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Enhancement of the diastereoselectivity in the addition of trimethylsilyl cyanide to chiral aldimines by catalysis with a chiral 1,2-diamine: unexpected mechanistic results

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Abstract

The modest diastereoselectivity usually observed on addition of TMSCN to chiral imines derived from 1-phenylethylamine is considerably enhanced by the use of a catalytic amount of a chiral diamine. NMR monitoring of the reaction introduces some evidence for a product-catalysed reaction.

Among the wide range of synthetic routes to α-aminoacids, the historical Strecker synthesis remains the most direct chemical access to this important class of compounds.[1] Indeed, α-aminonitriles obtained by addition of hydrogen cyanide to imines can be directly converted into the corresponding acids by acidic hydrolysis. Therefore, stereoselective versions of this reaction, leading to enantio- or diastereoenriched α-aminonitriles, have been widely investigated.[2–6] Enantioselective catalytic Strecker reactions have been developed based either on the use of chiral Brønsted bases (addition of a 'chiral HCN') or of chiral lewis acids (addition of cyanide to a chiral complex).[3,4] However, these catalysts remain expensive and difficult to access. Several efficient diastereoselective Strecker reactions have been developed, frequently involving chiral amines as the auxiliaries.[5,6] For economic reasons, cheap 1-phenylethylamine appeared to be a nice alternative, but showed only modest diastereoselection (35<d.e.<56%), although fractional crystallization can often be used to afford a diastereomerically pure product.[7,8]

We report herein a way to improve diastereoselection in the addition of TMSCN to imines **1** derived from (*R*)-1-phenylethylamine, by addition of a catalytic amount of chiral diamine **2**,[9] and give an insight into the mechanism of this reaction.

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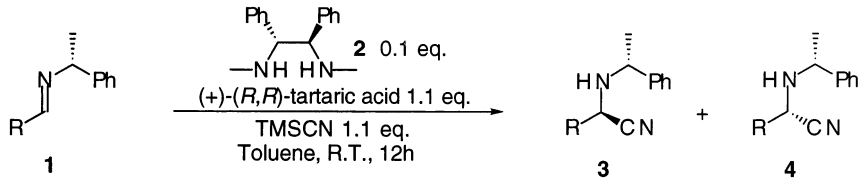
We first observed that (*R*)-**1a** (R = Ph) reacts with TMSCN in the presence of 1.1 equiv. of (*R*,*R*)-tartaric acid and 0.1 equiv. of diamine (*R*,*R*)-**2** (Scheme 1) with significant increase in the reaction rate and diastereoselectivity (12 h, **3a**/**4a** = 95:05), as compared with the reaction without these additives (6 days, **3a**/**4a** = 71:29).



Scheme 1.

On the basis of this result, the four different combinations of configurations of the three chiral species were tested. Any change in the configuration of the diamine and, more surprisingly, of the acid, led to a noticeable decrease in diastereoselectivity (reaching a minimum of 79:21 with an exchange of both diamine and tartaric acid), which implies that the two species are involved in the diastereoselection process. Furthermore, suppression of one of these two components simultaneously slowed down the reaction and eroded the diastereoselectivity. We then extended the previous reaction conditions to several aromatic and aliphatic aldimines. The results are collected in Table 1.

Table 1[a]

Imine	R-	d.r. **3**/**4**[b]	Yield (%)
1a	Ph	95:05 (71:29)	85
1b	3-Napht	94:06 (72:28)	86
1c	4-MeO–Ph	94:06 (80:20)	90
1d	3-Pyridyl	86:14 (79:21)	76
1e	*t*-Bu	79:21 (69:31)	78
1f	*c*-Hex	77:23 (71:29)	84

[a] The stereochemistry of **3** has been estimated from ^{1}H NMR spectra, on the basis of the study of Ogura (with R = Me) who established a correlation between the calculated most stable conformer of each diastereomer and the relative ^{1}H NMR shifts of the protons at the α-position to the cyano group (see Ref. 8d). Moreover, the stereochemistry of **3b** was confirmed by X-ray diffraction.

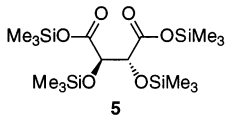
[b] The values in brackets correspond to the **3**/**4** ratio obtained with the non-catalysed addition of TMSCN to **1**.

This catalytic system exhibited a significant enhancement of the diastereoselectivity on aromatic imines **1a**–**c**, whereas its efficiency was less marked on the aromatic imine **1d** and aliphatic imines **1e**–**f**. The mixtures of α-aminonitriles **3**/**4** were obtained in good yields after purification.

In order to gain an insight into the mechanism, the experiment was carried out in toluene-d_8 and monitored by ^{1}H NMR spectroscopy, using **1a** as the starting material and 1 equiv. of *p*-methylanisole as an internal standard. It should be noted that this reaction reached completion within 5 hours, instead of the 12 hours initially required, which is probably a consequence of the higher concentration used for this experiment (0.2 vs 0.1 M).

As anticipated, HCN was produced in situ by reaction between tartaric acid and TMSCN, which is evidenced by the detection of tartaric derivative **5**. Less expected is the complete

silylation of the acid producing **5**,[†] whose structure was proven by independent synthesis of an authentic sample.[10]



5

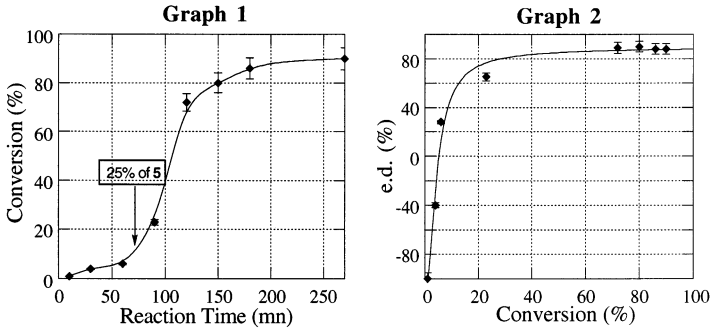


Figure 1.

The conversion profile related to the reaction time shows a slow evolution over 60 minutes, until 6% of product **3a**/**4a** is formed (Graph 1, Fig. 1). During this period, **5** is slowly produced, reaching the 25% maximum value (corresponding to the complete protolysis of TMSCN). The transformation of **1a** is dramatically accelerated and nearly complete in 90 minutes. The evolution of the diastereomeric excess in terms of the conversion is quite unusual (Graph 2, Fig. 1). Indeed, exclusive formation of **4a** (minor diastereomer) occurs at the early stage of the reaction (τ<4%); its production is essentially stopped to the benefit of **3a**. This is not observed when the same NMR experiment is carried out without diamine and tartaric acid (e.g. the d.r. is constant with conversion). This last observation implies that the system is either under thermodynamic control (and therefore evolves towards the formation of the most stable diastereomer) or subjected to autocatalysis. As a 77:23 **3a**/**4a** mixture has been submitted to our reaction conditions with no evolution of the ratio, we can consider that the kinetic evolution, the slow and exclusive formation of **4a** at the beginning of the reaction, are evidence for the involvement of **4a** in the transition state leading to the formation of **3a**. The roles of diamine **2** and tartaric acid remain unclear. An explanation of the influence of both reactants on diastereoselectivity would be the formation of an ammonium tartrate as one of the active species, although this salt has never been detected by ^{1}H NMR spectroscopy.

Carrying out the reaction with a small amount of **4a** as a catalyst was not possible as the diastereomers cannot be separated by any purification technique. This experiment would have brought further insight into the mechanism, as well as an expected enhancement of the diastereoselectivity.

In summary, we have developed a simple method to enhance the moderate diastereoselectivity usually observed upon addition of TMSCN to imines derived from 1-phenylethylamine, leading to diastereomeric ratios up to 95:05. ^{1}H NMR monitoring of the reaction provided some

[†] On the basis of this observation, reaction was expected to bring the same results with only 0.25 equiv. of acid. This was not the case, leading to a decrease in the reaction rate and diastereoselectivity, whereas 0.5 equiv. was perfectly efficient. This result confirms that tartaric acid does not only act as an 'HCN generator' but is also involved in the diastereoselection process. This was not predictable, considering the low solubility of tartaric acid in toluene.

evidence for an autocatalytic mechanism, in which the minor diastereomer is involved in the stereoselective formation of the major one.

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