 11.32 mg, 0.04 mmol) in either H_2O (1 mL) or H_2O–MeCN (1 mL, v/v = 9:1), was stirred at r.t. for 24 h. The reaction was quenched with sat. aq $NaHCO_3$ (3 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish the crude product, which was purified

by silica gel chromatography (typical eluent: PE–EtOAc, 25:1), to afford **4a** (41.6 mg, 100%). Tributyltin hydroxide (**5**) was recovered by eluting with MeOH.

Tributyltin Hydroxide (5)[12]
IR (film): 2955, 2923, 2854, 1073, 878, 773, 672 cm^{-1}.

^1H MNR ($CDCl_3$, 300 MHz): δ = 0.89–0.94 (t, *J* = 7.5 Hz, 9 H), 1.08–1.14 (m, 4 H), 1.25–1.38 (m, 8 H), 1.55–1.63 (m, 6 H), 1.86 (br, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 309 (2) [M + 2], 175 (6), 57 (27), 44 (100).

2-Phenyl-2-(phenylamino)acetonitrile (4a)[11a]
IR (film): 3372, 2923, 2230, 1602, 1503, 751, 693 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.05 (d, *J* = 8.4 Hz, 1 H), 5.40 (d, *J* = 8.4 Hz, 1 H), 6.76 (d, *J* = 9.0 Hz, 2 H), 6.89 (t, *J* = 7.5 Hz, 1 H), 7.26 (t, *J* = 7.8 Hz, 2 H), 7.44 (m, 3 H), 7.58 (m, 2 H).

2-(4-Methyloxyphenyl)-2-(phenylamino)acetonitrile (4b)[4f]
IR (film): 3365, 2934, 2839, 2230, 1604, 1511, 1307, 1253, 1180, 1031, 836, 752, 693 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.83 (s, 3 H), 3.99 (d, *J* = 8.1 Hz, 1 H), 5.34 (d, *J* = 8.1 Hz, 1 H), 6.76 (d, *J* = 9.0 Hz, 2 H), 6.95 (m, 3 H), 7.27 (d, *J* = 9.0 Hz, 2 H), 7.49 (d, *J* = 9.0 Hz, 2 H).

2-(3-Methyloxyphenyl)-2-(phenylamino)acetonitrile (4c)[11a]
IR (film): 3364, 2924, 2852, 2230, 1602, 1504, 1318, 1257, 1157, 1047, 785, 751, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.82 (s, 3 H), 4.06 (d, *J* = 8.4 Hz, 1 H), 5.38 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 2 H), 6.87–6.97 (m, 2 H), 7.11 (m, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 7.26 (dd, *J* = 7.5, 8.1 Hz, 2 H), 7.36 (t, *J* = 8.1 Hz, 1 H).

2-(4-Chlorophenyl)-2-(phenylamino)acetonitrile (4d)[11a]
IR (film): 3363, 2924, 2230, 1603, 1492, 1262, 1093, 1015, 752, 691 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.05 (d, *J* = 8.7 Hz, 1 H), 5.39 (d, *J* = 8.7 Hz, 1 H), 6.75 (d, *J* = 7.5 Hz, 2 H), 6.91 (m, 1 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.41 (d, *J* = 7.8 Hz, 2 H), 7.52 (d, *J* = 7.8 Hz, 2 H).

2-(4-Methyoxyphenylamino)-2-phenylacetonitrile (4e)[11a]
IR (film): 3348, 3034, 2934, 2834, 2230, 1513, 1453, 1244, 1180, 1033, 822, 744, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 3.80 (s, 3 H), 3.85 (d, *J* = 8.4 Hz, 1 H), 5.34 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 7.47 (m, 3 H), 7.62 (m, 2 H).

2-(4-Bromophenyl)-2-(phenylamino)acetonitrile (4f)[11d]
IR (film): 3385, 2926, 2235, 1603, 1503, 1265, 1074, 1012, 746, 704, 693 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.05 (d, *J* = 8.7 Hz, 1 H), 5.39 (d, *J* = 8.7 Hz, 1 H), 6.75 (d, *J* = 7.5 Hz, 2 H), 6.89 (m, 1 H), 7.26 (t, *J* = 7.5 Hz, 2 H), 7.46 (d, *J* = 7.8 Hz, 2 H), 7.58 (d, *J* = 7.8 Hz, 2 H).

2-(2,4-Dichlorophenyl)-2-(phenylamino)acetonitrile (4g)[11f]
^1H NMR ($CDCl_3$, 300 MHz): δ = 4.02 (d, *J* = 8.4 Hz, 1 H), 5.67 (d, *J* = 8.4 Hz, 1 H), 6.76 (d, *J* = 7.8 Hz, 2 H), 6.92 (m, 1 H), 7.27 (m, 2 H), 7.36 (dd, *J* = 2.4, 8.4 Hz, 1 H), 7.50 (d, *J* = 1.8 Hz, 1 H), 7.67 (d, *J* = 8.4 Hz, 1 H).

IR (film): 3373, 2925, 2230, 1603, 1503, 1265, 1104, 1049, 742, 691 cm^{-1}.

2-(Phenylamino)pentanenitrile (4h)[11b]
IR (film): 3371, 2962, 2932, 2874, 2232, 1604, 1505, 1465, 1313, 1260, 1155, 751, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 1.56 (m, 2 H), 1.85 (m, 2 H), 3.68 (d, *J* = 9.6 Hz, 1 H), 4.13 (dd, *J* = 7.2, 9.6 Hz, 1 H), 6.62 (d, *J* = 8.4 Hz, 2 H), 6.79 (m, 1 H), 7.17 (t, *J* = 7.5 Hz, 2 H).

3-Methyl-2-(phenylamino)butanenitrile (4i)[11b]
IR (film): 3375, 2967, 2931, 2876, 2230, 1604, 1505, 1467, 1315, 1271, 1155, 751, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.18 (t, *J* = 7.5 Hz, 6 H), 2.17 (m, 1 H), 3.78 (d, *J* = 9.6 Hz, 1 H), 4.03 (dd, *J* = 6.0, 9.6 Hz, 1 H), 6.70 (d, *J* = 8.7 Hz, 2 H), 6.85 (t, *J* = 7.5 Hz, 1 H), 7.25 (t, *J* = 7.5 Hz, 2 H).

2-Cyclohexyl-2-(phenylamino)acetonitrile (4j)[11a]
IR (film): 3382, 2929, 2852, 2224, 1605, 1507, 1446, 748, 688 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.18–1.28 (m, 6 H), 1.71–1.97 (m, 7 H), 3.79 (d, *J* = 9.0 Hz, 1 H), 4.13 (dd, *J* = 7.2, 9.0 Hz, 1 H), 6.70 (d, *J* = 7.5 Hz, 2 H), 6.85 (m, 1 H), 7.24 (t, *J* = 7.5 Hz, 2 H).

2-(Naphthalene-2-yl)-2-(phenylamino)acetonitrile (4k)[11e]
IR (film): 3368, 3054, 2237, 1602, 1503, 816, 750, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.10 (d, *J* = 8.4 Hz, 1 H), 5.39 (d, *J* = 8.4 Hz, 1 H), 6.78 (d, *J* = 7.2 Hz, 2 H), 6.90 (m, 1 H), 7.27 (t, *J* = 7.5 Hz, 2 H), 7.56 (m, 3 H), 7.90 (m, 3 H), 8.10 (s, 1 H).

2-(Furan-2-yl)-2-(phenylamino)acetonitrile (4l)[4f]
IR (film): 3368, 3054, 2925, 2230, 1604, 1501, 1249, 1015, 750, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.21 (d, *J* = 8.7 Hz, 1 H), 5.49 (d, *J* = 8.7 Hz, 1 H), 6.41 (dd, *J* = 1.8, 3.0 Hz, 1 H), 6.58 (dd, *J* = 1.8, 3.0 Hz, 1 H), 6.78 (d, *J* = 7.5 Hz, 2 H), 6.91 (m, 1 H), 7.24–7.30 (m, 2 H), 7.47 (d, *J* = 0.9 Hz, 1 H).

2-(Phenylamino)-2-(*p*-tolyl)acetonitrile (4m)[4f]
IR (film): 3365, 2926, 2230, 1605, 1502, 1266, 1091, 750, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 2.30 (s, 3 H), 4.02 (d, *J* = 8.4 Hz, 1 H), 5.27 (d, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 2 H), 6.78 (t, *J* = 7.5 Hz, 1 H), 7.12–7.19 (m, 4 H), 7.37 (d, *J* = 8.1 Hz, 2 H).

2-(4-Chlorophenylamino)-2-phenylacetonitrile (4n)[11a]
IR (film): 3365, 3030, 2230, 1601, 1498, 1089, 817, 758, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 4.09 (d, *J* = 8.4 Hz, 1 H), 5.39 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 7.45 (m, 3 H), 7.56 (m, 2 H).

2-(4-Methoxyphenylamino)-3-methylbutanenitrile (4o)
Brown oil.

IR (film): 3355, 2966, 2934, 2876, 2230, 1515, 1466, 1244, 1180, 1036, 822 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.17 (t, *J* = 6.6 Hz, 6 H), 2.13 (m, 1 H), 3.55 (d, *J* = 9.9 Hz, 1 H), 3.76 (s, 3 H), 3.95 (dd, *J* = 6.0, 9.9 Hz, 1 H), 6.70 (d, *J* = 9.0 Hz, 2 H), 6.82 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 19.2, 31.7, 54.1, 55.7, 115.0, 115.0, 116.2, 116.2, 119.1, 139.1, 153.9.

LRMS (EI): *m*/*z* (%) = 204 (45) [M^+], 161 (100).

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}N_2O$: 204.1263; found: 204.1266.

2-(4-Fluorophenylamino)-2-phenylacetonitrile (4p)[11c]
IR (film): 3363, 2919, 2230, 1608, 1511, 1225, 822, 747, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.99 (d, *J* = 8.4 Hz, 1 H), 5.35 (d, *J* = 8.4 Hz, 1 H), 6.69–6.73 (m, 2 H), 6.93–6.99 (m, 2 H), 7.43–7.47 (m, 3 H), 7.56–7.59 (m, 2 H).

2-(4-Bromophenylamino)-2-phenylacetonitrile (4q)[11c]

IR (film): 3370, 2919, 2230, 1594, 1494, 1073, 814, 751, 697 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.12 (d, *J* = 8.1 Hz, 1 H), 5.35 (d, *J* = 8.1 Hz, 1 H), 6.62–6.65 (d, *J* = 8.4 Hz, 2 H), 7.32–7.35 (d, *J* = 8.4 Hz, 2 H), 7.43–7.45 (m, 3 H), 7.54–7.57 (m, 2 H).

2-(*p*-Toluidino)-2-phenylacetonitrile (4r)[11c]

IR (film): 3356, 3037, 2911, 2230, 1612, 1520, 1453, 1291, 1124, 803, 747, 692 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.27 (s, 3 H), 3.90 (d, *J* = 8.1 Hz, 1 H), 5.37 (dd, *J* = 3.3, 8.1 Hz, 1 H), 6.68–6.71 (dd, *J* = 3.3, 8.4 Hz, 2 H), 7.06–7.10 (dd, *J* = 3.3, 8.4 Hz, 2 H), 7.42–7.46 (m, 3 H), 7.58–7.60 (m, 2 H).

2-(4-Methoxyphenyl)-2-(4-methoxyphenylamino)acetonitrile (4s)[11c]

IR (film): 3352, 3000, 2933, 2836, 2230, 1609, 1515, 1464, 1247, 1178, 1032, 824 cm^{-1}.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 (d, *J* = 8.4 Hz, 1 H), 3.77 (s, 3 H), 3.84 (s, 3 H), 5.28 (d, *J* = 8.4 Hz, 1 H), 6.75 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 6.96 (d, *J* = 8.1 Hz, 2 H), 7.51 (d, *J* = 8.1 Hz, 2 H).

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References

(1) Strecker, A. *Ann. Chem. Pharm.* **1850**, *75*, 27.
(2) (a) Ishitani, H.; Komiyama, S.; Kobayashi, S. *Angew. Chem. Int. Ed.* **1998**, *37*, 3186. (b) Kobayashi, S.; Busujima, T.; Nagayama, S. *Chem. Commun.* **1998**, 981. (c) Surendra, K.; Krishnaveni, N. S.; Mahesh, A.; Rao, K. R. *J. Org. Chem.* **2006**, *71*, 2532. (d) De S, K. *J. Mol. Catal. A: Chem.* **2005**, *225*, 167.
(3) (a) Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron Lett.* **1996**, *37*, 9221. (b) De S, K.; Gibbs, R. A. *Tetrahedron Lett.* **2004**, *45*, 7407. (c) De S, K. *Synth. Commun.* **2005**, *35*, 653. (d) De S, K.; Gibbs, R. A. *Synth. Commun.* **2005**, *35*, 961. (e) Kobayashi, S.; Ishitani, H.; Ueno, M. *Synlett* **1997**, 115. (f) Chen, W.-Y.; Lu, J. *Synlett* **2005**, 2993. (g) Fetterly, B. M.; Jana, N. K.; Verkade, J. G. *Tetrahedron* **2006**, *62*, 440.
(4) (a) Keith, J. M.; Jacobsen, E. N. *Org. Lett.* **2004**, *6*, 153. (b) Jiao, Z.; Feng, X.; Liu, B.; Chen, F.; Zhang, G.; Jiang, Y. *Eur. J. Org. Chem.* **2003**, 3818. (c) Kim, S. S.; Kwak, J. M. *Tetrahedron* **2006**, *62*, 49. (d) Royer, L.; De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 4595. (e) Martinez, R.; Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 8471. (f) Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Srinivas, M. *Tetrahedron* **2004**, *60*, 1767.
(5) Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Srinivas, M.; Vishnumurthy, P. *New J. Chem.* **2003**, *27*, 462.
(6) (a) Nagayama, S.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 567. (b) Obora, Y.; Baleta, A. S.; Tokunaga, M.; Tsuji, Y. *J. Organomet. Chem.* **2002**, *660*, 173. (c) Ishitani, H.; Komiyama, S.; Hasegawa, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 762.
(7) (a) Li, G.-l.; Zhao, G. *J. Org. Chem.* **2005**, *70*, 4272. (b) Li, G.-l.; Zhao, G. *Synlett* **2005**, 2540. (c) Li, G.-l.; Zhao, G. *Org. Lett.* **2006**, *8*, 633.
(8) Bordwell, F. G. *Acc. Chem. Res.* **1998**, *21*, 456.
(9) St-Denis, Y.; Chan, T. H. *Can. J. Chem.* **2000**, *78*, 776.
(10) Formanovskii, A. A.; Mikhura, I. B.; Sokolovskii, S. A.; Murakhovskaya, A. S.; Terent'ev, P. B.; Sharbatyan, P. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1988**, *24*, 930.
(11) (a) McEwen, W. E.; Grossi, A. V.; MacDonald, R. J.; Stamegna, A. P. *J. Org. Chem.* **1980**, *45*, 1301. (b) Neelakantan, L.; Hartung, W. H. *J. Org. Chem.* **1959**, *24*, 1943. (c) Barnikow, G.; Hagen, A.; Hagen, V.; Goeres, E.; Richter, D.; Fichtner, K. *Pharmazie* **1983**, *38*, 449. (d) El-Ahl, A.-A. S. *Synth. Commun.* **2003**, *33*, 989. (e) Lee, B. S.; Mahajan, S.; Janda, K. D. *Tetrahedron Lett.* **2005**, *46*, 807. (f) Van Daele, G. Patent US 4246429 **1980**, 63.
(12) Brown, J. M.; Chapman, A. C.; Harper, R.; Mowthorpe, D. J.; Davies, A. G.; Smith, P. J. *J. Chem. Soc., Dalton Trans.* **1972**, 338.