Organocatalysis

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Catalytic Asymmetric Acylcyanation of Imines**

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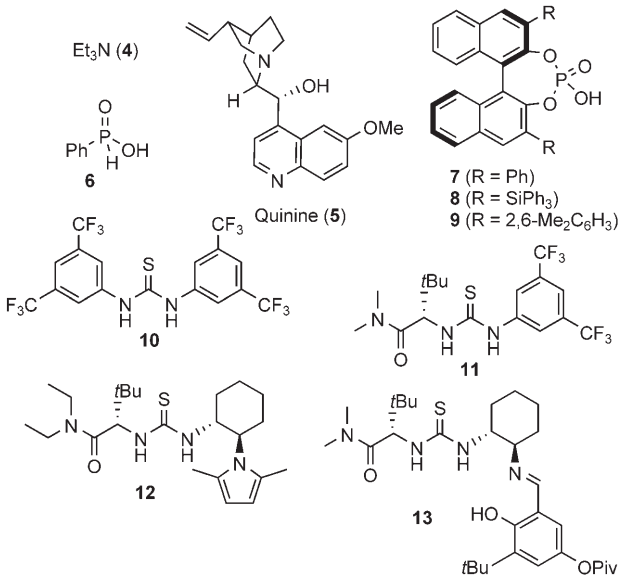
The Strecker reaction of preformed or in situ generated imines and hydrogen cyanide is arguably the most important method for the synthesis of α-amino acids.[1] Although there are already a number of useful and versatile variants of this transformation,[2,3] the Strecker reaction continues to challenge modern synthetic method development, and new variations are continuously being described. For example, the use of highly toxic and volatile HCN is problematic and therefore safer reagents are desirable. Herein we describe a novel variant of the Strecker reaction, the Brønsted acid catalyzed acetylcyanation of imines employing the conveniently useable and commercially available reagent acetyl cyanide (**1**). We identified thiourea catalyst **13** as an excellent and highly enantioselective catalyst of this (surprisingly) novel and perfectly atom-economic reaction.

A number of different cyanide sources have been proposed for the catalytic asymmetric Strecker reaction. In addition to HCN itself, trimethylsilyl cyanide (TMSCN), which generates HCN in the presence of an alcohol, has been used. In particular, the work of Jacobsen and co-workers[2] has led to a most versatile and broadly applicable catalyst of the Strecker reaction between preformed imines and HCN or TMSCN. Very recently, Maruoka and co-workers succeeded in developing yet another alternative approach by using the conveniently useable and nonvolatile potassium cyanide in a highly enantioselective phase-transfer-catalytic asymmetric Strecker reaction of preformed *N*-sulfonylated imines.[4]

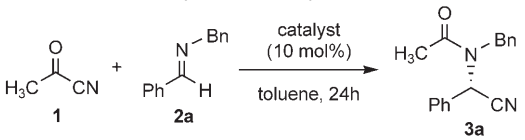
Remarkably, acetyl cyanide (**1**) has not yet been used in asymmetric Strecker reactions. Although this reagent and analogous α-oxonitriles have been used in the synthesis of cyanohydrin esters from carbonyl compounds,[5] its reaction with imines has been significantly less investigated. Thus, in 1958, Dornow and Lüpfert showed that α-oxonitriles readily react with imines to give the corresponding *N*-acylamino nitriles both in the absence of a catalyst and in the presence of a catalytic amount of triethylamine.[6] Realizing the potential of its reaction products for the synthesis of α-amino acids and their derivatives, we became interested in developing an asymmetric variant of this rarely used reaction.[7]

Building upon the observations of Dornow and Lüpfert,[6] we initially investigated chiral amines as catalysts of the reaction of benzaldehyde-derived imine **2a** with acetyl cyanide (Scheme 1, Table 1). Although triethylamine (**4**) is not a very active catalyst of this reaction, cinchona alkaloids, such as quinine (**5**), readily catalyzed the reaction at 0 °C but provided the racemic product **3a** (Table 1, entry 2). In addition to amines, we found Brønsted acid catalysts to significantly accelerate the reaction (Table 1, entry 3). We



Scheme 1. Brønsted bases and acids investigated as chiral catalysts for the asymmetric acylcyanation of imine **2a** (see Table 1). Piv = pivaloyl.

Table 1: Identification of an efficient catalyst for the asymmetric acylcyanation of imine **2a** (see Scheme 1).



Entry	Catalyst	*T* [°C]	Yield [%][a]	e.r.[b]
1	**4**	0	4	--
2	**5**	0	70	52:48
3	**6**	0	88	--
4[c]	**7**	−40	95	61:39
5[c]	**8**	−40	90	52:48
6[c]	**9**	−40	95	76:24
7	**10**	0	98	--
8	**11**	−40	99	60:40
9	**12**	−40	99	97:3
10	**13**	−40	98	>99:1

[a] Determined by GC. [b] Determined by HPLC. [c] Reaction time of 48 h.

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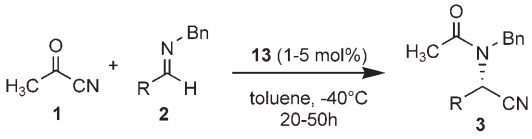
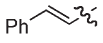
therefore investigated a number of chiral binol-derived phosphoric acid catalysts (Table 1, entries 4–6), which were recently introduced as powerful catalysts for a number of reactions[8] including the Strecker reaction.[9] Although the reaction of imine **2a** with acetyl cyanide **1** could be efficiently catalyzed with these catalysts, the highest achieved enantioselectivty (e.r. 76:24) was only modest. In the context of these studies, we then found that the reaction can not only be catalyzed by stronger, specific acid catalysts but also by hydrogen-bonding-type, general acid catalysts.[10] In particular, we identified the Schreiner thiourea catalyst **10** to be quite efficient in promoting the reaction (Table 1, entry 7).[11] Encouraged by this experiment, we also investigated chiral urea derivatives **11**–**13**, which are similar or identical to those introduced by Jacobsen and co-workers[2] (Table 1, entries 8–10). In particular, catalyst **13** turned out to be a highly enantioselective catalyst that formed the desired product in an essentially enantiomerically pure form (Table 1, entry 10). After further optimization, it was seen that this catalyst is generally applicable and catalyzes the reaction of acetyl cyanide with different imines in high yields and enantioselectivities (Table 2).

Table 2: Scope of the catalytic asymmetric acylcyanation of imines.



1 2 3

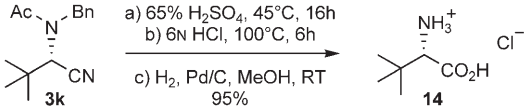
Entry[a]	R	Product	Yield [%][b]	e.r.[c]
1	Ph	**3a**	94	98:2
2	4-MeOC$_6$H$_4$	**3b**	95	98:2
3	4-ClC$_6$H$_4$	**3c**	87	99:1
4[d]	2-ClC$_6$H$_4$	**3d**	86	99:1
5	2-naphthyl	**3e**	92	98:2
6[d]	2-furyl	**3f**	94	94.5:5.5
7		**3g**	83	97:3
8[d]		**3h**	82	99:1
9[d]	*i*Pr	**3i**	87	97.5:2.5
10	*c*-hexyl	**3j**	88	96:4
11[d]	*t*Bu	**3k**	62	98:2
12[d]	*n*Bu	**3l**	76	97:3
13[d]	*t*BuCH$_2$	**3m**	87	98:2

[a] All reactions were run with 1 mol% of the catalyst, unless otherwise stated. [b] Yield of the isolated product after silica gel column chromatography. [c] Determined by HPLC. [d] 5 mol% of the catalyst.

As can be seen, the reaction gives products in very high enantioselectivities with all aromatic, heteroaromatic, aliphatic-branched and -unbranched, and unsaturated imines. Interestingly, the enantioselectivity depends on, among another things, the catalyst loading. For example, if the reaction of imine **2i** was run in the presence of 1 mol% of the catalyst, the desired product was obtained with an e.r. value of only 78:22. However, with 2 mol%, the e.r. value was 96:4 and reached 98:2 with 5 mol% of the catalyst (Table 2, entry 9). Additional increases in the catalyst loading did not improve the e.r. value any further. Presumably, uncatalyzed or substrate-catalyzed background reactions play a role at lower catalyst loadings.

Currently, we speculate that the reaction proceeds through an *N*-acyl iminium ion intermediate.[12] Its reaction with cyanide may be mediated by the hydrogen-bonding catalyst, which could activate cyanide or the *N*-acyl iminium ion, or both. Alternatively, a small amount of HCN may be released from the reagent to give the normal *N*-benzyl Strecker product. This product could, in turn, react with acetyl cyanide to form product **3** and regenerate HCN. That our reaction and that of Jacobsen and co-workers[2] both produce the same enantiomer suggests mechanistic similarities and possibly a similar transition-state structure.

The *N*-acylated products of the reaction (i.e. **3k**) can be readily converted into α-amino acids and their salts (i.e. **14**) in high yields and without racemization through acid-mediated hydrolysis and hydrogenolysis [Eq. (1)].



3k e.r. = 97.5:2.5 **14** e.r. = 97.5:2.5 (1)

In summary, we have developed an efficient and potentially useful new reaction, the Brønsted acid catalyzed acylcyanation of imines with acetyl cyanide as the cyanation reagent. The desired products **3** are formed in excellent yields and enantioselectivities if the readily available imines **2** are treated with acetyl cyanide (**1**) in the presence of catalyst **13**. Acetyl cyanide is commercially available and, as a liquid, is convenient to use. The scope of the acetylcyanation is remarkably high, and both aliphatic and aromatic imines can be used. Beyond its obvious use for the synthesis of amino acids and their derivatives, a powerful application of our reaction can be foreseen in the asymmetric synthesis of diverse sortiments of α-amidonitriles from three components, aldehydes, amines, and alkanoyl cyanides. The reaction may therefore find use in diversity-oriented synthesis and medicinal chemistry.

Experimental Section

General procedure: Imine **2** (0.5 mmol) and catalyst **13** (1–5 mol%) were placed into a dry Schlenk flask, dry toluene (1 mL) was added to the mixture, and the flask was then cooled under argon to −40°C. After stirring for 10 min, acetyl cyanide (50 μL, 1.5 equiv) was added to the mixture and stirred for a further 20–50 h at −40°C. The mixture was directly subjected to silica gel column chromatography (hexanes/ethyl acetate) to give the pure product **3**.

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