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o-Benzenedisulfonimide and its chiral derivative as Brønsted acids catalysts for one-pot three-component Strecker reaction. Synthetic and mechanistic aspects.

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Abstract

o-Benzenedisulfonimide (OBS) has efficiently catalysed the one-pot three-component reaction of ketones and aromatic amines with trimethylsilyl cyanide (TMSCN) giving the corresponding α-amino nitriles in excellent yields (23 examples; average yield 85%). Reaction conditions were very simple, green and efficient. Theoretical calculations have allowed us to explain the mechanism of this reaction which has been found to take place in two phases; the first consists of the nucleophytic addition of the aniline to the ketone and the subsequent dehydration to an imine; the second one consists of the formal addition of CN⁻ to the protonated imine. OBS acts in all steps of this mechanism. Without an acid catalyst, the reaction mechanism is more simple but barriers are sensibly higher. A chiral derivative of OBS was also used and gave fairly good results.
**Introduction**

The one-pot synthesis of α-amino nitriles via the reaction of a carbonyl compound, ammonia, and HCN (or other alkaline cyanide) in aqueous solution is a three-component reaction commonly known as the *Strecker* reaction.\(^1\) The importance of this reaction lies in the fact that α-aminonitriles are versatile intermediates for the synthesis of natural and non-natural amino acids,\(^2a\) amides, diamides and nitrogen-containing heterocycles.\(^2b\)

Over the years, several changes to the original protocol have been reported. Such modifications mainly consisted of varying the cyanide sources, using aliphatic or aromatic amines instead of ammonia, using either acids or bases as catalysts or organic solvents instead of H\(_2\)O.\(^3\) In particular, the toxic HCN has been replaced by a number of safer cyanating agents.\(^3\) They have generally been employed in the presence of Brønsted or Lewis acids,\(^4\) Lewis bases,\(^5\) metal complexes\(^6\) or mesoporous materials\(^7\) in the role of catalysts and in organic solvents such as toluene, CH\(_2\)Cl\(_2\), or MeCN. Trimethylsilyl cyanide (TMSCN) has been the most commonly used cyanide source.\(^3\)

It is interesting to note that the use of a catalyst is generally required when employing ketones,\(^8\) whereas it has been reported that no catalyst is necessary for aldehydes, especially in neat conditions.\(^9\) Nevertheless, it must be stressed that the direct three-component *Strecker* reaction with ketones as carbonyl partners has proven to be quite difficult.\(^8\) In fact it is usually performed by preparing ketimines as intermediates first and then adding the cyano group in the presence of a catalyst.\(^8,10\)

A number of different catalysts have been recently used in Brønsted acid catalysed direct *Strecker* reactions between ketones, amines and TMSCN in both heterogeneous and homogeneous conditions, these include: oxalic acid,\(^11a\) xanthan sulfuric acid,\(^11b\) BINOL-derived phosphoric acids,\(^6\) Nafion solid resins,\(^11c\) alumina supported tungstosilicic acid,\(^11d\) SBA 15 supported sulfonic acid,\(^11e\) Sn montmorillonite,\(^2b\) sulfamic acid-functionalized magnetic Fe\(_3\)O\(_4\) nanoparticles.\(^11f\)

Catalyst and/or solvent free-conditions were recently reported by Galletti\(^3\) (using acetone cyanohydrin as cyanide source in water), Matsumoto (under high pressure)\(^12\) and Onaka.\(^2b\)

![Figure 1](image)

**Figure 1** o-Benzenedisulfonimide (OBS) 1

In the light of growing interest in the one-pot three-component *Strecker* reaction, we wish to report that o-benzenedisulfonimide (OBS) 1 (Figure 1) can catalyse the *Strecker* reaction between ketones, aromatic amines and TMSCN under very mild and green conditions (Scheme 1).
Scheme 1  Three-component Strecker reaction catalyzed by 1

We have recently reported the use of OBS (1) in catalytic amounts as a safe, non-volatile and non-corrosive Brønsted acid in several acid-catalyzed organic reactions.\textsuperscript{13a} The catalyst, that possess high acidity (pK\textsubscript{a} -4.1 at 20 °C), was easily prepared,\textsuperscript{13b} recovered and purified, ready to be used in further reactions.

Results and discussion

Synthesis

Initially and in order to optimise the reaction conditions, the model reaction between acetofenone (2a), aniline (3a) and TMSCN (4) was studied under different reaction conditions (Table 1).

Table 1  Trial reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst; mol %</th>
<th>Time</th>
<th>Yield (% of 5a)\textsuperscript{a,b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat</td>
<td>-</td>
<td>24 h</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>-</td>
<td>48 h</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>neat</td>
<td>1; 2</td>
<td>6 h</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>neat</td>
<td>1; 5</td>
<td>5 min</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>1; 5</td>
<td>1 h</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>1; 5</td>
<td>2 h</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>1; 5</td>
<td>1 h</td>
<td>92</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>1; 5</td>
<td>24 h</td>
<td>62\textsuperscript{c}</td>
</tr>
<tr>
<td>9</td>
<td>H\textsubscript{2}O</td>
<td>1; 5</td>
<td>24 h</td>
<td>41\textsuperscript{c}</td>
</tr>
<tr>
<td>10</td>
<td>neat</td>
<td>HBF\textsubscript{4}. Et\textsubscript{2}O 54%; 5</td>
<td>12 h</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>neat</td>
<td>HCOOH; 5</td>
<td>24 h</td>
<td>43\textsuperscript{c}</td>
</tr>
<tr>
<td>12</td>
<td>neat</td>
<td>MeSO\textsubscript{3}H; 5</td>
<td>1 h</td>
<td>93</td>
</tr>
<tr>
<td>13</td>
<td>neat</td>
<td>NH\textsubscript{3}SO\textsubscript{3}H; 5</td>
<td>3 h</td>
<td>91</td>
</tr>
<tr>
<td>14</td>
<td>neat</td>
<td>2,4-(NO\textsubscript{2})\textsubscript{2}C\textsubscript{6}H\textsubscript{5}SO\textsubscript{3}H; 5</td>
<td>10 min</td>
<td>95</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Yields refer to the pure products. \textsuperscript{b}Reactants 2a and 3a were in equimolar amounts (5 mmol). TMSCN (4) was in slight excess (6 mmol). \textsuperscript{c}GC-MS analyses showed the presence of starting products 2a and 3a. In order to remove them, the crude residues were filtered on a buchner funnel and washed with a small amount of H\textsubscript{2}O and PE.
First of all, the reaction was performed without 1 in neat conditions and in an almost equimolar ratio (Table 1, entry 1) at room temperature. The target product, 2-phenyl-2-phenylaminopropanenitrile (5a) was obtained in a very good yield (93 %), exactly as reported by Onaka.\textsuperscript{2b} The reaction time, however, was long (24 hours). The presence of a solvent (CH$_2$Cl$_2$; Table 1, entry 2) further slowed the reaction down (48 hours) and decreased the yield (81 %).

When 1 was added as a catalyst (5 mol%) in neat conditions, a dramatic decrease in the reaction time was observed (5 min; Table 1, entry 4). The yield of 5a was always excellent (95%).

Polar, slightly polar solvents or H$_2$O were also tested (Table 1, entries 5–9). It was evident, however, that the best results were obtained in solvent-free reaction conditions. We performed the reaction in the presence of 5 mol% of five different Brønsted acids under neat conditions (Table 1; entries 10–14) to compare and contrast them with the catalytic activity of 1. The results showed that only with 2,4-dinitrobenzenesulfonic acid were both the reaction time and the yield similar to that obtained with 1.

In the light of these results, six different ketones 2 and ten different amines 3 were reacted with 4, usually in the presence of 5 mol% of 1 as a catalyst, at room temperature and under solvent-free conditions and provided excellent yields of α-aminonitriles 5 (average yields 85%). Table 2 shows the results.

**Table 2** Three-component Strecker reaction catalyzed by 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>R in 2,5</th>
<th>R’ in 3a</th>
<th>R” in 3,5</th>
<th>Products 5</th>
<th>Yield (%)$^{a,b}$</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>3a</td>
<td>5a</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>4-MeOC$_6$H$_4$</td>
<td>3b</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>3c</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>4-BrC$_6$H$_4$</td>
<td>3d</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>4-FC$_6$H$_4$</td>
<td>3e</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>2-MeOC$_6$H$_4$</td>
<td>3f</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>3-MeOC$_6$H$_4$</td>
<td>3g</td>
<td>84</td>
</tr>
<tr>
<td>8</td>
<td>4-MeC$_6$H$_4$</td>
<td>Me</td>
<td>2b</td>
<td>Ph</td>
<td>3a</td>
<td>88</td>
</tr>
<tr>
<td>9</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>Me</td>
<td>2c</td>
<td>Ph</td>
<td>3a</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>4-MeC$_6$H$_4$</td>
<td>Me</td>
<td>2b</td>
<td>4-MeOC$_6$H$_4$</td>
<td>3b</td>
<td>85</td>
</tr>
<tr>
<td>11</td>
<td>4-MeC$_6$H$_4$</td>
<td>Me</td>
<td>2b</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>3c</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>Me</td>
<td>2c</td>
<td>4-MeOC$_6$H$_4$</td>
<td>3b</td>
<td>84</td>
</tr>
<tr>
<td>13</td>
<td>Ph</td>
<td>Ph</td>
<td>2d</td>
<td>Ph</td>
<td>3a</td>
<td>75</td>
</tr>
<tr>
<td>14</td>
<td>Ph</td>
<td>Me</td>
<td>2a</td>
<td>NHMe</td>
<td>3h</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>Me</td>
<td>Me</td>
<td>2e</td>
<td>Ph</td>
<td>3a</td>
<td>85</td>
</tr>
</tbody>
</table>
In most cases, the presence of electron-donating or electron-withdrawing groups on the aromatic ring of 2 or 3 did not affect the times and the yields of the reactions. In fact, the majority of them reached completion after 5-10 minutes with excellent target products 5 yields (Table 2; entries 1, 2, 5–10, 12). In the absence of electronic effects, longer times were probably due to the low solubility of the solid amines 3c and 3d in 4 (Table 2; entries 3, 4, 11). The reactions was very fast and provides excellent yields even with aliphatic 2 (Table 2; entries 15, 16). On the other hand, in the
presence of the strong electron-withdrawing group CF₃, the reaction was difficult. It was necessary to heat the reaction mixture to 40 °C and to use 15 mol% of catalyst. However, the yield of 5c was quite good (Table 2; entry 17).

The reactions between aliphatic amines 3i or 3j, 2a and 4 did not occur because of the protonation of 3 by 1 (Table 2; entries 18, 19). However, it was possible to obtain 5r in the absence of 1 and the yield was quite good (Table 2; entry 18).

Steric effects were important for both 2 and 3. In fact the reaction with 3a, 4 and bulky 2d needed 15 mol% of 1 and heating at 40 °C for 6 hours (Table 2; entry 13). Moreover, although the reaction the reaction with 3h, 2a and 4 also needed 15% mol of 1; however, it was not necessary to heat it (Table 2; entry 14). In both cases the yields of 5m and 5n were good.

We also tested two different kinds of double Strecker reaction. It must be stressed that, to the best of our knowledge, this reaction using ketones as carbonyl partners, had only been performed previously by Matsumoto¹² and in that experiment it was done under high pressure. In the first case, we reacted 1,4-diaminobenzene (3k) with 2a or 2e and 4 in the presence of 10 mol% of 1 (Table 2; entries 21, 22). In the second, we reacted 1,4-diacetylbenzene (2i) with 3a or 3b again in the presence of 10 mol% of 1 (Table 2; entries 23, 24). In both cases we obtained excellent results.

As mentioned above, it has been reported that the aldehydes reacts easily without any catalyst in neat conditions.⁹ In fact, the reaction between 2h, 4 and 3a furnished 5t in almost quantitative yields after 15 min. The reaction was virtually instantaneous upon the addition of 1 (Table 2; entry 20).

With only four exceptions (Table 2; entries 14, 16–18), where compounds 5 were not solid, the work-up was very easy and convenient. It was sufficient to add H₂O to the crude residue, filter and wash the resulting solid with additional H₂O and a small amount of PE on a Buchner funnel. Furthermore, 1 was recovered in excellent yields (for example Table 3; entry 1, 89%), by simply evaporating the aqueous washings under reduced pressure. Recovered 1 was reused as a catalyst in another five consecutive reactions between 2a and 3a. The results are listed in Table 3. The reaction times increased after each run, but the yields of 5a and the recovery yield of 1 were consistently good.

**Table 3.** Consecutive runs with recovered 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time (min)</th>
<th>Yield (%) of 5a*</th>
<th>Recovery (%) of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>95⁵</td>
<td>91, 50 mg⁶</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>92</td>
<td>84, 42 mg²</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>90</td>
<td>81, 34 mg²</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>90</td>
<td>79, 27 mg¹</td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td>88</td>
<td>78, 21 mg⁷</td>
</tr>
<tr>
<td>6</td>
<td>45</td>
<td>88</td>
<td>76, 16 mg</td>
</tr>
</tbody>
</table>
Yields refer to the pure products. The reaction was performed with 5 mmol of 2a and 3a, 6 mmol of 4 and 5 mol % of 1 (55 mg, 0.25 mmol). Recovered 1 was used as a catalyst in entry 2. Recovered 1 was used as catalyst in entry 3. Recovered 1 was used as a catalyst in entry 4. Recovered 1 was used as a catalyst in entry 5. Recovered 1 was used as catalyst in entry 6.

Mechanism

Two different mechanisms have been proposed for this reaction in the literature (Scheme 2).

In the first one, the nitrogen atom of 3 carries out a nucleophilic attack on carbonyl group of 2 giving rise to an amino alcohol 7 which, by passing through an imine (or iminium ion) intermediate 8, affords 5 by the subsequent addition of CN⁻. An acid catalyst 6, interacting with the carbonyl group, facilitates the nucleophile attack of the nitrogen.

![Scheme 2](image)

Scheme 2 Mechanisms proposed in the literature for three-component Strecker reaction

In the second proposed mechanism, it was hypothesized that nucleophilic attack of CN⁻ occurs directly on 7, without passing through 8. Interestingly, Ma conjectured that the two mechanisms coexist.

The copious and homogeneous results collected in this work provide a good basis for some comments on the mechanism involved.

First of all, we decided to react 2a and 3a in the presence of 5 mol% of 1 and without 4 (see Collateral Proof 1 in Experimental). After 1 hour, the reaction mixture was quenched with water. GC-MS analyses showed that only a small amount of N-(1-phenylethylidene)benzeneamine 8a (about 4%) was present. On the other hand, a large amount of starting products 2a and 3a was detected. ¹H-NMR analyses (in anhydrous CDCl₃) performed on the crude residue before its quenching with water, showed the presence of a weak peak at δ = 2.18 ppm (see ¹H NMR spectrum on Supplementary Information). This could be the signal of the methyl group of 13a (see Scheme 3 below). In fact, ¹H-NMR analyses of the crude residue after its quenching with water, showed a small but significant shift (δ = 2.25 ppm) of this peak. In the literature, the reported δ of the methyl group of 8a is 2.25¹⁴ or 2.27¹⁴ ppm.
Interestingly, when the reaction was performed in the presence of 10 mol% of 1 (see Collateral Proof 4) a sharp increase in 13a (see Scheme 3) and, consequently, in 8a could be seen in both GC-MS and 1H-NMR analyses. However, upon adding 4 to the reaction mixture after 1 hour, aminonitrile 5a was formed almost immediately (see Collateral Proof 2). It must be stressed that we also obtained almost the same results when using MeCN as a solvent (see Collateral Proof 3).

A theoretical study of the acid-catalysed Strecker reaction (in MeCN) shows that this one takes place in two phases. These are illustrated in Schemes 3 and 4 while Figures 2 and 4 show the related enthalpy (dashed lines) and free energy (solid lines) profiles. To reduce the calculation times, OBS 1 was modelled by the acid HZ where the aromatic ring is substituted by a vinylidene.

Scheme 3  Mechanism of three-component acid-catalyzed Strecker reaction.  First phase

Figure 2  Enthalpy (dashed lines) and free energy (solid lines) profiles (in kcal mol\(^{-1}\)) for the first phase of the acid-catalysed Strecker reaction. See text and scheme 3 for the labels.
In the first phase (Scheme 3 and Figure 2), reactants 2a and 3a form a complex (2a•3a) which is followed by a reversible proton transfer from the acid ZH to the ketone yielding a new complex (9a•3a) between the protonated ketone (with Z as counterion) 9a and the aniline 3a. This equilibrium is followed by a transition structure (TS_{Add}) consisting of the very fast acid-catalysed nucleophilic addition of the aniline 3a to the protonated ketone 9a which yields the protonated adduct 10a. The catalytic role of acids in this reaction is well known and it has also been theoretically studied.\textsuperscript{15a} The second step (TS_{HZ-disp}) consists of the deprotonation of the nitrogen atom and the formation of the complex (11a) between the amino alcohol and ZH. This step is followed by the concerted asynchronous proton transfer and dehydration (through TS\textsubscript{HCO}, Figure 3) in 11a yielding a complex (12a) between the protonated imine and water. This process is the rate determining step of the first phase of the Strecker reaction and the energy (with respect to all reactants) of TS\textsubscript{HCO} is 0.5 kcal mol\textsuperscript{-1} in terms of enthalpy and 26.6 kcal mol\textsuperscript{-1} in term of Gibbs energy. Finally, the loss of H\textsubscript{2}O gives the free iminium (with its counterion Z) 13a, which is the reactant for the second phase of the reaction. As an alternative, 11a can also lose the acid (grey lines and labels in Figure 2) leaving the free amino alcohol 7a. However, this process is less competitive because it is reversible and less exoergic (in term of absolute free energy) than the irreversible dehydration and water loss (yielding 13a and H\textsubscript{2}O).

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure3.png}
\caption{Transition structure (TS\textsubscript{HCO}) for the rate determinin step of the first phase of the Strecker reaction}
\end{figure}

The energy profiles shown in Figure 2 take the isolated reactants as reference points for all energies. However, in neat conditions, the ketone and the aniline are already in tight contact, therefore the complex between these two reactants (2a•3a, \Delta G = 6.5 kcal mol\textsuperscript{-1}) is a better choice as a starting
point (and therefore as a reference for the energies). This leads to a general lowering of the free energy profiles because the reference is now the free energy of the complex. So, the free energy ($\Delta G^*_{\text{rds}}$ in Figure 2) of the rate determining transition structure ($\text{TS}_{\text{HCO}}$) is now 20.1 kcal mol$^{-1}$ ($\Delta H^*_{\text{rds}} = 4.9$ kcal mol$^{-1}$). In this condition phase 1 is exoergic both in term of enthalpy (-5.8 kcal mol$^{-1}$) and Gibbs free energy (-5.1 kcal mol$^{-1}$).

TMSCN 4 appears in the second phase of the reaction (Scheme 4) and can react with the iminium 13a (black energy profiles and labels in Figure 4) or with the deprotonated immine 8a (grey energy profiles and labels in Figure 4). The first pathway is the preferred as can be seen from the enthalpy and free energy profiles shown in Figure 4. This pathway is also the simplest because the formation of the complex (13a-4) between the reactants is immediately followed ($\text{TS}^\prime_{\text{add}}$, Figure 5) by the addition of 4 to the iminium yielding the final product 5a and 14 (trimethylsilyl bound to Z). The second pathway, after reaction with H$_2$O, yields the silanol 15. Indeed, instead of the latter, we detected on GC-MS analyses bis(trimethylsilyl) ether, possibly due of acid-catalyzed dehydration of 15.

![Scheme 4](image_url)  

**Scheme 4** Mechanism of three-component acid-catalysed Strecker reaction. Second phase.
Figure 4  Enthalpy (dashed lines) and free energy (solid lines) profiles (in kcal mol\(^{-1}\)) for the second phase of the acid-catalyzed Strecker reaction. See text and scheme 4 for the labels.

Figure 5  Transition structure (TS'\(_{\text{Add}}\)) for the rate determining step of the second phase of the Strecker reaction.

The rate determining step of this phase (TS'\(_{\text{Add}}\)) is also the slowest step of the whole Strecker reaction in MeCN. Its enthalpy (with respect to the reactants 2a, 3a, 4 and HZ) is quite low (4.9 kcal mol\(^{-1}\)) but its Gibbs energy is 28.7 kcal mol\(^{-1}\).
The alternative pathway requires, as its first step, the endothermic loss of the acid HZ from the iminium 13a. This process presents an unfavourable reaction enthalpy which is not fully compensated for by the entropy gain which in turn leads to positive reaction free energy (ΔG = 6.3 kcal mol⁻¹, to compare with the exoergic loss of HZ from 11a, ΔG = -8.2 kcal mol⁻¹). Therefore, the whole free energy reaction profile of this pathway, now starting from the free imine 8a, is raised with respect to the previous one. We will briefly describe it for the sake of comparison. The first step is the addition (through TS_{Si/Add}) of 4 to yield the Si adduct 16. Then, the Si-CN bond breaks in the rate determining step TS_{CN-Det} (ΔG = 22.1 kcal mol⁻¹, ΔH = 36.7 kcal mol⁻¹ with respect to reactants 2a, 3a and 4) leading to complex 17 which is followed by the addition of the cyanide (TS_{CN-Add}) yielding adduct 18. This intermediate, after reaction with H₂O (not shown) will lead to the final products 5a and 15.

As for the first phase of the reaction, we expect to find all species in tight contact in neat conditions, therefore, the starting point (and reference for the energies) for second phase should be the complex (13a•4) between the iminium and TMSCN. This leads again to a general lowering of the free energy profiles. The free energy (ΔG*_{rds} in Figure 4) of the rate determining transition structure (TS'_{Add}) is now 20.7 kcal mol⁻¹ (ΔH*_{rds} = 20.3 kcal mol⁻¹).

To combine the two phases in neat conditions, we should bear in mind that the starting point should be a complex of all the reactants but the acid (2a, 3a and 4). However, because 4 is not involved in the first phase, the smaller complex 2a•3a is already a reliable starting point (and energy reference point). Once the iminium 13a (located 5.1 kcal mol⁻¹ below the Gibbs energy of complex 2a•3a) is formed this reacts in the second phase with 4. Since we assume that 4 had already been present as “inactive spectator” from the very beginning, we also assume that its complex with the iminium (13a•4) presents the same energy as the iminium alone. Therefore, the free energy of TS'_{Add} with respect to the complex 2a•3a•4 would be 15.2 kcal mol⁻¹. Because the free energy of TS_{HCO} is, as had been estimated previously for these conditions, 20.1 kcal mol⁻¹, this is the rate determining step of the Strecker reaction in neat conditions. This value is 8 kcal mol⁻¹ lower than the value for the rate determining state in MeCN and explains why the reaction is much faster in neat conditions than in solvent (compare entries 4 and 5 in Table 1).

An important point of note in the second phase is that HZ (and therefore, 1) is made available for a new conversion of the reactants only after the reaction of 13a (the complex between the iminium and Z) with 4. In fact, after the dehydration of 11a, HZ is not available for further reaction because it is bound to the imine. This feature is confirmed by the experimental findings (see before) which show that, without 4, the reaction stops after the formation of an amount of iminium proportional to the amount of the acid 1. On the basis of the theoretical study, the intermediate specie between
phases 1 and 2 of the Strecker reaction should be 13a (and not 8a) seeing as dissociation here is thermodynamically unfavourable (although 8a is possibly the specie really detected in the analytical procedure). After reaction with 4, the acid is recycled into a new phase 1. This work would not be complete without the study of the three-component Strecker reaction without the acid catalyst. The mechanism is simple and Scheme 2 already contains all the necessary elements while Figure 6 shows the relative enthalpy and free energy profiles. As we were interested to simulate the neat conditions the complexes between reactants were assumed as starting points.

![Figure 6](image_url)

**Figure 6** Enthalpy (dashed line) and free energy (solid line) profiles (in kcal mol\(^{-1}\)) for the uncatalyzed Strecker reaction. See text and scheme 2 for the labels.

The first step is the nucleophilic addition of the aniline 3a to the ketone 2a. Without any other molecule, this step shows a very high free energy barrier (more than 40 kcal mol\(^{-1}\), see Supplementary data). This is not a surprise, similar values have already been encountered in other studies.\(^{15}\) However, in neat conditions a second aniline 3a molecule can assists the reaction leading to a distinct reduction in the barrier.\(^ {15a,c}\) Starting from a complex between the three reactants 3a-2a-3a, the free energy barrier (TS\(^{-}\)\_Add) is now 30 kcal mol\(^{-1}\), still 10 kcal mol\(^{-1}\) higher than the same step with acid catalyst. Moreover, the reaction is endoergic; the free energy of the amino alcohol 7a is 7 kcal mol\(^{-1}\) above that of the reactant complex. The second irreversible phase of the reaction is the exchange of the hydroxyl with the cyanide from the TMSCN 4. Its free energy barrier is 30.2 kcal mol\(^{-1}\). Taking into account the fact that we start from the adduct from the first phase, the free energy of this rate determining step (TS\(_{\text{Exch}}\), Figure 7) is 37.4 kcal mol\(^{-1}\). This value is 17.3 kcal mol\(^{-1}\) higher that the one found for the catalysed reaction (20.1 kcal mol\(^{-1}\)) and confirms
the fundamental role of the acid catalyst. The whole reaction (product is the complex between 5a and 15) is, in any case, exoergic by 24 kcal mol\(^{-1}\) in term of enthalpy and 28 kcal mol\(^{-1}\) in term of free energy.

![Figure 7 Transition structure (TS\_Exch) for the rate determining step of the uncatalyzed Strecker reaction](image-url)

**Use of a chiral catalyst**

We have very recently reported\(^\text{16}\) the preparation of a chiral derivative of 1, namely (R)-(\-)\-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (19, Figure 8).

![Figure 8. Chiral derivative of 1.](image-url)

We decided to test it as a chiral catalyst in this reaction. First of all we analysed 5a on a GC with a chiral column and its two enantiomers were clearly detected (see chromatogram 1 in Supporting Information). In an initial proof, reacting 2a, 3a and 4 in the presence of 5 mol% of 19 at room temperature we found a poor enantioselectivity (ee 32%, chromatogram 2 in Supplementary Information). There was, however, a slight increase in enantioselectivity (ee 56%, chromatogram 3 in Supporting Information) upon cooling the reaction to 0 °C. No significant results were obtained upon further cooling. It must be stressed that the catalytic asymmetric Strecker reaction has been
usually performed starting from imines\textsuperscript{17} and and has been described as a one-pot three-component Strecker reaction catalysed by a chiral catalyst in a few papers.\textsuperscript{8,17a} Although the results obtained with 19 as chiral catalyst are fairly good, further investigations into its role are currently underway.

**Conclusion**

In summary, a new application of the organocatalyst OBS (1) has been reported. This strong bench-stable Brønsted acid has been shown to efficiently catalyse the three-component Strecker reaction between ketones, amines and TMSCN in very easy and green conditions.

From the mechanistic point of view, the acid-catalysed three-component Strecker reaction has been found to take place in two phases: the first one consists of the nucleophilic addition of the aniline to the ketone and the subsequent dehydration to an imine; the second one consists of the formal addition of cyanide to the protonated imine. The Brønsted acid acts in all steps of this mechanism. In solvent (MeCN) the rate determining step (rds) appears in the second phase (TS\textsubscript{\text{Add}}) which presents an enthalpy of 4.9 kcal mol\textsuperscript{-1} and a Gibbs energy of 28.7 kcal mol\textsuperscript{-1} with respect to the reactants. In neat conditions, where all reactants but the acid are already in tight contact, the starting points are the complexes of all the reactants except the acid and the rds is now the dehydration (TS\textsubscript{H\text{CO}}, first phase) whose energies are: \(\Delta H = 17.3\) and \(\Delta G = 20.1\) kcal mol\textsuperscript{-1}.

The reaction mechanism is simpler without the acid catalyst but barriers are higher and the rds is found in the exchange of the hydroxyl group with the ciano group (TS\textsubscript{\text{Exch}}) whose energies (in neat conditions) are \(\Delta H = 32.1\) and \(\Delta G = 37.4\) kcal mol\textsuperscript{-1}. The fundamental role of the Brønsted acid is evident from the presence of lower energy barrier for the catalysed reaction. This had already been stressed in literature but the mechanism has never really been explored,\textsuperscript{7,8,11b} with one exception\textsuperscript{16c} where the catalytic role of the BINOL-phosphoric acid in the addition of HCN to the imine was fully explored.

The use of chiral catalyst (R)-(\textendash)-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimid (19) allowed us to obtain fair enantioselectivity.

**Theoretical method**

The reaction mechanism was investigated using the density functional method (DFT),\textsuperscript{18} with the recently developed functional M06-2X.\textsuperscript{19} All stationary points were optimised and characterised with the 6-31+G(d)\textsuperscript{20a,b} basis set and the nature of the critical points was checked by vibrational analysis.\textsuperscript{21} For the transition structures (TS), when the inspection of the normal mode related to the imaginary frequency was not sufficient to confidently establish its connection with the initial and
final stable species, IRC calculations were performed. The energy values are then refined through single-point calculations with the basis set 6-311+G(2df,p) and combined with the thermal corrections obtained with the smaller basis set to get enthalpy (H) and free energy values (G) at room temperature. Solvent effects (MeCN) were introduced both in geometry optimisation and single point calculations by the Polarized Continuum Method (PCM). Calculations were performed by the quantum package Gaussian 09-A.02. Figures 3, 5, 7 were obtained with the graphical program Molden.

Experimental

General

Analytical grade reagents and solvents were used and reactions were monitored by GC, GC-MS and TLC. Petroleum ether (PE) refers to the fraction boiling in the range 40–70 °C. Room temperature is 20–25 °C. Mass spectra were recorded on an HP 5989B mass selective detector connected to an HP 5890 GC, cross-linked methyl silicone capillary column. Chiral analyses were performed on a Perkin Elmer Autosystem GC connected to a J&W Scientific Cyclosil-B column; stationary phase: 30% heptakis (2,3-di-O-methyl-6-O-α-butyldimethylsilyl)-β-cyclodextrin in DB-1701. 1H NMR and 13C NMR spectra were recorded on a Brucker Avance 200 spectrometer at 200 and 50 MHz respectively. IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer as solutions in CHCl3. o-Benzenedisulfonimide (1) and (R)-(−)-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (19) were prepared as reported in the literature. All the reagents were purchased from Sigma-Aldrich. The structures and purity of the products 5a, 5b, 5d, 5g, 5h, 5i, 5l, 5m, 5o, 5p, 5q, 5r, 5t, 5u, 5w were confirmed by comparison of their physical and spectral data with those reported in the literature. Products 5n and 5v are known in the literature, but no physical and spectral data are reported. Satisfactory microanalyses were obtained for the new compounds 5c, 5e, 5f, 5j, 5k, 5x. Spectral and physical data of the known products 5 are reported on Supplementary Information.

2-Phenyl-2-phenylaminopropanenitrile (5a): representative procedure for the preparation of Strecker adducts 5

TMSCN (4; 0.60 g, 6 mmol) was added to a mixture of OBS (1; 5 mol %; 55 mg, 0.25 mmol), acetophenone (2a; 0.60 g, 5 mmol) and aniline (3a; 0.46 g, 5 mmol) The mixture was stirred at room temperature for 5 min until the GC and GC-MS analyses showed the complete disappearance of 2a and 3a and the complete formation of product 5a. The by-product bis(trimethylsilyl) ether,
MS (EI) m/z: (%) 162 [M⁺](10), 147 (100) was also detected. However, it was impossible to isolate it.

Cold water (20 ml) was added to the reaction mixture, under vigorous stirring. The resulting solid was filtered on a buchner funnel and washed with additional cold water (2 x 5 ml) and small amount of PE (5 ml). It was virtually pure (GC, GC-MS, ¹H NMR, ¹³C NMR) title compound 5a, a white solid; yield: 95% (1.05 g). The aqueous washings were collected and evaporated under reduced pressure. After the removal of the water, virtually pure (¹H NMR) o-benzenedisulfonimide (1) was recovered (50 mg, 91 % yield). The recovered 1 was employed in another five catalytic cycles under the conditions described above, reacting with 2a and 3; Table 3 reported the yields of 5a and the yields of recovered 1.

2-(4-Nitrophenylamino)-2-phenylpropanenitrile (5c): yellow solid; 1.08 g (yield 81%); mp 134–135 °C (EtOH). Found: C, 67.35; H, 4.92; N, 15.80. C₁₅H₁₃N₃O₂ requires: C, 67.41; H, 4.90; N, 15.72%. ¹H NMR (200 MHz, CDCl₃): δ = 1.95 (s, 3H), 5.21 (br s, 1H), 6.50 (d, J = 9.2 Hz, 2H), 7.33–7.52 (m, 5H), 7.95 (d, J = 9.2 Hz, 2H). ¹³C NMR (50 MHz, CDCl₃): δ = 33.1, 56.7, 115.8, 120.0, 120.7, 124.8, 126.4, 129.3, 142.9, 147.3, 148.3. MS (EI) m/z: (%) 240 [M⁺-HCN](72), 225 (100), 179 (60). IR (CHCl₃) ν (cm⁻¹): 3429 (NH), 2248 (CN).

2-(4-Fluorophenylamino)-2-phenylpropanenitrile (5e): pale grey solid; 1.10 g (yield 92%); mp 125–126 °C (EtOH). Found: C 75.05; H 5.39; F 7.82; N 11.74. C₁₅H₁₃FN₂ requires: C 74.98; H 5.45; F 7.91; N 11.66%. ¹H NMR (200 MHz, CDCl₃): δ = 1.87 (s, 3H), 6.41–6.48 (m, 2H), 6.72–6.81 (m, 2H), 7.32–7.40 (m, 3H), 7.53–7.58 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): δ= 33.3, 57.9, 115.6, 116.0, 117.6 (d, J₂ = 7.6 Hz), 120.9, 125.1, 128.9, 129.5, 140.0. 159.4 (d, J = 236.5 Hz). MS (EI) m/z: (%) 213 [M⁺-HCN](65), 198 (100). IR (CHCl₃) ν (cm⁻¹): 3431 (NH), 2256 (CN).

2-(2-Methoxyphenylamino)-2-phenylpropanenitrile (5f): pale brown solid; 1.06 g (yield 84%); mp 80–81 °C (EtOH). Found: C 76.08; H 6.44; N 11.15. C₁₆H₁₈N₂O requires: C 76.16; H 6.39; N 11.10%. ¹H NMR (200 MHz, CDCl₃): δ 1.93 (s, 3H), 3.86 (s, 3H), 4.90 (br s, 1H), 6.19–6.23 (m, 1H), 6.56–6.79 (m, 3H), 7.29–7.38 (m, 3H), 7.55–7.60 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): δ = 33.6, 55.7, 57.1, 109.8, 114.3, 119.4, 120.9, 125.1, 128.7, 129.4, 133.5, 140.4, 147.5. MS (EI) m/z: (%) 225 [M⁺-HCN](45), 210 (100). IR (CHCl₃) ν (cm⁻¹): 3430 (NH), 2258 (CN).

2-(4-Methoxyphenylamino)-2-(4-tolyl)propanenitrile (5j): pale grey solid; 1.13 g (yield 85%); mp 88–89 °C (EtOH). Found: C 76.59; H 6.87; N 10.54. C₁₇H₁₈N₂O requires: C 76.66; H 6.81; N 10.52%. ¹H NMR (200 MHz, CDCl₃): δ = 1.83 (s, 3H), 2.31 (s, 3H), 3.65 (s, 3H), 6.50 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H). ¹³C NMR (50 MHz, CDCl₃): δ = 26.6, 33.0, 55.7, 57.7, 114.3, 114.8, 117.7, 124.9, 128.4, 129.3, 129.8, 138.0,
153.4. MS (EI) m/z: (％) 239 [M⁺-HCN](70), 225 (100). IR (CHCl₃) ν (cm⁻¹): 3438 (NH), 2241 (CN).

2-(4-Nitrophenylamino)-2-(4-tolyl)propanenitrile (5k): yellow solid; 1.15 g (yield 82％); mp 102–103 °C (EtOH). Found: C 68.40; H 5.37; N 14.85. C₁₆H₁₃N₂O₂ requires: C 68.31; H 5.37; N 14.94％。¹H NMR (200 MHz, CDCl₃): δ = 1.95 (s, 3H), 2.32 (s, 3H), 5.04 (br s, 1H), 6.52 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H). ¹³C NMR (50 MHz, CDCl₃): δ 21.2, 33.2, 56.7, 113.6, 114.5, 124.7, 125.8, 126.6, 130.4, 135.6, 139.3, 149.3. MS (EI) m/z: (％) 254 [M⁺-HCN](75), 239 (100), 193 (50). IR (CHCl₃) ν (cm⁻¹): 3421 (NH), 2255 (CN).

2-(N-Methyl-N-phenylamino)-2-phenylpropanenitrile (5n): viscous oil; 0.86 g (yield 73％)。¹H NMR (200 MHz, CDCl₃): δ = 1.48 (s, 3H), 2.62 (s, 3H), 6.53–6.68 (m, 1H), 7.09–7.51 (m, 9H)。¹³C NMR (50 MHz, CDCl₃): δ = 31.3, 40.7, 66.2, 112.7, 117.4, 120.0, 128.5, 128.8, 129.1, 129.2, 129.4, 148.9. MS (EI) m/z: (％) 236 [M⁺](20), 208 (70), 118 (100), 77 (35). IR (CHCl₃) ν (cm⁻¹): 2249 (CN).

2,2’-(1,4-Phenylenediamino)bis(2-methylpropanenitrile) (5v): white solid; 1.11 g (yield 92％); mp 143–144 °C (EtOH)。¹H NMR (200 MHz, CDCl₃): δ = 1.60 (s, 12 H), 6.88 (s, 4H)。¹³C NMR (50 MHz, CDCl₃): δ = 27.9, 49.9, 115.8, 120.4, 138.4. MS (EI) m/z: (％) 188 [M⁺-2 HCN](85), 173 (100), 117 (30), 79 (22). IR (CHCl₃) ν (cm⁻¹): 3418 (NH), 2257 (CN).

2,2’-(1,4-Phenylenedioxy)bisanilino]bis[2-(4-methoxyphenylamino)propanenitrile] (5x): white solid; 1.74 g (yield 92％); mp 122–123 °C (EtOH). Found: C 73.38; H 6.19; N 13.09. C₂₉H₂₆N₄O₂ requires: C 73.33; H 6.14; N 13.14％。¹H NMR (200 MHz, CDCl₃): δ = 1.85 (s, 6H), 3.65 (s, 6H), 6.47 (d, J = 9.0 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 7.66 (s, 4H)。¹³C NMR (50 MHz, DMSO-d₆): δ = 32.5, 55.7, 57.6, 114.7, 117.2, 121.9, 126.3, 138.9, 141.5, 153.0. MS (EI) m/z: (％) 372 [M⁺-2 HCN](65), 357 (100). IR (CHCl₃) ν (cm⁻¹): 3429 (NH), 2255 (CN).

Collateral proofs

1. A mixture of 1 (5 mol％; 55 mg, 0.25 mmol), 2a (0.60 g, 5 mmol) and 3a (0.46 g, 5 mmol) was stirred at room temperature for 1 hour。¹H NMR (anhydrous CDCl₃) analysis of the reaction mixture showed, among others, a weak peak at δ = 2.18 ppm (probably the methyl group of 13a; see the spectrum on Supplementary Information). Then, the reaction mixture was poured into water and extracted with Et₂O (100 ml). On GC and GC-MS analysis of crude residue, a small amount of N-(1-phenylethylidene)benzeneamine (8a), MS (EI) m/z: (％) 195 [M⁺](60), 180 (100), 77 (35) was detected (about 4％) besides unreacted 2a and 3a. The ¹H NMR analysis of the crude residue showed the shift of the methyl group at δ = 2.25 ppm.
2. The formation of a white precipitate and the disappearance of 2a and 3a was observed almost immediately upon the addition of TMSCN (4; 0.60 g, 6 mmol) to a reaction mixture prepared as above. The precipitate was filtered on a buchner funnel and washed with additional cold water (2 x 5 ml) and small amount of PE (5 ml). It was virtually pure (GC, GC-MS, 1H NMR, 13C NMR) 5a, 1.00 g (yield 90%).
3. The reaction described in entry 1 was performed with MeCN as a solvent. We obtained almost the same results.
4. The reaction described in entry 1 was performed with 10 mol% (101 mg, 0.5 mmol) of 1. A significative increase in the quantity of 8a was observed. In fact, the amount of 8a increased up (about 9%) in GC analyses. Furthermore, the 1H NMR analyses of the reaction mixture (performed with anhydrous CDCl₃ and before its quenching with H₂O) showed an increase in the peak height at δ = 2.18 ppm.

**Chiral sulfonimide 19 as a catalyst**

4 (37 mg, 0.37 mmol) was added to a mixture of (R)-(-)-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (19; 5 mol%; 5 mg, 0.0154 mmol), 2a (37 mg, 0.308 mmol) and 3a (29 mg, 0.308 mmol) that had been cooled to 0 °C. The mixture was stirred at 0 °C for 3 hours until the GC and GC-MS analyses showed the complete disappearance of 2a and 3a and the complete formation of product 5a. After the same work-up as above, 5a was recovered (60 mg, 88 % yield). After analyzing 5a on a GC with a chiral column the presence of two enantiomers was found; ee was 56%. When the same reaction was performed at room temperature, the ee was only 32%. The GC spectra are reported in Supplementary Information. The reaction did not complete and ee was about 50% when the reaction was cooled to -10 °C, for 6 hours.

**Acknowledgments**

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Electronic supplementary information (ESI) available: 1. General procedure for the preparation of Strecker adducts 5; 2. 1H, 13C NMR, IR and MS data of known products 5a, 5b, 5d, 5g,5h, 5i, 5l, 5m, 5o, 5p, 5q, 5r, 5t, 5u, 5w; 3. 1H NMR and 13C spectra of unknown product 5c, 5e, 5f, 5j, 5k,5n,5v, 5x; 4. 1H NMR spectrum of the crude residue of the reaction described in the second collateral proof (see Experimental); 5. GC spectra of the reaction performed with chiral catalyst 19; 6. Tabulated energies (in a.u. and kcal mol⁻¹). 7. Cartesian coordinates. See DOI:
References


