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The Catalytic Acylcyanation of Imines

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Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: The catalytic acylcyanation of aldimines with acylcyanides and a direct three-component variant involving the generation of an imine in situ have been developed. Furthermore, a highly enantioselective version has been established, culminating in the first organocatalytic asymmetric three-component Strecker reaction. Jacobsen thiourea catalysts were found to catalyze the reaction with excellent enantioselectivities, whereas binol phosphates (binol = 1,1′-bi-2,2′-naphthol) proved to be catalytically active but only modestly enantioselective. A large number of different substrates could be used in the processes described, thus illustrating the potential of our reaction for the generation of diversity within the attractive α-amino carbonyl framework. Furthermore, a novel cyclic amidine was obtained from the reaction of acetyl cyanide with ketimines.

Keywords: acylcyanation · enantioselectivity · imines · multicomponent reactions · organocatalysis

Introduction

Discovered in 1850,[1] the Strecker reaction has been identified as one of the most efficient methods for the preparation of α-amino nitriles, which are useful intermediates in the synthesis of α-amino acids.[2] In recent years, considerable effort has been devoted toward the development of asymmetric Strecker reactions.[3,4] Despite rapid progress in this field, volatile and highly toxic HCN is used in most Strecker variants. As an alternative, trimethyl silyl cyanide (TMSCN) is also used. However due to its high toxicity and price, access to alternative cyanation reagents is desirable. Acyl cyanides are less toxic and have previously been used for the acylcyanation of carbonyl compounds.[5] Surprisingly, however, the reaction of acyl cyanides with imines has not been investigated very much. 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] A survey of the literature revealed that there are no other catalytic versions of this reaction. Realizing the potential of the stable products of the *N*-acylamino nitrile reaction for the synthesis of α-amino acids and their derivatives, we became interested in developing a catalytic as well as asymmetric version of this rarely used reaction.[7] We recently described the development of a thiourea-catalyzed acylcyanation of imines and also showed that this reaction can be conducted as a three-component reaction by generating the imine in situ.[8,9] Moreover, the Jacobsen thiourea catalysts were identified to be effective and highly enantioselective catalysts for both the acylcyanation of imines as well as its three-component variant.[10,11] Herein we present the full details of our studies. We also show how our attempts at extending the chemistry to ketimines led to the development of a new synthesis of cyclic amidines.[12]

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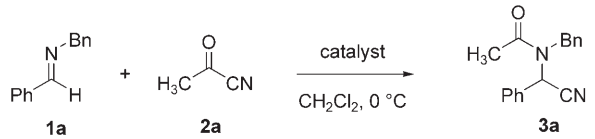
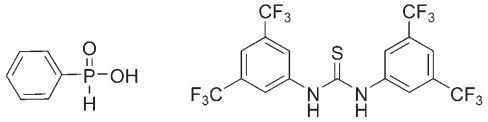
Results and Discussion

Catalytic Acylcyanation of Aldimines

Building upon the observations of Dornow and Lüpfert, we initially investigated triethylamine as catalyst for the reaction of benzaldehyde-derived imine **1a** with acetyl cyanide (**2a**); however, only 4% conversion into the product **3a** was obtained with dichloromethane as the solvent (Table 1, entry 1). Reasoning that in addition to base catalysis, an acid-catalyzed pathway should be possible as well, we next investigated different Brønsted acid catalysts to promote the reaction. Whereas highly acidic TFA did not give any conversion (Table 1, entry 2), moderately acidic phenyl phosphinic acid (**4**) gave good conversion (Table 1, entry 3). We then found that the reaction can be catalyzed not only by

Table 1. Catalytic acylcyanation of imine **1a**.





Entry[a]	Catalyst	[mol%]	*t* [h]	Conv. [%][b]
1	Et_3N	20	72	4
2	TFA	20	72	0
3	**4**	20	24	90
4	**5**	10	24	99
5	**5**	2	24	98
6	**5**	1	24	93

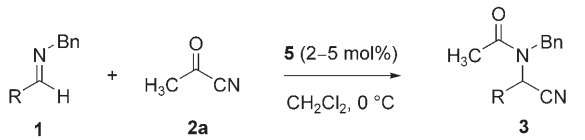
[a] All reactions were performed with 0.1 mmol of imine **1a** with 0.15 mmol of acetyl cyanide (**2a**). [b] Determined by GC. Bn = benzyl, TFA = trifluoroacetic acid.

stronger, specific acid catalysts but also by hydrogen-bonding-type, general acid catalysts.[13] In particular, the Schreiner thiourea catalyst **5**[14] was found to be quite efficient in promoting the reaction (Table 1, entry 4). A decrease in catalyst loading from 10 mol% to 2 mol% essentially preserved the conversion (Table 1, entry 5), but a decrease to only 1 mol% lowered the yield somewhat (Table 1, entry 6). Consequently, 2–5 mol% of catalyst **5** was used in subsequent experiments.

Using dichloromethane as the solvent and thiourea **5** as the catalyst (2–5 mol%), we explored the scope of this reaction (Table 2). The selected reaction conditions turned out to be broadly useful for a variety of substrates. Both aromatic aldimines (Table 2, entries 1–4) with electron-donating and -withdrawing substituents as well as heteroaromatic aldimines (Table 2, entries 5 and 6) can be used with comparable efficiencies. Furthermore, aliphatic branched, unbranched, and unsaturated aldimines can also be employed to give moderate to good yields of the desired product **3** (Table 2, entries 7–10).[8]

Abstract in German: Die katalytische Acylcyanierung von Iminen mit Acetylcyanid und ihre direkte Dreikomponentenvariante wurden entwickelt. Darüber hinaus konnte eine hoch-enantioselelektive Version beschrieben werden, die schließlich zur Entdeckung der ersten organokatalytischen asymmetrischen Dreikomponenten-Strecker-Reaktion führte. Jacobsens Thioharnstoff-Katalysatoren katalysieren die Reaktion mit hohen Enantioselektivitäten während Binol-Phosphorsäuren die Reaktion zwar katalysieren, aber dabei nur mäßige Enantioselektivitäten liefern. Eine Reihe verschiedener Substrate konnten in den beschriebenen Verfahren eingesetzt werden, wobei das Potential der Reaktion für die Erzeugung von Diversität innerhalb der attraktiven α-Aminocarbonyl Substratklasse illustriert wurde. Darüber hinaus wurde eine neue Klasse zyklische Amidine in der Reaktion von Acetylcyanid mit Ketiminen erzeugt.

Table 2. Catalytic acylcyanation of various imines.



Entry[a]	R	*t* [h]	Yield [%][b]
1	Ph	24	88
2	4-$MeOC_6H_4$	24	84
3	4-ClC_6H_4	24	79
4	2-ClC_6H_4	24	83
5	2-furyl	24	67
6	3-pyridyl	24	96
7[c]	*i*Pr	48	76
8[c]	*t*Bu	48	64
9[c]	1-cyclohexenyl	48	82
10[c]	*t*$BuCH_2$	48	81

[a] All reactions were performed with 2 mol% of the catalyst unless otherwise stated. [b] Yield of pure product after silica-gel column chromatography. [c] 5 mol% of the catalyst was used.

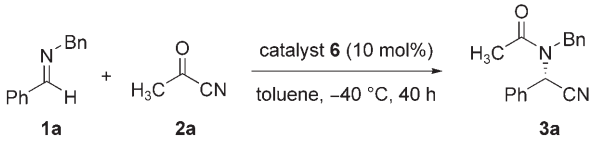
Catalytic Asymmetric Acylcyanation of Aldimines

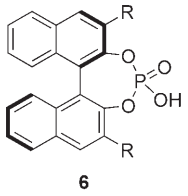
To develop an asymmetric version of our acylcyanation, we initially prepared several chiral binol-derived phosphoric acid catalysts (**6a–m**; binol = 1,1′-bi-2,2′-naphthol), which were recently introduced as powerful catalysts for a number of reactions by Akiyama and Terada and their co-workers.[15] As demonstrated by Rueping et al., chiral phosphoric acids also catalyze the Strecker reaction with high enantioselectivities.[4i] However, although we found that these catalysts gave N-acetylated amino nitrile product **3a** in high yields, the enantioselectivities were only moderate (Table 3, entries 1–13). In the best case, the use of catalyst **6m** led to **3a** with 58% *ee* (Table 3, entry 13). We also prepared 1,1′-binaphthyl-2,2′-disulfonic acid (**6n**);[16] however, it gave the racemic product **3a** with moderate conversion (Table 3, entry 14).

We then prepared a range of chiral thiourea catalysts **7–12**, some of which are similar or identical to those introduced by Jacobsen and co-workers.[3] Catalyst **7** and **8** gave an almost-racemic product (Table 4, entries 1 and 2). Catalyst **9** provided product **3a** in moderate enantioselectivity (Table 4, entry 3). The best results were obtained with catalysts **10–12** (Table 4, entries 4–6). Remarkably, catalysts **11** and **12** gave the product essentially in enantiomerically pure form. These thiourea derivatives were previously developed by Jacobsen and co-workers as highly enantioselective catalysts for the asymmetric Strecker reaction of preformed imines with HCN.[3]

In the further optimization, we tried to lower the catalyst loading and found that 1 mol% of catalyst **11** is sufficient to give the product in high yield as well as with excellent enan-

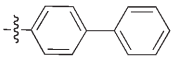
Table 3. Catalytic asymmetric acetylcyanation of imine **1a** with catalyst **6**.

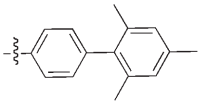


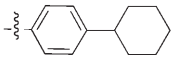


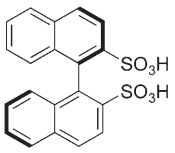
6

6a (R = Ph)
6b (R = 2-naphthyl)
6c (R = 2,4,6-*i*Pr$_3$C$_6$H$_2$)
6d (R = 4-NO$_2$C$_6$H$_4$)
6e (R = 3,5-Me$_2$C$_6$H$_3$)
6f (R = SiPh$_3$)
6g (R = 9-anthracenyl)
6h (R = 9-phenanthryl)

6i R = 

6j R = 

6k R = 



6n

6l R = CHPh$_2$
6m R = 2,6-Me$_2$C$_6$H$_3$

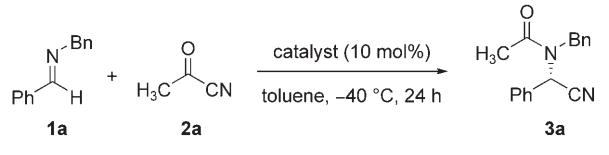
Entry[a]	Catalyst	Conversion [%][b]	*ee* [%][c]
1	**6a**	95	20
2	**6b**	95	14
3	**6c**	95	16
4	**6d**	92	10
5	**6e**	95	16
6	**6f**	90	4
7	**6g**	70	24
8	**6h**	70	34
9	**6i**	95	20
10	**6j**	95	30
11	**6k**	90	22
12	**6l**	90	40
13	**6m**	95	52
14	**6n**	68	0

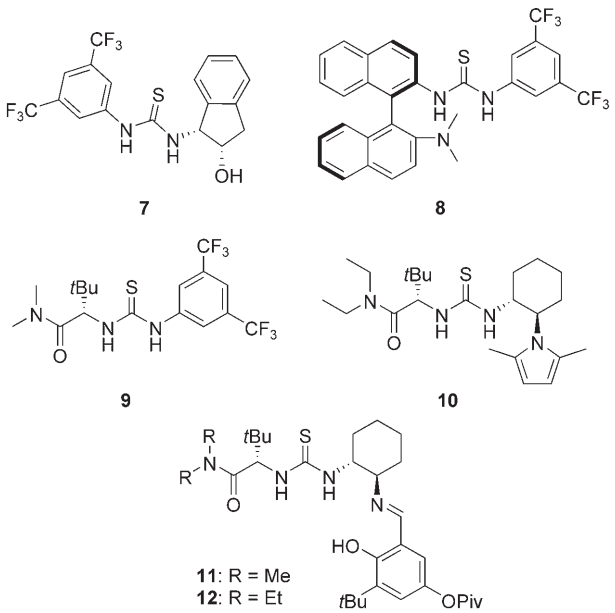
[a] Reaction conditions: Aldimine **1a** (0.1 mmol), acetyl cyanide (**2a**; 0.15 mmol), and catalyst **6** (0.01 mmol) were stirred together at –40 °C in dry toluene (0.5 mL). [b] Determined by GC. [c] Determined by HPLC.

tioselectivity. This catalyst was then investigated with a number of different imines (Table 5), and it was found that products with very high enantioselectivities were obtained with aromatic, heteroaromatic, aliphatic branched and unbranched, and unsaturated imines. Notably, high enantioselectivity (96% *ee*) was observed for the important pivalaldehyde-derived imine **1k**.[10]

N-Acylated α-amino nitrile **3k** was converted into *t*-leucine salt **13** by acid-mediated hydrolysis and hydrogenolysis (Scheme 1). Compound **3k** was first converted into the N-acylated amino acid **14**, which was further hydrolyzed to obtain carboxylic acid **15**. The benzyl group was then removed by hydrogenation. The amino acid salt **13** obtained was converted into *N*-Fmoc amino acid **16** with 95% *ee*. An authentic sample of this compound was independently prepared form L-*t*-leucine, and the absolute configuration of our product was determined to be *S*. Notably, the stereochemistry of our reaction products is the same as in the case of the Strecker reaction performed by Jacobsen and coworkers.

Table 4. Catalytic asymmetric acetylcyanation of imine **1a** with thiourea catalysts.





7 8 9 10

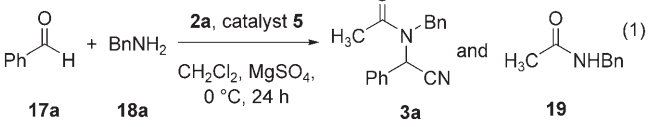
11: R = Me
12: R = Et

Entry[a]	Catalyst	Conversion [%][b]	*ee* [%][c]
1	**7**	99	2
2	**8**	99	2
3	**9**	99	20
4	**10**	98	94
5	**11**	99	>98
6	**12**	99	>98

[a] Reaction conditions analogous to those described in Table 3 were used. [b] Determined by GC. [c] Determined by HPLC.

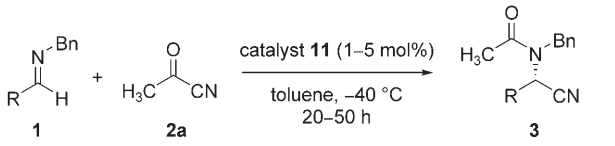
Three-Component Catalytic Acylcyanation of Aldimines

In an attempt to circumvent imine preformation and develop an in situ three-component variant, we initially found that stirring of benzaldehyde (**17a**), benzylamine (**18a**), $MgSO_4$, catalyst **5**, and acetyl cyanide (**2a**) at 0 °C for 24 h in dichloromethane resulted in poor yield of the desired product **3a** and considerable side-product formation. Not unexpectedly, a considerable amount of *N*-benzyl acetamide (**19**) was formed, which resulted from the direct reaction of benzylamine with acetyl cyanide [Eq. (1)].



(1)

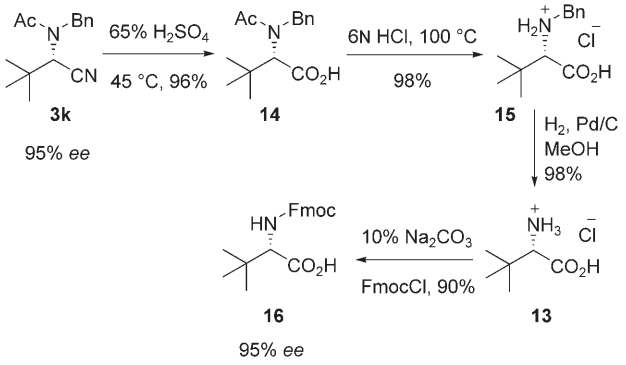
Table 5. Scope of the catalytic asymmetric acylcyanation.



1 2a 3

Entry[a]	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**3a**	94	96
2	4-$MeOC_6H_4$	**3b**	95	96
3	4-ClC_6H_4	**3c**	87	98
4[d]	2-ClC_6H_4	**3d**	86	98
5	2-naphthyl	**3e**	92	96
6[d]	2-furyl	**3f**	94	89
7		**3g**	83	94
8[d]	1-cyclohexenyl	**3h**	82	98
9[d]	*i*Pr	**3i**	87	95
10	cyclohexyl	**3j**	99	92
11[d]	*t*Bu	**3k**	62	96
12[d]	*n*Bu	**3l**	76	94
13[d]	$tBuCH_2$	**3m**	87	96

[a] All reactions were performed 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 was used.

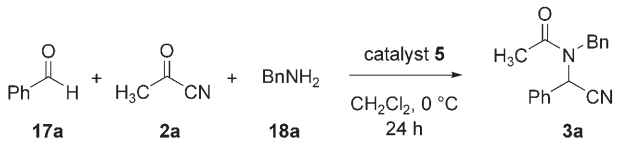


Scheme 1. Conversion of α-amino nitrile **3k** to the α-amino acid salt **13** and determination of the absolute configuration. Fmoc = 9-fluorenylmethoxycarbonyl.

We envisioned that to suppress this side reaction, the order of reagent mixing may be crucial. Thus, when acetyl cyanide was added last, significant conversion into the desired product was realized (Table 6, entry 1). Interestingly, use of molecular sieves as the drying reagent further improved the conversion (Table 6, entry 2). The best result was obtained when the mixture of aldehyde, amine, additive, and catalyst was stirred at room temperature before the addition of acetyl cyanide at 0°C (Table 6, entry 3). Lowering of the catalyst loading to 1 mol% resulted in lower yield of the product and considerable side-product formation (Table 6, entry 4).

After establishing suitable reaction conditions, we explored the scope of this new reaction. Different aldehydes (aryl and alkyl) and amines (benzyl and alkyl) gave the products in moderate to high yields (Scheme 2). The third component of our reaction can also be varied. For example,

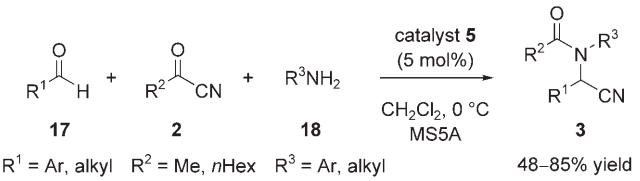
Table 6. Optimizing the reaction condition for the one-pot, three-component acylcyanation.



17a 2a 18a 3a

Entry[a]	**5** [mol%]	Additive	Conversion [%][b]
1	5	$MgSO_4$	86
2	5	MS5A	92
3[c]	5	MS5A	99
4[c]	1	MS5A	70

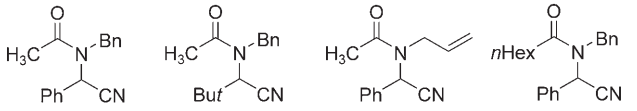
[a] Reaction conditions: aldehyde **17a**, amine **18a**, additive, and catalyst **5** were stirred together at 0°C for 2 h before acetyl cyanide (**2a**; 1.5 equiv) was added. [b] Determined by GC. [c] Aldehyde **17a**, amine **18a**, additive, and catalyst **5** were stirred together at room temperature for 2 h before acetyl cyanide (**2a**; 1.5 equiv) was added at 0°C. MS5A = 5-Å molecular sieves.



17 2 18 3

R^1 = Ar, alkyl R^2 = Me, *n*Hex R^3 = Ar, alkyl 48–85% yield

Selected examples:



36 h, 80% yield | 48 h, 48% yield | 48 h, 68% yield | 36 h, 72% yield

Scheme 2. Catalytic three-component acylcyanation with different aldehydes, amines, and acyl cyanides.

commercially available heptanoyl cyanide was used with similar efficiency.[9]

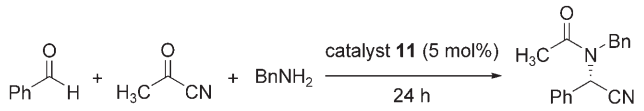
Although the reaction may not strictly be considered a three-component reaction but, rather, an in situ sequence, it improves the original two-step protocol significantly in terms of practicality.

Three-Component Catalytic Asymmetric Acylcyanation of Aldimines

Catalytic asymmetric three-component Strecker reactions are highly useful for the preparation of chiral α-amino acid derivatives. However, only Kobayashi and co-workers developed a direct catalytic asymmetric three-component Strecker reaction of aldehydes, aromatic amines, and HCN by using a chiral zirconium catalyst.[17] We reasoned that the extension of our acylcyanation methodology to an attractive one-pot three-component catalytic asymmetric acyl-Strecker reaction could be possible. Such a process would constitute the first organocatalytic asymmetric three-component Strecker-type reaction.[18]

We decided to explore our three-component (or in situ) variant by using Jacobsen thiourea catalyst **11**, which gave high enantioselectivities in the analogous preformed imine variant. According to our findings in the non-asymmetric three-component version, we added acetyl cyanide last to realize efficient conversion into the desired product (Table 7, entry 1). However, the product was formed with

Table 7. Optimization of the reaction conditions for the three-component acylcyanation.



17a **2a** **18a** **3a**

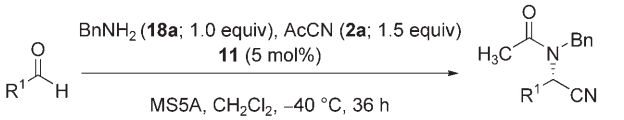
Entry[a]	Solvent	Additive	*T* [°C]	Yield [%]	*ee* [%]
1	toluene	$MgSO_4$	0	84	14
2	toluene	MS5A	0	10	60
3	CH_2Cl_2	none	0	63	48
4	CH_2Cl_2	$MgSO_4$	0	68	56
5	CH_2Cl_2	MS5A	0	66	74
6	CH_2Cl_2	MS5A	−40	83	88
7[b]	CH_2Cl_2	MS5A	−40	85	94
8[c]	CH_2Cl_2	MS5A	−40	98	94

[a] Aldehyde, amine, additive, and catalyst were stirred for 2 h at 0 °C before acetyl cyanide was added. [b] Aldehyde, amine, and additive were stirred for 2 h at 0 °C before the catalyst and acetyl cyanide (at −40 °C) were added. [c] Aldehyde, amine, and additive were stirred for 2 h at room temperature before the catalyst and acetyl cyanide (at −40 °C) was added.

poor enantioselectivity. By switching the drying reagent to MS5A and the solvent to dichloromethane, the enantioselectivity was significantly improved (Table 7, entries 2–5). Even higher enantioselectivity was observed after the temperature was lowered to −40 °C (Table 7, entry 6). Finally, we found that the best result (98 % yield, 94 % *ee*) was obtained when the aldehyde was first mixed with the amine and MS5A for 2 h at room temperature before the catalyst and acetyl cyanide were added subsequently at −40 °C (Table 7, entries 7 and 8).

With the optimal reaction conditions in hand, we initiated a study to explore the scope of this new catalytic asymmetric three-component reaction. First, the reaction of a variety of aldehydes **17** with benzylamine (**18a**) as the amine component and acetyl cyanide (**2a**) was examined (Table 8). Interestingly, the reactions took place efficiently in good to excellent yields with high enantioselectivities for all studied aldehydes. In particular, high enantioselectivities were observed with aromatic (Table 8, entries 1–4) and α,β-unsaturated (Table 8, entry 5) aldehydes. But even an aliphatic branched and an α-trisubstituted aldehyde gave excellent enantioselectivities (Table 8, entries 6 and 7). In the case of the α-unbranched aldehydes, slightly lower *ee* values were obtained (Table 8, entries 8 and 9). However, for 3,3-dimethylbutanal, the *ee* was significantly increased (92 %) by using 10 mol % of catalyst **11**.

Table 8. Catalytic asymmetric acylcyanation of different aldehydes with acetyl cyanide (**2a**) and benzylamine (**18a**).



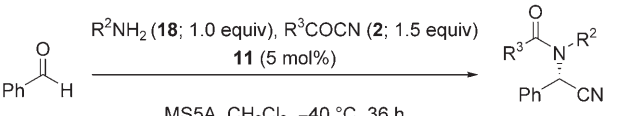
17 **3**

Entry[a]	R^1	Product	Yield [%][b]	*ee* [%][c]
1	Ph	**3a**	94	94
2	4-$MeOC_6H_4$	**3b**	88	94
3	4-ClC_6H_4	**3c**	78	92
4	2-naphthyl	**3e**	92	94
5		**3g**	82	94
6	*i*Pr	**3i**	92	92
7	*t*Bu	**3k**	46	94
8	*n*Bu	**3l**	75	88
9[d]	$tBuCH_2$	**3m**	97	92

[a] Reaction conditions were as described for Table 7, entry 8. [b] Yield of the isolated product after silica-gel column chromatography. [c] Determined by HPLC. [d] 10 mol % of catalyst **11** was used.

A variety of amines were investigated next with benzaldehyde (**17a**) as the aldehyde component (Table 9). It turned out that three different benzyl amines can be used to give the products in high yields and with excellent enantioselectivities (Table 9, entries 1–3). The electronic properties of

Table 9. Catalytic asymmetric acylcyanation of benzaldehyde (**17a**) with different amines and acyl cyanides.



17a **3**

Entry[a]	R^2	R^3	Product	Yield [%][b]	*ee* [%][c]
1	4-$MeOC_6H_4CH_2$	Me	**3n**	95	94
2	4-$ClC_6H_4CH_2$	Me	**3o**	93	94
3	1-naphthyl-CH_2	Me	**3p**	92	94
4	2-furyl-CH_2	Me	**3q**	83	80
5	allyl	Me	**3r**	88	88
6	*n*-pentyl	Me	**3s**	76	74
7	Bn	*n*Hex	**3t**	84	88

[a] Reaction conditions analogous to those described for Table 8 were used. [b] Yield of the isolated product after silica-gel column chromatography. [c] Determined by HPLC.

the aromatic system of the amine component do not seem to influence the yield and enantioselectivity of the reaction. Furfurylamine, which has a heteroaromatic moiety, can also be employed (Table 9, entry 4). Allylamine was also used and still gave the desired product with good results (Table 9, entry 5). Moreover, the reaction also afforded the product with a simple alkyl amine, though with slightly lower enantioselectivity (Table 9, entry 6). Apparently, the third component of our reaction can also be varied. In preliminary experiments, we found that heptanoyl cyanide reacts with benzaldehyde and benzylamine to provide product **3t** in 84 % yield and with 88 % *ee* (Table 9, entry 7).[11]

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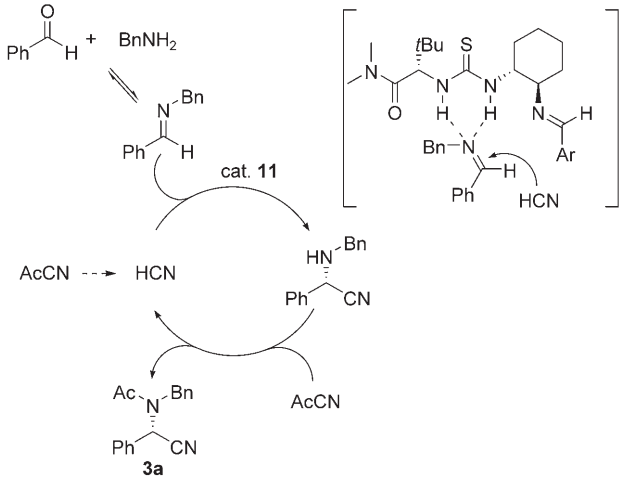
Mechanism

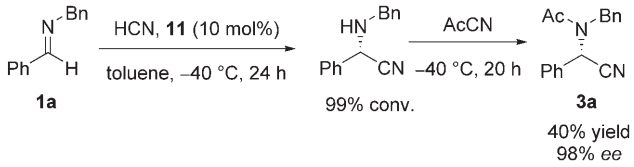
In principle, two mechanisms should be considered. First, the imine (generated in situ) may react with traces of HCN formed in the reaction mixture or introduced with acetyl cyanide. The resulting α-amino nitrile product would then be acetylated by acetyl cyanide to give the observed product (Scheme 3). Accordingly, the mechanism of the key Strecker



Scheme 3. Possible Jacobsen–Strecker mechanism: alternative A.

step would be identical to that of the Jacobsen variant, in which the urea is proposed to activate the imine through general acid catalysis. Consistent with this hypothesis is the fact that the absolute stereochemistry is identical and that high enantioselectivities are obtained with all classes of imines in both reactions.

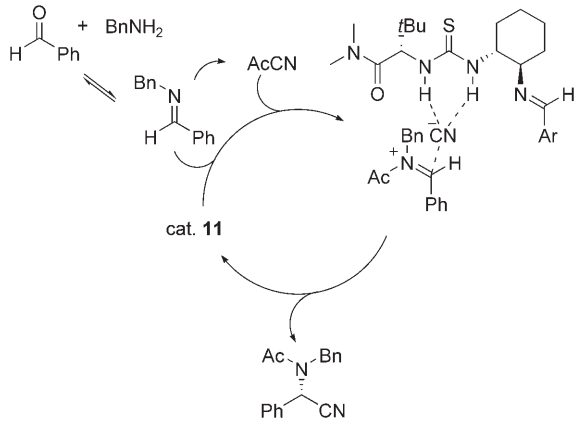
To validate this mechanism, we carried out another experiment. We first conducted the hydrocyanation of imine **1a** with catalyst **11** and HCN at −40 °C (Scheme 4). Subse-



Scheme 4. Hydrocyanation followed by derivatization.

quently, acetyl cyanide (**2a**) was added. However, after 20 h, product **3a** was obtained in only 40% yield (98% *ee*). Under our original conditions, the product was obtained in 96% yield. Therefore, the intermediacy of the Strecker product is questionable, and the above mechanism appears unlikely.

In an interesting alternative mechanism, the reaction could proceed via an *N*-acyl iminium ion intermediate.[19] This species may be formed by the reaction of the imine with acetyl cyanide (Scheme 5). The role of the urea catalyst



Scheme 5. Alternative mechanism involving the *N*-acyl iminium ion: alternative B.

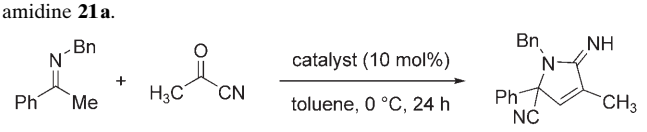
in this scheme would be to bind cyanide, thus effectively creating a chiral counteranion nucleophile, which could react enantioselectively with the *N*-acyl iminium ion.

This mechanism is supported by the recent discovery of an acyl-Pictet–Spengler reaction by Taylor and Jacobsen,[19e] which also proceeds via an *N*-acyl iminium ion and is catalyzed by a thiourea catalyst. The original Jacobsen–Strecker reaction potentially proceeds by an analogous mechanism.

Amidine Formation in the Reaction with Ketimines

We became interested in extending our acylcyanation chemistry to ketimines. Previously, the Jacobsen catalyst was used in the enantioselective Strecker reaction of ketimines with HCN.[3d] According to our findings in the catalytic acylcyanation of aldimines, we used **4** and **5** as the catalysts. Remarkably, however, when we used acetophenone-derived benzyl imine **20a** as the substrate for the reaction with acetyl cyanide **2a** (1.5 equiv) and catalyst **5**, we did not obtain the desired addition product. Instead we isolated the novel five-membered amidine derivative **21a** in 50% yield (Table 10, entry 1). Its structure was unambiguously assigned by ^{1}H and ^{13}C NMR spectroscopy, heteronuclear multiple quantum coherence (HMQC) experiments, and HRMS. With catalyst **4**, the yield was slightly higher (60%; Table 10, entry 2). As the stoichiometry of the reaction requires

Table 10. Optimization of the reaction conditions for the formation of amidine **21a**.



20a **2a** **21a**

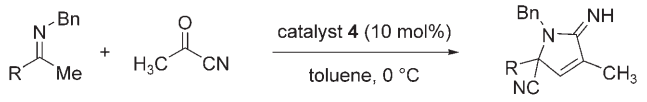
Entry	Catalyst	**2a** [equiv]	Conversion [%][a]
1	**5**	1.5	50
2	**4**	1.5	60
3	**4**	3.0	95

[a] Determined by GC.

2 equivalents of acetyl cyanide, we increased its amount even further. High conversion (95%) was obtained when 3.0 equivalents of acetyl cyanide (**2a**) was used (Table 10, entry 3). From a survey of the literature, we found that there were no previous reports that describe the synthesis of amidines of type **21a**.

Product **21a** was isolated in 75% yield after silica-gel column chromatography (Table 11, entry 1). Aliphatic-ketone-derived ketimine **20b** could also be used in this novel reaction and provided product **21b** in 40% yield (Table 11, entry 2). Amidines **21** are rather stable and are not hydrolyzed even after treatment with 6N HCl at room temperature for 24 h. The use of different chiral thiourea and phosphoric acid catalysts gave only poor enantioselectivity ($\leq$4% *ee*) for amidine **21a**.

Table 11. Formation of amidines from different ketimines.

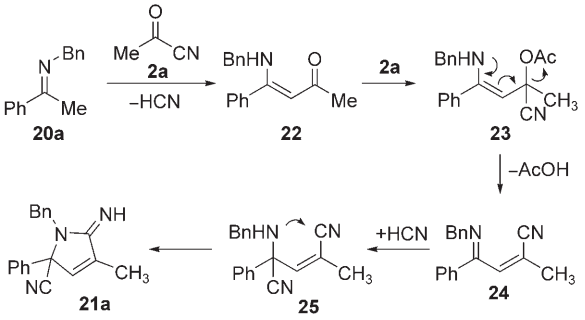


20 **2a** **21**

Entry[a]	R	*t* [h]	Product	Yield [%][b]
1	Ph	24	**21a**	75
2	*i*Pr	48	**21b**	40

[a] Reaction conditions: Ketimine **20** (0.5 mmol.), catalyst **4** (0.05 mmol), and acetyl cyanide (**2a**; 1.5 mmol) was stirred together at 0°C in dry toluene (1.5 mL). [b] Yield of the isolated product after silica-gel column chromatography.

A plausible mechanism for the formation of **21a** may involve an initial C-acylation of imine **20a** via its enamine tautomer to furnish enaminone **22** (Scheme 6). Intermediate **22**, upon further reaction with acetyl cyanide, provides acetate **23**. Imine **24** is then generated upon elimination of AcOH. Hydrogen cyanide, which is liberated in the formation of **22**, then adds to imine **24** to provide cyano nitrile **25**. Its cyclization generates amidine **21a**.



Scheme 6. Possible mechanism for the formation of amidine **21a**.

Conclusions

In summary, we have developed an efficient and potentially useful new reaction: the catalytic acylcyanation of imines with acetyl cyanide as the cyanation reagent. The scope of the acetylcyanation is remarkably high, and both aliphatic and aromatic imines can be used. We have also developed the first organocatalytic asymmetric variant of the classical three-component Strecker reaction. The operational simplicity, practicability, and mild reaction conditions render it an attractive approach for the generation of different α-amido nitriles. Our reaction avoids the use of highly toxic HCN, does not require preformation of the imine intermediate, and avoids the need for derivatization of the normally unstable Strecker product (i.e., with trifluoroacetic anhydride (TFAA)). Furthermore, we reported novel amidines **21** from the reaction of acetyl cyanide **2a** with ketimines **20**. These amidines are new and may be attractive building blocks in heterocyclic chemistry and potentially in organocatalysis.

Experimental Section

Syntheses

General procedure for the catalytic asymmetric acylcyanation of **1**: Aldimine **1** (0.5 mmol), acetyl cyanide (**2a**; 0.75 mmol), and catalyst **11** (0.005 mmol) were placed in a dry flask. Dry toluene (2.5 mL) was added to the mixture, which was then stirred for 20–50 h at −40°C. The mixture was directly subjected to silica-gel column chromatography to isolate pure product **3**.

General procedure for the catalytic asymmetric three-component acylcyanation: Aldehyde **17** (0.5 mmol), amine **18** (0.5 mmol), and MS5A were placed in a dry Schlenk flask. Dry dichloromethane (2.0 mL) was added, and the mixture was stirred for 2 h at room temperature. Catalyst **11** (0.025 mmol) was then added, and the flask was cooled to −40°C. After the mixture was stirred for 10 min, **2a** (0.75 mmol) was added, and the mixture was stirred for 36 h at −40°C. The mixture was directly subjected to silica-gel column chromatography to isolate pure product **3**.

General procedure for the catalytic formation of **21**: Ketimine **20** (0.5 mmol), **2a** (1.5 mmol), and catalyst **4** (0.05 mmol) were placed in a dry flask. Dry toluene (1.5 mL) was added to the mixture, which was then stirred for 24–48 h at 0°C. The mixture was directly subjected to silica-gel column chromatography (80% EtOAc/hexane) to isolate pure product **21**.

Spectral Data

3a: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.44–7.38 (m, 5H), 7.31–7.24 (m, 3H), 7.14–7.07 (m, 3H), 4.58 (d, J=17.6 Hz, 1H), 4.49 (d, J=12.9 Hz, 1H), 2.14 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=171.3, 135.3, 131.9, 129.1, 128.8, 128.4, 127.4, 125.9, 116.1, 49.2, 48.3, 21.7 ppm; HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}N_2O$: 264.126062 $[M]^+$; found: 264.126260.

21a: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.29–7.06 (m, 11H), 6.30 (d, J=1.5 Hz, 1H), 4.55 (d, J=15.9 Hz, 1H), 4.17 (d, J=15.9 Hz, 1H), 2.01 ppm (d, J=1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.9, 135.8, 135.3, 133.1, 129.6, 129.2, 128.4, 128.0, 127.5, 126.2, 115.8, 68.5, 46.0, 11.6 ppm; HRMS (EI): *m*/*z* calcd for $C_{19}H_{17}N_3$: 287.141997 $[M]^+$; found: 287.142249.

21b: ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.32–7.17 (m, 11H), 6.20 (d, J=1.4 Hz, 1H), 4.72 (d, J=16.1 Hz, 1H), 4.43 (d, J=16.0 Hz, 1H), 2.12–2.05 (m, 1H), 1.92 (d, J=1.5 Hz, 3H), 1.08 (d, J=6.9 Hz, 3H), 0.49 ppm (d, J=6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=169.5, 137.9, 136.5, 129.5, 128.3, 127.5, 127.2, 116.8, 69.5, 45.7, 33.3, 18.0, 14.5, 11.3 ppm; HRMS (EI): *m*/*z* calcd for $C_{16}H_{19}N_3$: 253.157552 $[M]^+$; found: 253.157896.

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