o-Benzenedisulfonimide and its chiral derivatives as Brønsted acid catalyst for one-pot three-component Strecker reaction. Synthetic and mechanistic aspects.

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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 cianide (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 nucleophylic 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using either acids or bases as catalysts or organic solvents instead of H_2O.[3] In particular, the toxic HCN has been replaced by a number of safer cyanating agents.[3] They have generally been employed in the presence of Brønsted or Lewis acids,[4] Lewis bases,[5] metal complexes[6] or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_2Cl_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,[8] Nafion solid resins,[11c] alumina supported tungstosilicic acid,[11d] SBA 15 supported sulfonic acid,[11e] Sn montomorillonite,[2b] sulfamic acid-functionalized magnetic Fe_3O_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]

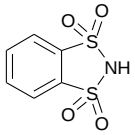

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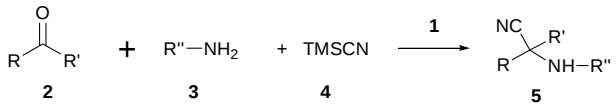
Figure 1 *o*-Benzenedisulfonimide (OBS) **1**

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**

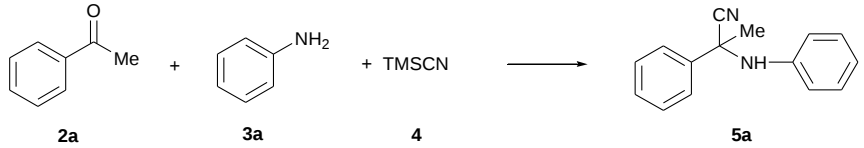
We have recently reported the use of OBS (**1**) in catalytic amounts as a safe, non-volatile and non-corrosive Brønsted acid in several acid-catalyzed organic reactions.[13a] The catalyst, that possess high acidity (pk_a -4.1 at 20 °C), was easily prepared,[13b] recovered and purified, ready to be used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



2a **3a** **4** **5a**

Entry	Solvent	Catalyst; mol %	Time	Yield (%) of **5a** [a,b]
1	neat	-	24 h	93
2	CH_2Cl_2	-	48 h	82
3	neat	**1;** 2	6 h	93
4	neat	**1;** 5	5 min	95
5	MeCN	**1;** 5	1h	92
6	CH_2Cl_2	**1;** 5	2 h	90
7	THF	**1;** 5	1 h	92
8	Toluene	**1;** 5	24 h	62[c]
9	H_2O	**1;** 5	24 h	41[c]
10	neat	HBF_4. Et_2O 54%; 5	12 h	80
11	neat	HCOOH; 5	24 h	43[c]
12	neat	$MeSO_3H$; 5	1 h	93
13	neat	NH_2SO_3H; 5	3 h	91
14	neat	2,4-$(NO_2)_2C_6H_3SO_3H$; 5	10 min	95

[a]Yields refer to the pure products. [b]Reactants **2a** and **3a** were in equimolar amounts (5 mmol). TMSCN (**4**) was in slight excess (6 mmol). [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_2O and PE.

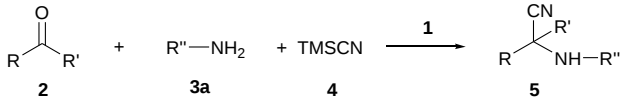
First of all, the reaction was performed without **1** in neat conditions and in an almost equimolar ratio (Table 1, entry 1) at room temperature. The target product, 2-phenyl-2-phenylaminopropanenitrile (**5a**) was obtained in a very good yield (93 %), exactly as reported by Onaka.[2b] The reaction time, however, was long (24 hours). The presence of a solvent (CH_2Cl_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%).

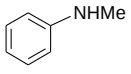
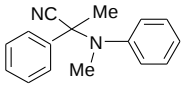
Polar, slightly polar solvents or H_2O were also tested (Table 1, entries 5–9). It was evident, however, that the best results were obtained in solvent-free reaction conditions. We performed the reaction in the presence of 5 mol% of five different Brønsted acids under neat conditions (Table 1; entries 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**.

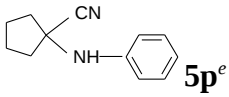
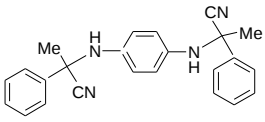
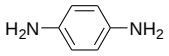
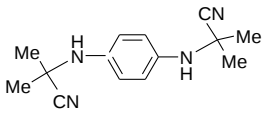
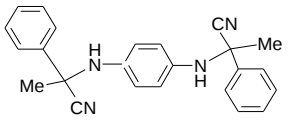
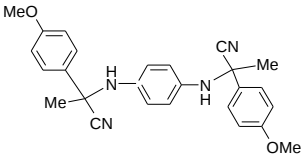
In the light of these results, six different ketones **2** and ten different amines **3** were reacted with **4**, usually in the presence of 5 mol% of **1** as a catalyst, at room temperature and under solvent-free conditions and provided excellent yields of α-aminonitriles **5** (average yields 85%).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

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



2 **3a** **4** **5**

Entry	R in **2,5**	R' in **2,5**		R'' in **3,5**		Products **5**	Yield (%)[a,b]	Time
1	Ph	Me	**2a**	Ph	**3a**	**5a**	95	5 min
2	Ph	Me	**2a**	4-$MeOC_6H_4$	**3b**	**5b**	92	5 min
3	Ph	Me	**2a**	4-$NO_2C_6H_4$	**3c**	**5c**	81	1 h
4	Ph	Me	**2a**	4-BrC_6H_4	**3d**	**5d**	73	2 h
5	Ph	Me	**2a**	4-FC_6H_4	**3e**	**5e**	92	10 min
6	Ph	Me	**2a**	2-$MeOC_6H_4$	**3f**	**5f**	84	5 min
7	Ph	Me	**2a**	3-$MeOC_6H_4$	**3g**	**5g**	84	5 min
8	4-MeC_6H_4	Me	**2b**	Ph	**3a**	**5h**	88	5 min
9	4-$NO_2C_6H_4$	Me	**2c**	Ph	**3a**	**5i**	81	10 min
10	4-MeC_6H_4	Me	**2b**	4-$MeOC_6H_4$	**3b**	**5j**	85	5 min
11	4-MeC_6H_4	Me	**2b**	4-$NO_2C_6H_4$	**3c**	**5k**	82	1 h
12	4-$NO_2C_6H_4$	Me	**2c**	4-$MeOC_6H_4$	**3b**	**5l**	84	10 min
13	Ph	Ph	**2d**	Ph	**3a**	**5m**[c]	75	6 h
14	Ph	Me	**2a**		**3h**	 **5n**[d,e]	73	2 h
15	Me	Me	**2e**	Ph	**3a**	**5o**	85	5 min

16		[f]	**2f**	Ph	**3a**	 **5p**[e]	85	10 min
17	CF_3	Me	**2g**	Ph	**3a**	**5q**[c,e]	72	5 h
18	Ph	Me	**2a**	$PhCH_2$	**3i**	**5r**[e,g]	75	24 h
19	Ph	Me	**2a**	*n*-Bu	**3j**	**5s**[g,h]	[i]	24 h
20	Ph	H	**2h**	Ph	**3a**	**5t**[j]	95	1 min
21	Ph	Me	**2a**		**3k**	 **5u**	87[k]	30 min
22	Me	Me	**2e**		**3k**	 **5v**	92[k]	5 min
23		[l]	**2i**	Ph	**3a**	 **5w**	95[m]	5 min
24		[l]	**2i**	4-$MeOC_6H_4$	**3b**	 **5x**	92[m]	5 min

[a]All the reactions were performed with 5 mol% of **1**. The reactants **2** and **3** were used in equimolar amounts (5 mmol). TMSCN was in slight excess (6 mmol). [b]Yields refer to the pure and isolated products. [c]The reaction was performed with 15 mol % of **1** and heating to 40 °C. [d]The reaction was performed with 15 mol % of **1** at room temperature. [e]The reaction mixture was poured into Et_2O-H_2O (50 ml, 1:1). The aqueous layer was separated and extracted with Et_2O (2 x 50 ml). The combined organic extracts were washed with H_2O (2 x 50 ml) and dried over Na_2SO_4. After solvent removal under reduced pressure, the crude residue was the virtually pure (GC, GC-MS, ^1H NMR, ^{13}C NMR) compounds **5**. [f]The reactant was cyclopentanone (**2f**). [g]The reaction was performed without catalyst **1**. In the presence of **1**, no traces of **5r** were detected. [h]The reaction was performed without catalyst **1**. [i]After 24 hours, only few traces of **5s** were detected on GC-MS analyses. MS (EI) : *m/z* (%) = 202 [M^+](1), 175 (80). [j]The reaction was performed without catalyst **1**, the reaction time was 15 min and the yields of **5t** 95%. [k]The reaction was performed with 10 mmol of **2a**, 5 mmol of **3n, 12** mmol of **4** and with 10 mol% of **1**. [l]The reactant was 1,4-diacetylbenzene (**2i**). [m] The reaction was performed with 5 mmol of **2i**, 10 mmol of **3a** or **3b, 12** mmol of **4** and 10 mol% of **1**.

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 CF_3, 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 Matsumoto[12] 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 H_2O to the crude residue, filter and wash the resulting solid with additional $H_2O$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**.

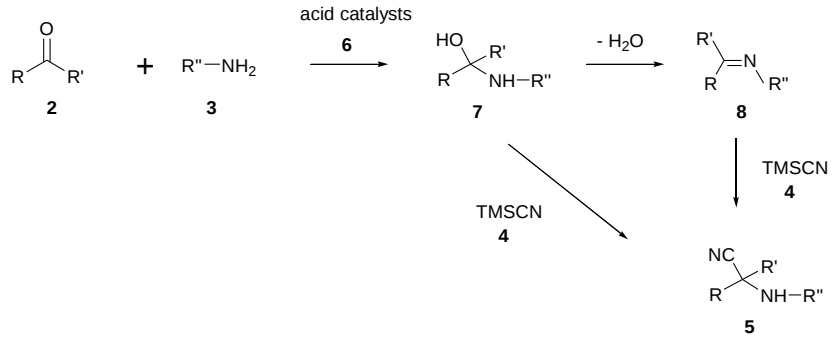
Entry	Time (min)	Yield (%) of **5a**[a]	Recovery (%) of **1**
1	5	95[b]	91, 50 mg[c]
2	15	92	84, 42 mg[d]
3	20	90	81, 34 mg[e]
4	30	90	79, 27 mg[f]
5	40	88	78, 21 mg[g]
6	45	88	76, 16 mg

[a]Yields refer to the pure products. [b]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). [c]Recovered **1** was used as a catalyst in entry 2. [d] Recovered **1** was used as catalyst in entry 3. [e]Recovered **1** was used as a catalyst in entry 4. [f] Recovered **1** was used as a catalyst in entry 5. [g]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^-.[4e,11b,12] An acid catalyst **6**, interacting with the carbonyl group, facilitates the nucleophile attack of the nitrogen.



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

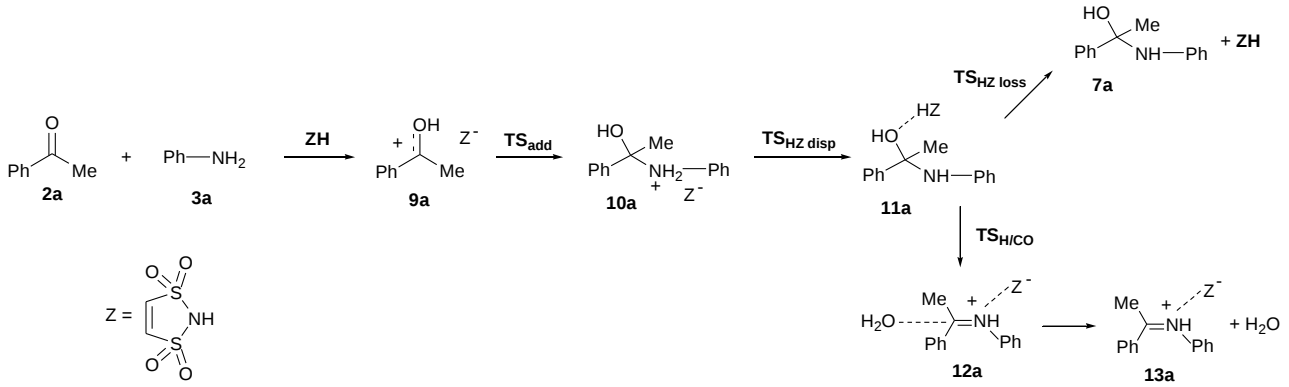
In the second proposed mechanism, it was hypothesized that nucleophilic attack of CN^- occurs directly on **7**, without passing through **8**.[7] Interestingly, Ma conjectured that the two mechanisms coexist.[8]

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. ^{1}H-NMR analyses (in anhydrous $CDCl_3$) performed on the crude residue *before* its quenching with water, showed the presence of a weak peak at δ = 2.18 ppm (see ^{1}H NMR spectrum on Supplementary Information). This could be the signal of the methyl group of **13a** (see Scheme 3 below). In fact, ^{1}H-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 2.25[14a] or 2.27[14b] 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 ^{1}H-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

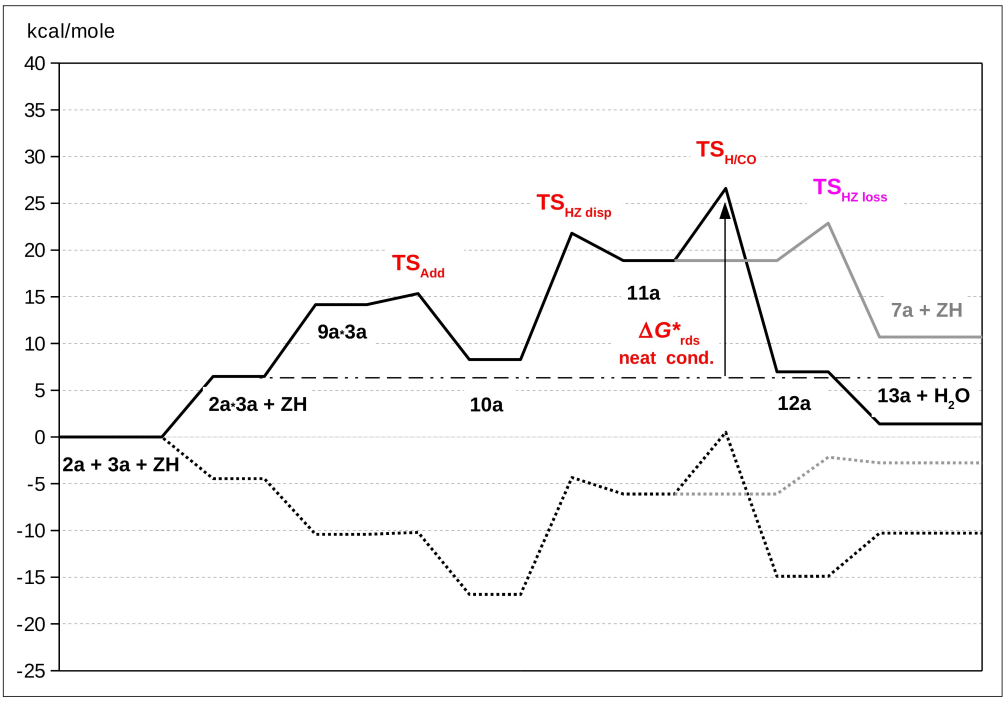


Figure 2 Enthalpy (dashed lines) and free energy (solid lines) profiles (in kcal mol^{-1}) for the first phase of the acid-catalysed *Strecker* reaction. See text and scheme 3 for the labels

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 $\mathbf{Z}^-$ as counterion) **9a** and the aniline **3a**. This equilibrium is followed by a transition structure ($\mathbf{TS_{Add}}$) 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.[15a] The second step ($\mathbf{TS_{HZ\text{-}disp}}$) 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 $\mathbf{TS_{H/CO}}$, 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 $\mathbf{TS_{H/CO}}$ is 0.5 kcal mol^{-1} in terms of enthalpy and 26.6 kcal mol^{-1} in term of Gibbs energy. Finally, the loss of H_2O gives the free iminium (with its counterion $\mathbf{Z}^-$) **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_2O) .

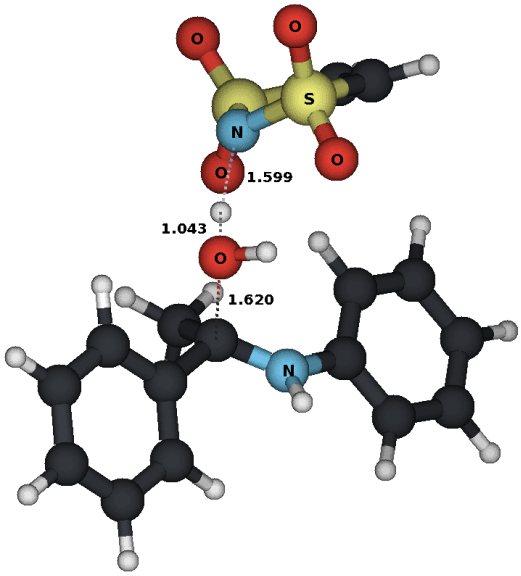
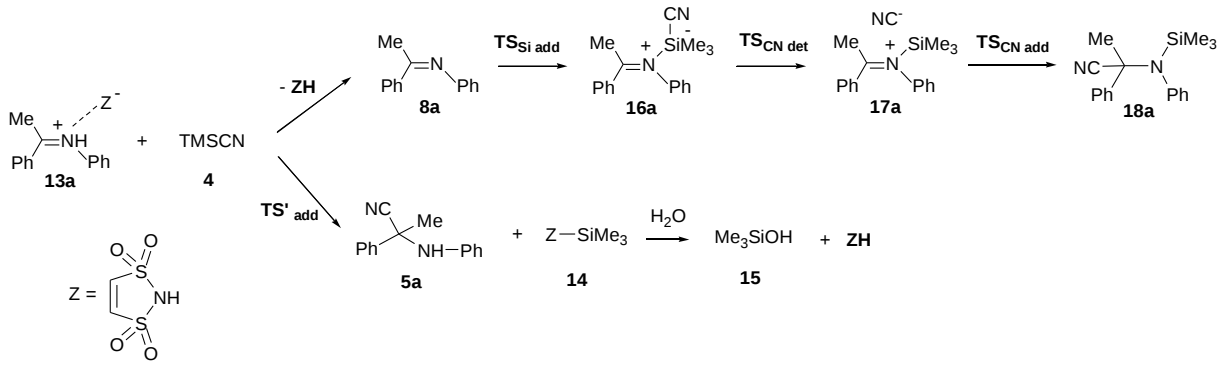


Figure 3 Transition structure ($\mathbf{TS_{H/CO}}$) for the rate determinin step of the first phase of the *Strecker* reaction

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**, ΔG = 6.5 kcal mol^{-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 (ΔG^*_{rds} in Figure 2) of the rate determining transition structure ($\mathbf{TS_{H/CO}}$) is now 20.1 kcal mol^{-1} (ΔH^*_{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 ($\mathbf{TS'_{Add}}$, Figure 5) by the addition of **4** to the iminium yielding the final product **5a** and **14** (trimethylsilyl bound to $\mathbf{Z^-}$). The second pathway, after reaction with H_2O, 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 Mechanism of three-component acid-catalysed *Strecker* reaction. Second phase.

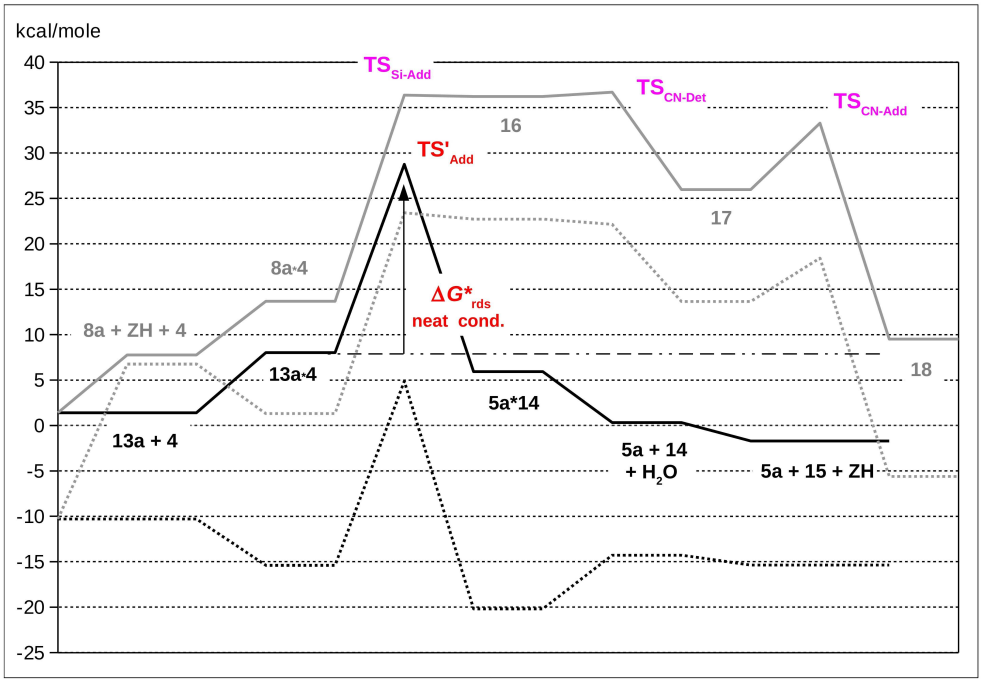


Figure 4 Enthalpy (dashed lines) and free energy (solid lines) profiles (in kcal mol^{-1}) for the second phase of the acid-catalyzed *Strecker* reaction. See text and scheme 4 for the labels

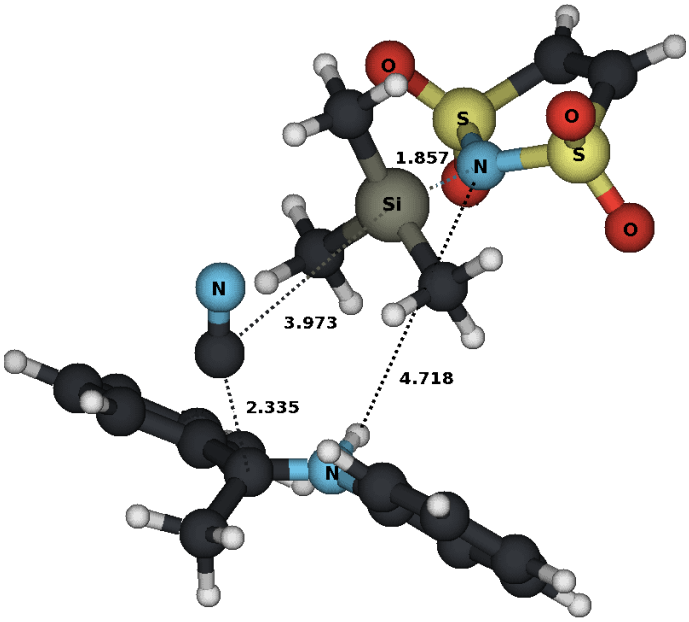


Figure 5 Transition structure (**TS'**$_{Add}$) for the rate determining step of the second phase of the *Strecker* reaction

The rate determining step of this phase (**TS'**$_{Add}$) 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 $\mathbf{TS}_{\mathbf{Si\text{-}Add}}$) of **4** to yield the Si adduct **16**. Then, the Si-CN bond breaks in the rate determining step $\mathbf{TS}_{\mathbf{CN\text{-}Det}}$ (ΔG = 22.1 kcal mol^{-1}, ΔG = 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 ($\mathbf{TS}_{\mathbf{CN\text{-}Add}}$) yielding adduct **18**. This intermediate, after reaction with H_2O (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 ($\boldsymbol{\Delta G^*_{rds}}$ in Figure 4) of the rate determining transition structure ($\mathbf{TS'_{Add}}$) is now 20.7 kcal mol^{-1} ($\boldsymbol{\Delta H^*_{rds}}$ = 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 $\mathbf{TS'_{Add}}$ with respect to the complex **2a*****3a*****4** would be 15.2 kcal mol^{-1}. Because the free energy of $\mathbf{TS_{H/CO}}$ 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 $\mathbf{Z}^-$) 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.

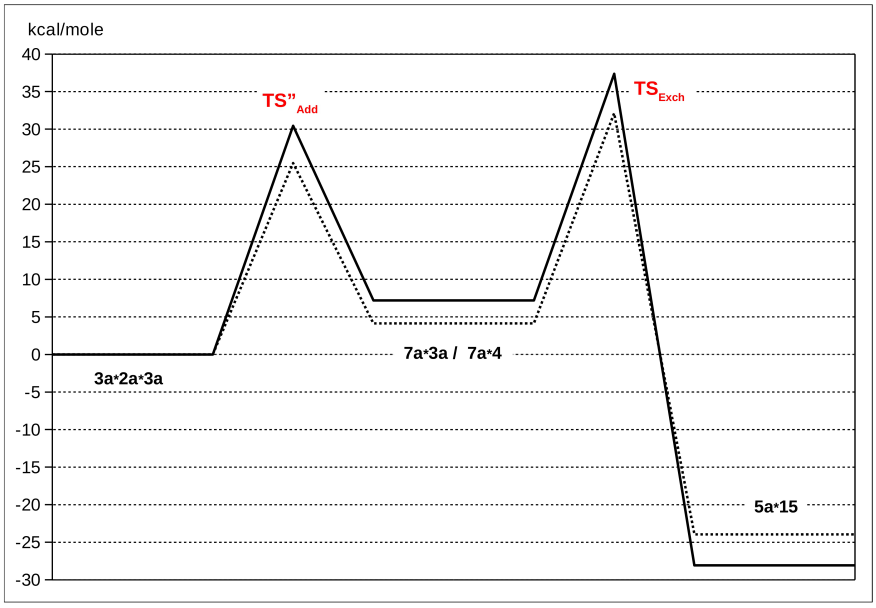


Figure 6 Enthalpy (dashed line) and free energy (solid line) profiles (in kcal mol^{-1}) for the uncatalyzed *Strecker* reaction. See text and scheme 2 for the labels.

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$_{Exch}$**, 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.

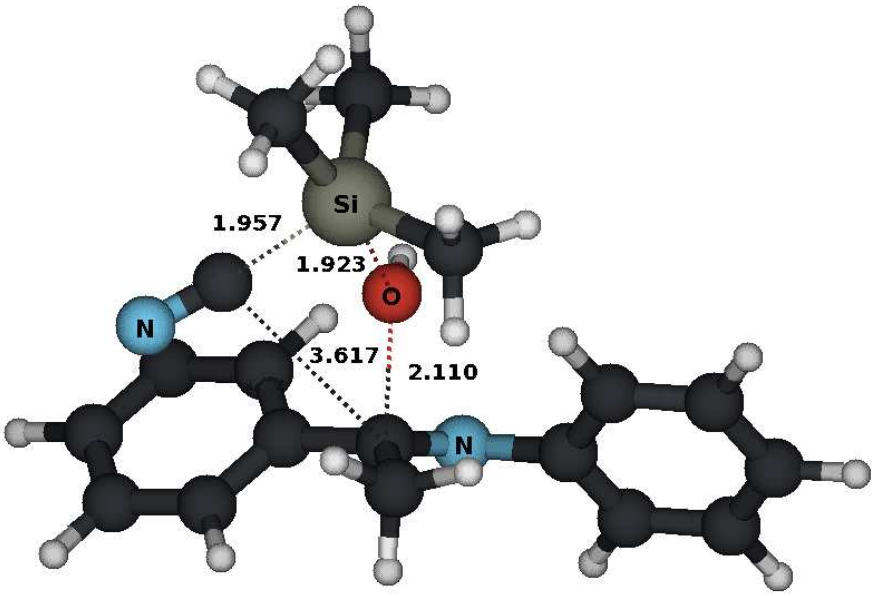
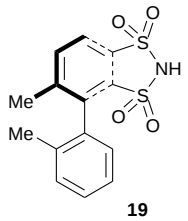


Figure 7 Transition structure ($\mathbf{TS_{Exch}}$) for the rate determining step of the uncatatalyzed *Strecker* reaction

Use of a chiral catalyst

We have very recently reported[16] the preparation of a chiral derivative of **1**, namely *(R)-(-)*-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (**19**, Figure 8).



19

Figure 8. Chiral derivative of **1**.

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[17] and and has been described as a one-pot three-component *Strecker* reaction catalysed by a chiral catalyst in a few papers.[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 nucleophylic 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'$_{Add}$**) which presents an enthalpy of 4.9 kcal mol^{-1} and a Gibbs energy of 28.7 kcal mol^{-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$_{H/CO}$**, first phase) whose energies are: ΔH = 17.3 and ΔG = 20.1 kcal mol^{-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$_{Exch}$**) whose energies (in neat conditions) are ΔH = 32.1 and ΔG = 37.4 kcal mol^{-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,[7,8,11b] with one exception[16c] where the catalytic role of the BINOL-phosphoric acid in the addition of HCN to the immine was fully explored.

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

Theoretical method

The reaction mechanism was investigated using the density functional method (DFT),[18] with the recently developed functional M06-2X.[19] All stationary points were optimised and characterised with the 6-31+G(d)[20a,b] basis set and the nature of the critical points was checked by vibrational analysis.[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[22] calculations were performed. The energy values are then refined through single-point calculations with the basis set 6-311+G(2df,p)[20c,d] 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).[23] Calculations were performed by the quantum package Gaussian 09-A.02.[24] Figures 3, 5, 7 were obtained with the graphical program Molden.[25]

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-*t*-butyldimethylsilyl)-β-cyclodextrin in DB-1701. ^{1}H NMR and ^{13}C 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 $CHCl_3$. *o*-Benzenedisulfonimide (**1**)[13a] and (*R*)-(-)-4-methyl-3-(2-tolyl)-1,2-benzenedisulfonimide (**19**)[16] were prepared as reported in the literature. All the reagents were purchased from Sigma-Aldrich. The structures and purity of the products **5a,**[12] **5b,**[8] **5d,**[8] **5g,**[8] **5h,**[11b] **5i,**[4e] **5l,**[8] **5m,**[2] **5o,**[8] **5p,**[11a] **5q,**[4c] **5r,**[11b] **5t,**[26] **5u,**[12] **5w**[12] were confirmed by comparison of their physical and spectral data with those reported in the literature. Products **5n**[27]and **5v**[28] 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, ^{1}H NMR, ^{13}C 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 (^{1}H 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. $C_{15}H_{13}N_3O_2$ requires: C, 67.41; H, 4.90; N, 15.72%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) 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. $C_{15}H_{13}FN_2$ requires: C 74.98; H 5.45; F 7.91; N 11.66%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): δ= 33.3, 57.9, 115.6, 116.0, 117.6 (d, J_2 = 7.6 Hz), 120.9, 125.1, 128.9, 129.5, 140.0. 159.4 (d, J_1 = 236.5 Hz). MS (EI) *m/z*: (%) 213 [M^+ -HCN](65), 198 (100). IR ($CHCl_3$) 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. $C_{16}H_{16}N_2O$ requires: C 76.16; H 6.39; N 11.10%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) 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. $C_{17}H_{18}N_2O$ requires: C 76.66; H 6.81; N 10.52%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) 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. $C_{16}H_{15}N_3O_2$ requires: C 68.31; H 5.37; N 14.94%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) ν (cm^{-1}): 3421 (NH), 2255 (CN).

2-(*N*-Methyl-*N*-phenylamino)-2-phenylpropanenitrile (5n): viscous oil; 0.86 g (yield 73%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.48 (s, 3H), 2.62 (s, 3H), 6.53–6.68 (m, 1H), 7.09–7.51 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) 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). ^{1}H NMR (200 MHz,$CDCl_3$): δ = 1.60 (s, 12 H), 6.88 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): 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 ($CHCl_3$) ν (cm^{-1}): 3418 (NH), 2257 (CN).

2,2'-(1,4-Phenylene)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. $C_{26}H_{26}N_4O_2$ requires: C 73.33; H 6.14; N 13.14%. ^{1}H NMR (200 MHz, $CDCl_3$): 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). ^{13}C 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 ($CHCl_3$) 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. ^{1}H NMR (anhydrous $CDCl_3$) 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 Et_2O (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 ^{1}H 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, ^{1}H NMR, ^{13}C 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 ^{1}H NMR analyses of the reaction mixture (performed with anhydrous $CDCl_3$ and before its quenching with H_2O) 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

This work has been supported by the University of Torino.

Electronic supplementary information (ESI) available: 1. General procedure for the preparation of Strecker adducts **5**; 2. ^{1}H, ^{13}C NMR, IR and MS data of known products **5a, 5b, 5d, 5g,5h, 5i, 5l, 5m, 5o, 5p, 5q, 5r, 5t, 5u, 5w**; 3. ^{1}H NMR and ^{13}C spectra of unknown product **5c, 5e, 5f, 5j, 5k,5n,5v, 5x;** 4. ^{1}H 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:

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