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Organocatalyzed Strecker reactions

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Contents

1. Introduction

Organocatalysis has emerged during the last decade as one of the major issues in the development of catalytic chemical technology.[1] As for conventional catalysis with transition-metal complexes, by using organic catalysts large quantities of products are expected to be prepared using a minimal amount of small organic molecules. Moreover, in the case of working with enantiomerically pure organic catalysts (asymmetric organocatalysis), optically active compounds would be obtained in a parallel way to the classical metal-mediated asymmetric catalysis.[2] In this context, many important reactions have been carried out with excellent enantioselectivities using organic catalysts.[3] Among them are aldol condensations,[4] multicomponent reactions,[5] including Mannich reactions,[6] conjugate additions,[7] and α-heterofunctionalization of carbonyl compounds.[8]

The three-component Strecker reaction as well as the direct hydrocyanation of imines (modified Strecker reaction) is fundamental carbon–carbon bond-forming processes,[9] which represents one of the simplest methods for preparing α-amino acids (Scheme 1).[10] The whole process, encompassing both cyanide addition and hydrolysis of the resulting α-amino nitrile can be made enantioselective, finally affording optically active α-amino acids, through the use of both metal-based and metal-free asymmetric catalysts. Because of the synthetic utility of α-amino nitriles[11] many efforts have been directed to the development of catalytic asymmetric approaches to these compounds, as mentioned in the previous literature concerning catalytic asymmetric nucleophilic additions to imines.[12] Although metal-assisted hydrocyanation of imines is still in many instances, the preferred approach, in the future the economically and ecologically more attractive strategy is likely to be organic catalysis. Indeed, a good part of research into the catalytic Strecker reaction during recent years has been devoted to the development of efficient organocatalysts for such a reaction.[13]

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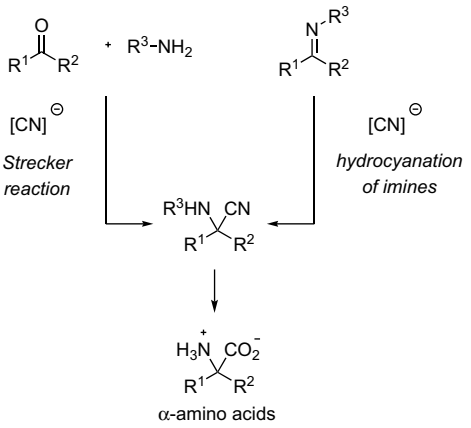


Scheme 1. Synthesis of α-amino nitriles and α-amino acids through Strecker reactions.

In this review, we describe a detailed and critical overview of organocatalyzed hydrocyanation of imines and related compounds. Emphasis is placed on processes in which a chiral non-racemic organic catalyst is used thus leading to optically active compounds. The reactions are classified by the type of catalysts. Comments on the challenges and opportunities that arise from the use of such catalysts are also provided.

2. Catalysis by hydrogen-bonding interactions

2.1. Brønsted acids

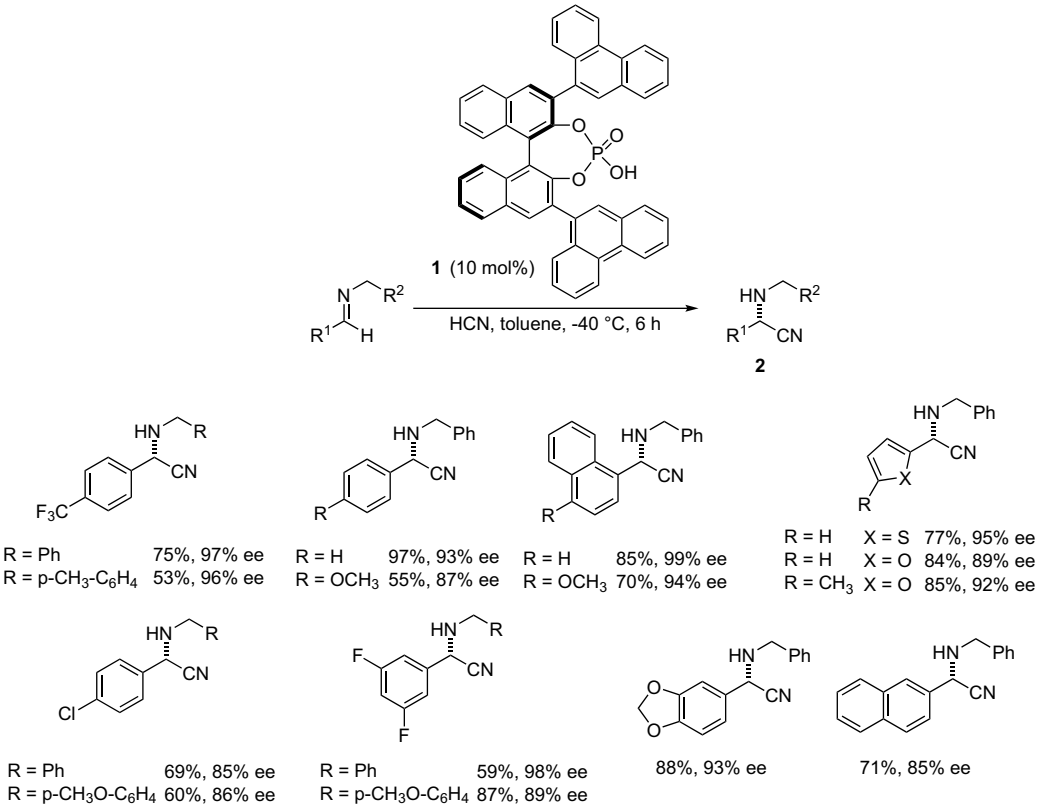
The direct hydrocyanation of imines in an acidic medium using HCN is one of the most efficient methods for the synthesis of α-amino nitriles. In order to introduce chirality in the reaction, considerable efforts have been made in the development of chiral phosphates, which effectively promote the hydrocyanation reaction. Thus, the catalytic use of chiral BINOL phosphates promoted the reaction of aromatic imines with HCN to afford (*S*)-α-amino nitriles **2** (Scheme 2).[14]

The influence of the aromatic substituent at the 3,3′-positions was crucial for the enantioselectivity of the reaction. The authors studied several 3,3′-substituents including phenyl, biphenyl, naphthyl, and other substituted aromatic rings and the best selectivities were obtained with the most sterically congested 3,3′-bis-(9-phenanthryl) BINOL **1** at low temperature in toluene as a solvent. On the other hand, far lower ee values were found in the reactions carried out in other solvents such as chloroform, dichloromethane, acetonitrile, and tetrahydrofuran, demonstrating that the best ee value corresponded to nonpolar aromatic solvents. In general, the best results were obtained with *N*-benzyl imines.

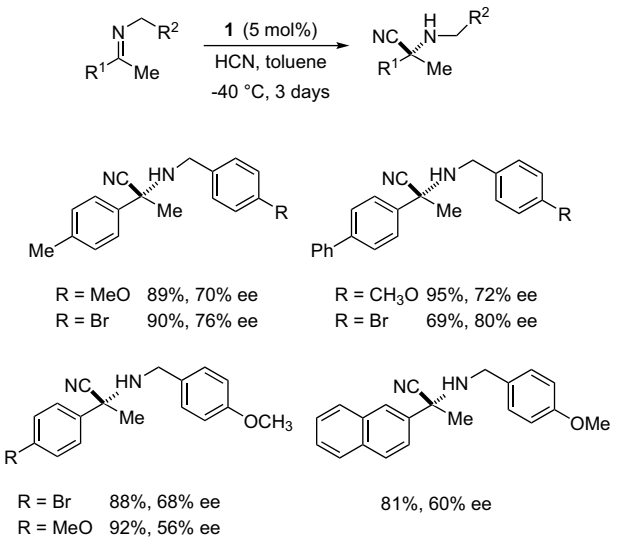
The use of chiral BINOL phosphate **1** can be successfully applied to the HCN addition to aromatic ketimines, which afforded lower ee values than aldimines.[15] Addition of catalytic quantities (5 mol %) of chiral Brønsted acid **1** afforded good results, particularly with *N*-benzyl-protected ketimines, but did not attain the same values observed for aldimines (Scheme 3).

The activation of imines took place by catalytic protonation, in which an intermediate iminium **3** is generated. This intermediate then underwent addition of HCN to furnish chiral α-amino nitrile **2** and to regenerate the phosphate, as illustrated in the catalytic cycle depicted in Scheme 4.

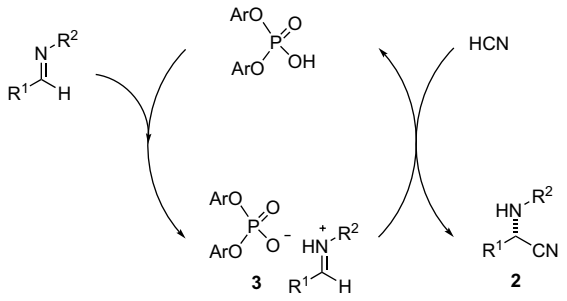
List and co-workers highlighted the feasibility of using acetyl cyanide instead of the volatile and highly toxic HCN in the presence of acid catalysts.[16] Good conversions were found with phenylphosphoric acid in both toluene and dichloromethane, but when BINOL-derived phosphoric acids **4a**–**c** were used as catalysts low enantioselectivities were obtained (Scheme 5).[17] This seminal work, however, served to confirm that the reaction could not only be catalyzed by strong acid catalysis, but also by hydrogen-bonding-type



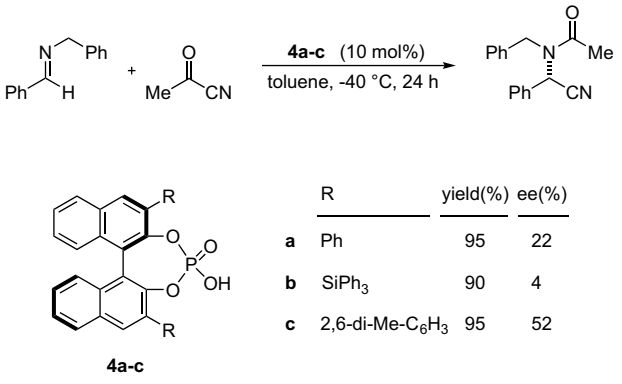
Scheme 2. Hydrocyanation of aldimines catalyzed by BINOL phosphates.



Scheme 3. Hydrocyanation of ketimines catalyzed by BINOL phosphates.



Scheme 4. Catalytic cycle for imine activation by phosphates.

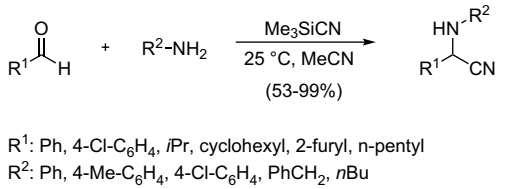


	R	yield(%)	ee(%)
a	Ph	95	22
b	$SiPh_3$	90	4
c	2,6-di-Me-C_6H_3	95	52

Scheme 5. Organocatalytic acylcyanation of imines.

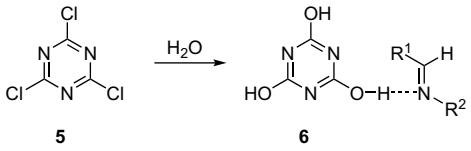
general acid catalysts, thus opening new possibilities for other catalysts such as thioureas (see below).

The three-component Strecker reaction has been recently reported to be catalyzed at room temperature by sulfamic acid.[18] The corresponding α-amino nitriles were isolated in 74–96% chemical yield, the reaction showing a broad scope. A variety of aromatic aldehydes and imines were used as suitable substrates. An aliphatic aldehyde such as isobutyraldehyde also gave excellent yields with both aniline and benzylamine. The reaction was conducted without avoiding the presence of moisture and the chosen solvent was acetonitrile. The authors pointed out that water formed in situ or as a trace residue in the solvent may exert a pivotal role on the course of the reaction. Indeed, previous work published two years before, by Yus and co-workers,[19] undoubtedly demonstrated that the influence of a Lewis acid on the Strecker reaction carried out in acetonitrile is negligible, since the reaction proceeded with comparable chemical yields and reaction rates (Scheme 6).



Scheme 6. Non-catalyzed Strecker reaction in acetonitrile as solvent.

Within this context, it has been reported[20] that the synthesis of α-amino nitriles from aldehydes, amines, and trimethylsilyl cyanide is catalyzed by the presence of 2,4,6-trichloro-1,3,5-triazine (TCT) **5**. The authors invoked the in situ formation of cyanuric acid **6**, which would activate the imine through hydrogen-bonding interactions as depicted in Scheme 7. Compound **5** is known to react with emerging water (from imine formation) to furnish **6**. The authors confirmed the complete failure of the reaction under strictly anhydrous conditions and corroborated that only the corresponding intermediate imines were isolated upon catalytic addition of HCl and in the absence of TCT **5**. These experiments, however, do not seem sufficient to confirm whether the observed catalytic activity was a consequence of either the incipient water as reported by Yus and co-workers[19] or the cyanuric acid formed in situ.



Scheme 7. Proposed catalytic activity for cyanuric acid **15**.

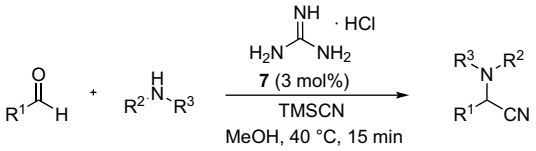
The catalytic effect of the water formed in situ after generation of the imine had already been reported by Gibson and co-worker 15 years ago.[21] Thus, it seems clear that by choosing the appropriate solvent (acetonitrile) it is not necessary to add any additional catalyst.

2.2. Protonated ammonium salts

Protonated organic catalysts offer great scope for a variety of organic reactions.[22] Commercially available guanidine hydrochloride **7** has been reported as a remarkable catalyst for the three-component Strecker reaction.[23] A great variety of aliphatic and aromatic aldehydes and amines can be used to furnish the corresponding α-amino nitriles in excellent chemical yields (Scheme 8).

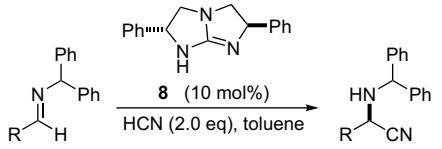
Corey and co-worker[24] have demonstrated the utility of a chiral bicyclic guanidine as a catalyst for the hydrocyanation of arylimines (Scheme 9).

The guanidine **8** is, on its own, catalytically inactive and requires the action of HCN, added in a twofold excess, to give an active protonated complex, which acts as a bifunctional catalyst by also activating the imine through a hydrogen-bonding interaction. The cyanide attack was proposed to take place within the ion pair on **9**, providing a good enantioselectivity as a consequence of the π-stacking between a phenyl group of the catalyst and the benzhydryl protecting group of the imine (Fig. 1). Further DFT calculations[25] demonstrated that two competitive pathways to amino nitriles could be invoked: (i) isomerization of HCN to HNC and then addition to imine and (ii) addition of HCN to imine to provide an intermediate amino isonitrile, which isomerizes to the final α-amino nitrile.



R^1	R^2	R^3	Yield (%)
*t*Bu	H	Ph	89
$PhCH_2$	H	Ph	84
nC_5H_{11}	H	Ph	97
Ph	H	Ph	94
4-Cl-C_6H_4	H	Ph	98
2-furyl	H	Ph	82
4-pyridyl	H	Ph	95
cinnamyl	H	Ph	90
*i*Pr	Et	Et	88
nC_5H_{11}	Et	Et	91
Ph	Et	Et	94
4-Cl-C_6H_4	Et	Et	94
2-furyl	Et	Et	84
4-pyridyl	Et	Et	88
4-MeO-C_6H_4	Et	Et	90
Ph	$PhCH_2$	$PhCH_2$	96
*i*Pr	$PhCH_2$	$PhCH_2$	96

Scheme 8. Strecker reaction catalyzed by guanidine hydrochloride **7**.



R	*T* (°C)	t (h)	Yield (%)	ee (%)
Ph	-40	20	96	86
Ph	-20	8	99	82
4-Me-C_6H_4	-40	20	96	80
3,5-diMe-C_6H_3	-40	16	96	79
2-Me-C_6H_4	-20	12	88	50
4-*t*Bu-C_6H_4	-40	72	80	85
4-TBSO-C_6H_4	-40	38	98	88
4-MeO-C_6H_4	-40	28	99	84
4-F-C_6H_4	-40	23	97	86
4-Cl-C_6H_4	-20	20	88	81
1-naphthyl	-20	12	90	76

Scheme 9. Asymmetric hydrocyanation of imines catalyzed by **8**.

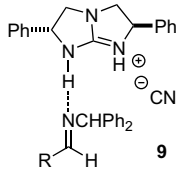
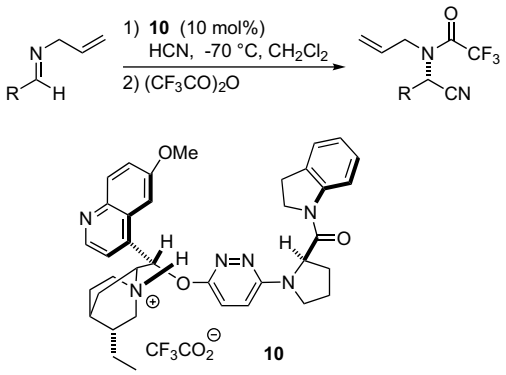


Figure 1. Model for activation of compound **9**.

The crystalline stable trifluoroacetate **10** acted as an excellent catalyst for the Strecker reaction of *N*-allyl aromatic aldimines **11** (Scheme 10).[26]



R	t (h)	Yield (%)	ee (%)
Ph	36	95	92
4-MeO-C_6H_4	36	95	90
4-Me-C_6H_4	36	94	87
4-F-C_6H_4	24	96	89
4-Br-C_6H_4	40	88	85
4-CN-C_6H_4	24	92	80
2-Me-C_6H_4	40	86	89
3-Me-C_6H_4	40	98	>99
3-MeO-C_6H_4	40	96	>99
3,5-di-Me-C_6H_3	48	88	90
1-naphthyl	40	95	79

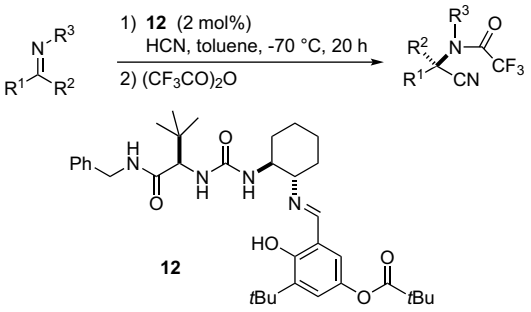
Scheme 10. Enantioselective Strecker reaction of *N*-allyl imines.

In this case, the *N*-allyl derivatives led to higher enantioselectivities than the corresponding *N*-benzyl compounds. In contrast to the reaction illustrated in Scheme 9 the best solvent was found to be dichloromethane, with toluene giving rise to much lower ees of α-amino nitriles. This observation is in agreement with an enzyme-like model, which invokes the formation of a U-shaped binding pocket contributing to hold the aldehyde-derived part of the aldimine. Further support for this model is given by the fact that aliphatic aldimines, particularly those with bulky groups unable of interacting with the pocket, led to poor enantioselectivities.

2.3. Ureas and thioureas

Jacobsen and co-worker developed certain ureas and thioureas as catalysts for the asymmetric Strecker reaction by screening parallel synthetic libraries on solid phase.[27] After validating the best results by the preparation of soluble analogues,[28] the urea **12** emerged as the most efficient catalyst, even at loadings of 2 mol %. Both aldimines[29] and ketimines[30] gave rise to excellent enantioselectivities (Scheme 11).

The presence of bulky substituents at both the amino acid position and at the 3-position of the salicylimine moiety is crucial for achieving a high enantioselectivity. Structural and mechanistic studies including isotope shift experiments also demonstrated that only the two urea hydrogens of **12** interacted with the imine. Moreover, several dedicated experimental observations clearly indicated the *Z*-isomer as that involved in the substrate–catalyst complex. Both NMR experiments and DFT calculations allowed the determination of a detailed 3-D structure of the substrate-bound complex[31] and the design of thiourea catalysts **13** and **14** as much more efficient organic catalysts for the hydrocyanation of imines. A comparison between *ent*-**12** and **13** for selected substrates using only 1 mol % of catalyst clearly demonstrated the benefits and synthetic utility of using thiourea catalysts (Scheme 12).[31]

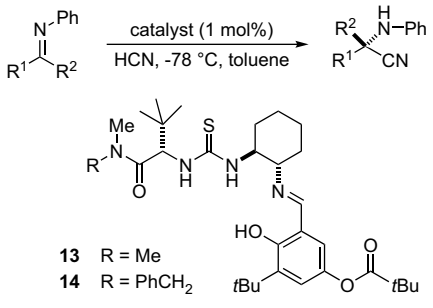


R^1	R^2	R^3	Yield (%)	ee (%)
Ph	H	allyl	74	95
*t*Bu	H	allyl	75	95
4-MeO-C_6H_4	H	allyl	98	95
3-MeO-C_6H_4	H	allyl	99	93
2-MeO-C_6H_4	H	allyl	93	77
4-Me-C_6H_4	H	allyl	99	95
3-Me-C_6H_4	H	allyl	97	96
2-Me-C_6H_4	H	allyl	96	95
4-Br-C_6H_4	H	allyl	89	89
3-Br-C_6H_4	H	allyl	87	90
2-Br-C_6H_4	H	allyl	88	95
4-*t*Bu-C_6H_4	H	allyl	89	97
*t*Bu	H	benzyl	88	96
cyclohexyl	H	benzyl	85	87
cyclohexyl	H	allyl	88	86
1-cyclohexenyl	H	benzyl	90	91
$(Me)_3CCH_2$	H	benzyl	85	90
$Me(CH_2)_4$	H	benzyl	69	78
$(Me)_2CH$	H	benzyl	74	79
cyclopropyl	H	benzyl	89	91
cyclooctyl	H	allyl	65	90
Ph	Me	allyl	97	90
4-Me-C_6H_4	Me	allyl	98	91
4-Br-C_6H_4	Me	allyl	100	93
4-NO_2-C_6H_4	Me	allyl	100	93
4-MeO-C_6H_4	Me	allyl	98	88
4-CF_3-C_6H_4	Me	allyl	100	95
3-Br-C_6H_4	Me	allyl	97	91
2-Br-C_6H_4	Me	allyl	45	42
*t*Bu	Me	allyl	98	70

Scheme 11. Hydrocyanation of imines catalyzed by urea **12**.

The above-mentioned NMR studies showed that the imine is activated through hydrogen-bonding interactions with both urea hydrogens adopting a perpendicular disposition to the (thio)urea plane (Fig. 2).

Modifications to the amide bond and urea moieties as well as variations of the amino acid confirmed the optimal results for catalysts **13** and **14**.[32] Thiourea **14** was shown to be efficient with both aromatic and aliphatic aldimines.[27] Following the seminal work of Jacobsen, novel bifunctional catalysts **15** bearing both a thiourea moiety and an imidazole unit were prepared (Fig. 3).[33] However, poor enantioselectivities were observed with aromatic aldimines.



R^1	R^2	ee (%) (*ent*-**12**)	ee (%) (**13**)
*i*Pr	H	80	97
nC_5H_{11}	H	79	96
*t*Bu	Me	70	86
Ph	H	96	99.3
*t*Bu	H	96	99.3

Scheme 12. Comparison between Jacobsen's urea and thiourea catalysts.

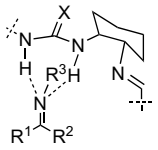


Figure 2. Proposed model for (thio)urea hydrogen-bonding interactions.

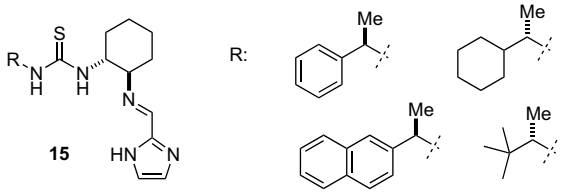


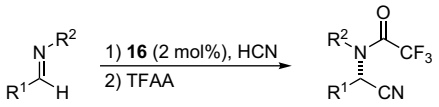
Figure 3. Imidazole-derived thioureas.

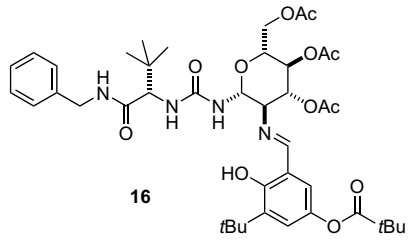
The urea **16** developed by Kunz and co-workers proved to be an efficient catalyst for a variety of aromatic *N*-allyl aldimines (Scheme 13).[34]

In order to avoid the use of the volatile and highly toxic HCN, List and co-workers developed the catalytic acylcyanation of imines using acyl cyanides and the thiourea **27** (Scheme 14).[16] The same authors described the asymmetric version of the reaction, the best results being obtained with Jacobsen's thiourea **23**, although only acylcyanation of *N*-benzyl benzaldimine **7** was reported.[17]

Thiourea **17** also catalyzed the three-component Strecker reaction, as shown in Scheme 15.[35] Notably, an important background contribution was present in the reaction since a conversion of up to 42% was observed in the absence of any catalyst. On the other hand, the reaction led to good conversions for both aromatic and aliphatic aldehydes, thus showing a broad scope by using mild reaction conditions.

The same group developed the enantioselective version of the reaction by using thiourea **20** as a catalyst.[36] Both aromatic and aliphatic amidonitriles were prepared in excellent yields and enantioselectivities from the corresponding aldehydes, benzylamine, and acetyl cyanide by using 5 mol % of catalyst **20** (Scheme 16).





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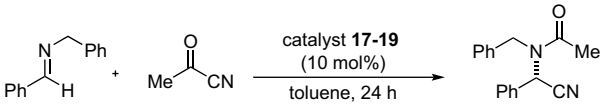
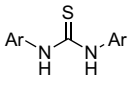
R^1	R^2	Yield (%)	ee (%)
2-Me-C_6H_4	allyl	81	69
3-Me-C_6H_4	allyl	93	78
4-Me-C_6H_4	allyl	83	75
2-MeO-C_6H_4	allyl	98	64
3-MeO-C_6H_4	allyl	96	66
4-MeO-C_6H_4	allyl	79	82
2-Br-C_6H_4	allyl	79	72
3-Br-C_6H_4	allyl	83	74
4-Br-C_6H_4	allyl	77	84
4-^{t}Bu-C_6H_4	allyl	82	84
4-NO_2-C_6H_4	allyl	67	0
2-furfuryl	allyl	87	50
1-naphthyl	allyl	78	80
2-naphthyl	allyl	73	76
cyclohexyl	benzyl	60	47
Ph	4-Br-$C_6H_4CH_2$	63	50
Ph	allyl	72	84

Scheme 13. Hydrocyanation of aldimines catalyzed by urea **26**.





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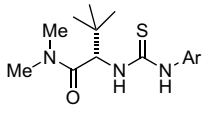
Ar: 3,5-di-CF_3-C_6H_3



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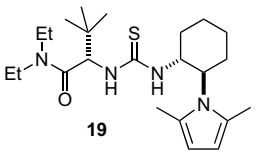

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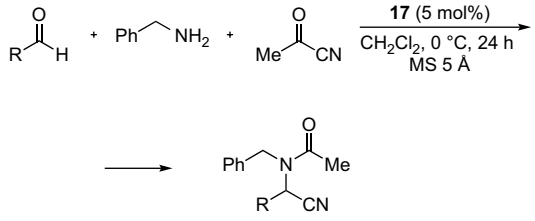
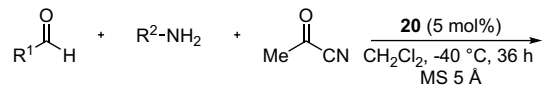
catalyst	*T* (°C)	Yield (%)	ee (%)
17	0	99	-----
18	-40	99	20
19	-40	98	94
13	-40	98	>99

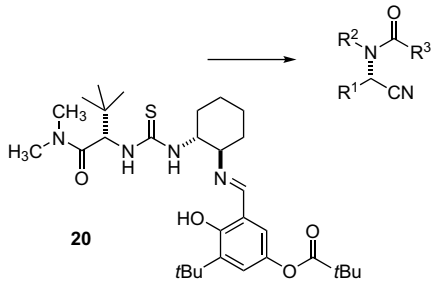
Scheme 14. Acylcyanation of imines catalyzed by thioureas.



R	t (h)	Yield (%)
Ph	36	80
4-MeO-C_6H_4	36	82
4-Cl-C_6H_4	48	73
2-naphthyl	36	83
2-furyl	36	76
3-pyridyl	36	84
*i*Pr	36	78
*t*Bu	48	48
1-cinnamyl	36	85
nC_5H_{11}	36	82

Scheme 15. Three-component Strecker reaction catalyzed by thiourea **17**.





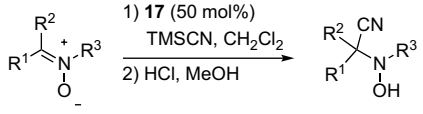
20

R^1	R^2	Yield (%)	ee (%)
Ph	$PhCH_2$	94	94
4-MeO-C_6H_4	$PhCH_2$	88	92
4-Cl-C_6H_4	$PhCH_2$	78	92
2-naphthyl	$PhCH_2$	92	94
(*E*)-PhCH=CH	$PhCH_2$	82	92
*i*Pr	$PhCH_2$	92	92
*t*Bu	$PhCH_2$	46	94
*n*Bu	$PhCH_2$	75	92
$tBuCH_2$	$PhCH_2$	97	94
Ph	4-MeO-$C_6H_4CH_2$	95	94
Ph	4-Cl-$C_6H_4CH_2$	93	94
Ph	1-naphthylCH_2	92	94
Ph	2-furylCH_2	83	80
Ph	Allyl	88	92
Ph	*n*pentyl	76	74

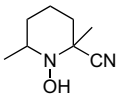
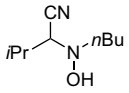
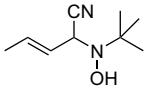
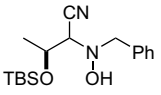
Scheme 16. Enantioselective three-component Strecker reaction catalyzed by thiourea **20**.

Ureas and thioureas have also been used to catalyze the nucleophilic addition of trimethylsilyl cyanide to nitrones.[37] The best results were observed with thiourea **17**. Although the reaction showed a considerable background contribution a marked

acceleration in the formation of the products was observed in the presence of 0.5 equiv of **17** (Scheme 17).



21

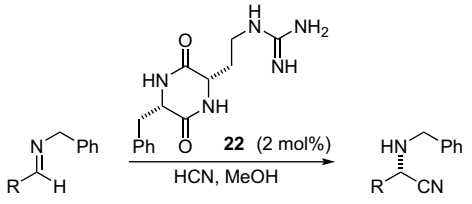
21	T (°C)	t (h)[a]	Yield (%)
	-78	1.5 (15)	75 (79)
	0	0.25 (75)	92 (95)
	rt	1.5 (20)	85 (85)
	rt	1 (24)	96 (72)

[a]values in parentheses correspond to reaction in absence of catalyst

Scheme 17. Organocatalyzed TMSCN addition to nitrones.

2.4. Other H-bonding catalysts

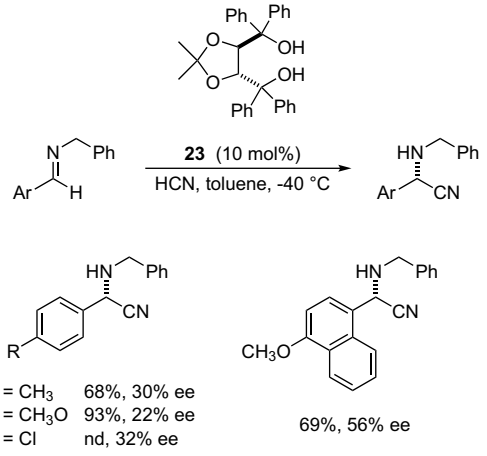
One of the earliest works, published in 1996, on the organocatalyzed Strecker reaction used the diketopiperazine **22** as a chiral catalyst (Scheme 18).[38] By using **22** some variation was observed in the enantioselectivity, depending on the substrate. Whereas the hydrocyanation of aromatic aldimines took place generally with high enantiomeric excess, giving rise to (*S*)-α-amino nitriles **23**, the presence of electron-withdrawing groups at the aromatic ring led to essentially racemic products (Scheme 18). A similar trend was also observed for aliphatic imines as well as those derived from pyridine and furan. Although NMR experiments did not demonstrate deuterium exchange, the authors did not discard racemization of the final product via rapid reversibility of HCN addition.



R	*T* (°C)	Yield (%)	ee (%)
Ph	-25	97	>99
4-Cl-C_6H_4	-25	97	83
4-Cl-C_6H_4	-75	94	>99
4-MeO-C_6H_4	-75	90	96
3-Cl-C_6H_4	-75	80	>99
3-MeO-C_6H_4	-75	82	80
3-NO_2-C_6H_4	-75	71	<10
3-pyridyl	-75	86	<10
2-furyl	-75	94	32
*i*Pr	-75	81	<10
*t*Bu	-75	80	17

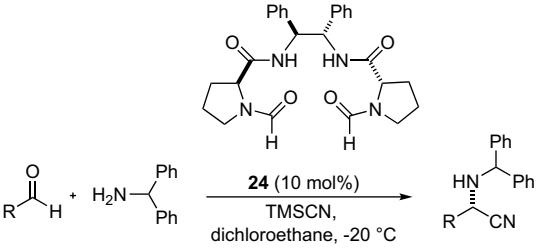
Scheme 18. Asymmetric Strecker reaction catalyzed by **22**.

TADDOL **23**, which is an excellent ligand for metal-based asymmetric catalysis,[39] is per se an organic catalyst for the hydrocyanation of aromatic *N*-benzyl imines (Scheme 19).[15] As illustrated in Scheme 19, some enantioselection could be observed, the use of other benzyl protecting groups resulting in a loss of selectivity. Even though the observed ees were low, these results were of interest since they constituted the first example of an enantioselective Strecker reaction catalyzed by a diol.



Scheme 19. Hydrocyanation of imines catalyzed by TADDOL **51**.

C_2-symmetric chiral non-racemic bisformamide **24** catalyzed the three-component Strecker reaction, furnishing α-amino nitriles in excellent yields and good enantioselectivities (Scheme 20).[40]



R	time (h)	Yield (%)	ee (%)
Ph	10	99	81
4-Me-C_6H_4	10	98	84
2-Me-C_6H_4	10	99	80
3-Me-C_6H_4	10	97	76
4-MeO-C_6H_4	10	96	85
3-MeO-C_6H_4	14	97	76
4-Cl-C_6H_4	50	98	83
3-Cl-C_6H_4	60	74	73
2-Cl-C_6H_4	50	81	75
4-Br-C_6H_4	60	85	86
4-Ph-C_6H_4	14	94	86
2-naphthyl	50	75	81
*t*Bu	14	92	73
2-furyl	14	94	43

Scheme 20. Organocatalytic acylcyanation of imines.

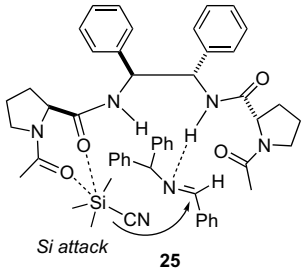
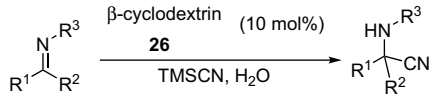


Figure 4. Transition structure for hydrocyanation catalyzed by bisformamide **24**.

Optimization of the reaction conditions including solvent effects, catalyst loading, molar ratio, and concentration showed compound **24** to efficiently catalyze the reaction (Scheme 20).

The observed enantioselectivity can be explained on the basis of the invoked transition structure **25** (Fig. 4) in which the in situ-generated imine is activated by a hydrogen bond through the imine nitrogen coordinating to the amide hydrogen, and the trimethylsilyl cyanide is activated by two oxygens coordinated to silicon. The bifunctional role exerted by catalyst **53** through transition structure **54** is supported by DFT calculations.

The addition of trimethylsilyl cyanide to imines in water is catalyzed by β-cyclodextrin **26** (Scheme 21).[41]

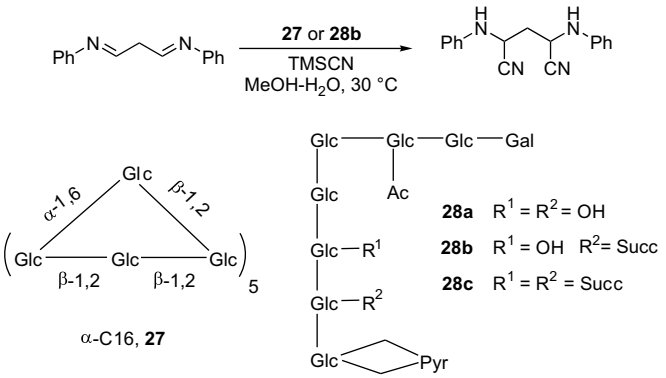


R^1	R^2	R^3	t (h)	Yield (%)
Ph	H	Ph	1	98
Ph	H	4-F-C_6H_4	1	98
Ph	H	2-Me-C_6H_4	1	96
Ph	H	2-MeO-C_6H_4	1	95
Ph	H	$PhCH_2$	1.5	92
4-Br-C_6H_4	H	Ph	1	98
4-Cl-C6H_4	H	4-F-C_6H_4	1	98
4-Me-C_6H_4	H	Ph	1	96
4-Me-C_6H_4	H	Tosyl	1	94
2,4,6-tri-Me-C_6H_2	H	Ph	1	94
4-MeO-C_6H_4	H	Ph	1	96
2,4-di-MeO-C_6H_3	H	Ph	1	94
4-allyloxy-C_6H_4	H	Ph	1	95
4-NO_2-C_6H_4	H	Ph	2	90
(*E*)-PhCH=CH	H	Ph	2	90
1-naphthyl	H	4-F-C_6H_4	1	92
2-naphthyl	H	Ph	1	95
*n*decyl	H	Ph	2	90
Ph	Me	Ph	2	94
4-Me-C_6H_4	Me	Ph	2	94
2-naphthyl	Me	Ph	2	92
cyclohexyl	Me	Ph	2	90

Scheme 21. Hydrocyanation of imines catalyzed by β-cyclodextrin **26**.

The activation of the imine is postulated to occur through hydrogen-bonding of a cyclodextrin hydroxyl with the imine nitrogen. The reaction showed a broad scope with aromatic aldimines and ketimines. Some variation of the nitrogen protecting group was also possible.

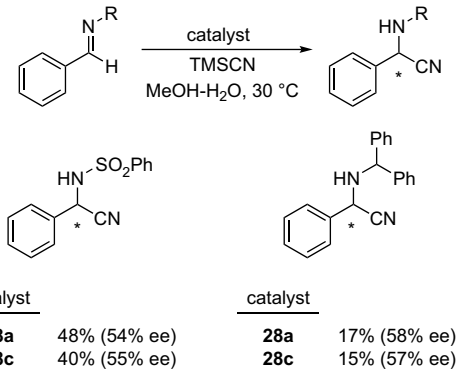
Similarly, some microbial carbohydrates, such as α-cyclosophorohexadecaose (α-C16) **27** derived from *Xanthomona* sp. and succinoglycan monomers **28a–c** derived from *Rhizobium* sp., acted as catalysts in the double trimethylsilylcyanation of malonaldehyde bis(phenylimine) (Scheme 22).[42]



Glc:D-Glucose; Gal:D-Galactose; Ac: acetyl; Succ: Succinyl; Pyr: Pyruvyl

Scheme 22. Trimethylsilylcyanation of imines catalyzed by microbial carbohydrates.

The reaction proceeded in a mixture of methanol–water at 30 °C and furnished bis α-amino nitriles in quantitative yield. Whereas the reaction catalyzed by α-C16 **27** afforded racemic substrates, further studies with succinoglycan monomers **28b**,**c** having acetyl and succinyl groups as substituents led to lower chemical yields but moderate enantioselectivities (Scheme 23). Thus, it can be suggested that several types of carbohydrates could be further applied as environmentally friendly catalysts in the future.



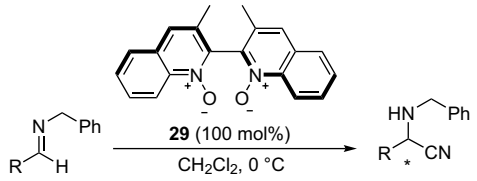
Scheme 23. Trimethylsilylcyanation of imines catalyzed by succinoglycan monomers.

3. Catalysis by Lewis bases

3.1. *N*-Oxides

Chiral *N*-oxides have been used in catalytic asymmetric processes involving both metal-free and metal-containing reactions.[43] The use of stoichiometric amounts of chiral *N*-oxide **29** promoted the asymmetric reaction of several aromatic *N*-benzyl imines and trimethylsilyl cyanide (Scheme 24).[44] The enantioselectivity of the reaction appeared to be sensitive to the aryl substituent, since *R* or *S* enantiomers were obtained depending on the substrate. The enantiomeric excesses were only modest (37–73% ee).

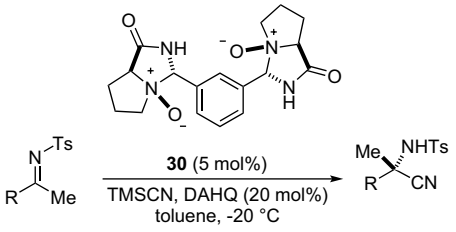
Some optimization of the reaction conditions including temperature, imine concentration, ratio of imine to cyanating agent and amount of the promoter led to ee values of 95% in particular cases (R=2-Cl-C_6H_4); however, no information about the obtained



R	t (h)	Yield (%)	ee (%)	configuration
Ph	24	64	61	*S*
Ph	48	95	58	*S*
4-MeO-C_6H_4	30	88	45	*R*
4-Cl-C_6H_4	57	93	68	*R*
3-Cl-C_6H_4	96	90	73	*S*
3-NO_2-C_6H_4	96	63	73	*S*
2-furyl	30	70	37	*R*

Scheme 24. Hydrocyanation of imines promoted by *N*-oxide **29**.

absolute configuration of the α-amino nitriles was given.[45] The same authors reported the catalytic hydrocyanation of ketimines using 5 mol% of chiral *N*-oxide **30** at −20 °C. Under these conditions *N*-tosyl ketimines were converted into (*S*)-α-amino nitriles with moderate enantioselectivities (Scheme 25).



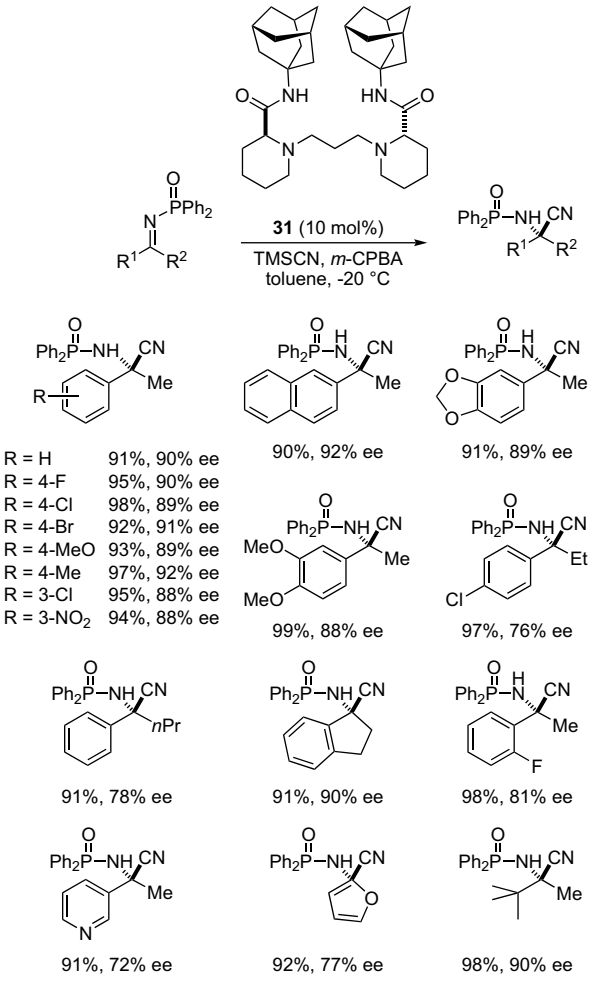
R	t (h)	Yield (%)	ee (%)
Ph	68	99	85
4-Me-C_6H_4	80	94	61
4-Cl-C_6H_4	80	91	71
4-Br-C_6H_4	80	90	71
4-MeO-C_6H_4	80	92	76
3,4-di-MeO-C_6H_3	70	95	91
2-naphthyl	80	98	71
(*E*)-PhCH=CH	80	99	61
cyclohexyl	68	99	85
*t*Bu	70	95	77

DAHQ: 2,5-di-(1-adamantyl)hydroquinone

Scheme 25. Catalytic hydrocyanation of ketimines.

In this reaction a hydroquinone is used as an additive to achieve good conversion values and higher enantioselectivities. In particular, the sterically hindered 2,5-di-(1-adamantyl)hydroquinone (DAHQ) gave rise to the best results when used in a 20 mol% catalytic amount.[46] Notably, in addition to aromatic substrates, aliphatic compounds such as ketimines bearing cyclohexyl and *tert*-butyl groups also provided acceptable results in both chemical yield and enantiomeric excess.

A considerable increase of enantioselectivity in the hydrocyanation of ketimines was achieved when the chiral *N*,*N*′-dioxide was generated in situ by oxidation with *m*-CPBA of the corresponding diamine **67**. In addition, the use of the *N*-diphenylphosphinoyl group also contributed to the enhancement of the enantioselectivity (Scheme 26).[47]



Scheme 26. Catalytic hydrocyanation of *N*-diphenylphosphinoyl ketimines.

The catalyst prepared in situ could be easily recovered and reused five times without any loss in catalytic activity or enantioselectivity. That the *N*,*N*′-dioxide was the actual catalyst was demonstrated because no reaction took place only in the presence of the diamine **31** (without *m*-CPBA) and identical results were obtained with the in situ-generated and the isolated *N*-oxide obtained from **31**. The *N*,*N*′-dioxide can act as a bifunctional catalyst by activating the ketoimine through hydrogen-bonding, thus controlling the reaction conformation. According to the model illustrated in Figure 5 the formation of the (*R*)-isomer is favored since the *Si* attack avoids steric repulsions between the phenyl phosphinoyl group and the bulky 1-adamantylamide.

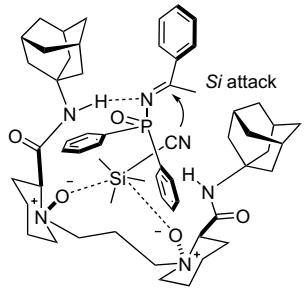
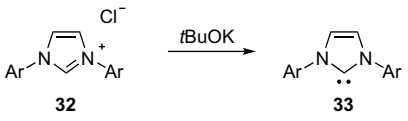


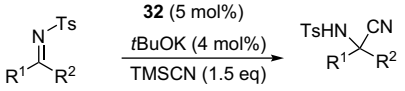
Figure 5. Proposed model for catalytic activity of *N*,*N*′-dioxides.



Ar: 2,4,6-trimethylphenyl

Scheme 27. Synthesis of carbene **33**.

The mechanism of the Strecker reaction catalyzed by chiral *N*-oxides has been investigated using DFT at the B3LYP/6-31G* level.[48] These calculations indicated that two reaction pathways are comparable for both non-catalyzed and catalyzed processes. In the catalytic Strecker reaction, the silyl cyanide reagent is strongly activated by coordination of the oxygen atom to the silicon atom. The reason for such an activation is the strong electron-donating character of the N–O functionality.



R^1	R^2	solvent	*T* (°C)	t (min)	Yield (%)
Ph	H	THF	0	45	97
4-MeO-C_6H_4	H	THF	0	300	98
4-Cl-C_6H_4	H	THF	0	30	84
1-naphthyl	H	THF	0	30	87
cyclohexyl	H	THF	0	60	87
1-phenethyl	H	THF	0	360	82
*t*BuCH_2	H	THF	0	300	86
Ph	Me	DMF	rt	180	93
4-Me-C_6H_4	Me	DMF	rt	180	99
4-MeO-C_6H_4	Me	DMF	rt	60	59
Ph	Ph	DMF	rt	240	88
*i*Bu	*i*Bu	DMF	rt	5	94
*i*Pr	*i*Pr	DMF	rt	5	84
(*E*)-PhCH=CH	Ph	DMF	rt	120	98

Scheme 28. TMSCN addition to imines catalyzed by the heterocyclic carbene **33**.

In addition to *N*,*N*′-dioxides, it has been reported that other Lewis bases such as the nitrogen- and oxygen-containing anions generated from imides or carboxylic acids catalyzed the Strecker-type reaction between *N*-tosylimine and trimethylsilyl cyanide in water containing DMF.[49]

3.2. Heterocyclic carbenes

Heterocyclic carbenes act as excellent organic catalysts in a variety of reactions including benzoin condensations, Stetter reactions, Diels–Alder reactions, 1,2-additions, and polymerizations.[50] Recently, Kondo and Aoyama have reported the first cyanation of aldimines[51] and ketimines[52] catalyzed by the *N*-heterocyclic carbene **33** prepared in situ from imidazole **32** and potassium *tert*-butoxide (Scheme 27).

Carbene **33** generated in situ from 5 mol % of **32**, catalyzed the addition of trimethylsilyl cyanide to imines, affording the corresponding α-amino nitriles with excellent yields (Scheme 28). As expected, aldimines were more reactive than ketimines and, whereas the hydrocyanation of the former was carried out in THF at 0 °C, hydrocyanation of the latter worked better in DMF at room temperature.[51,52]

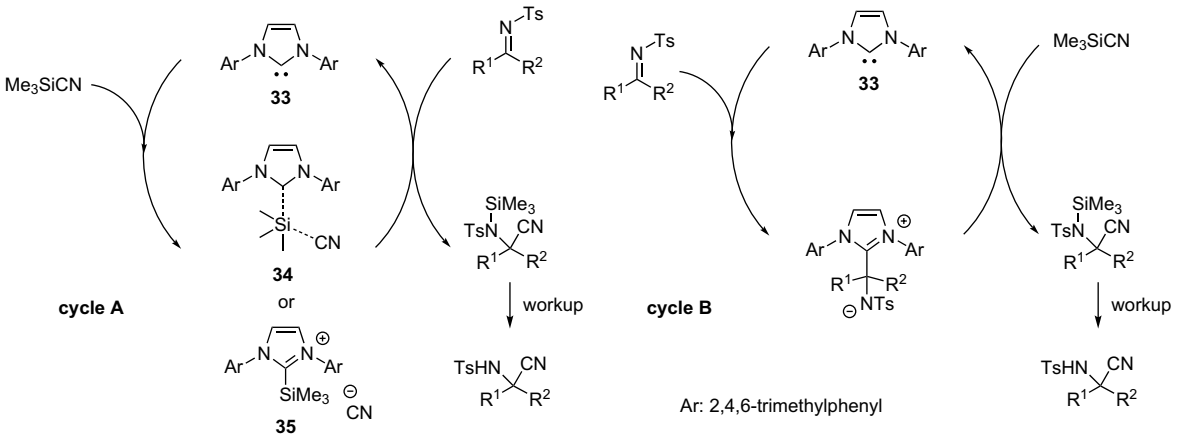
The active intermediate in the process was assumed to be the hypervalent silicate **34** formed from the carbene **33** and trimethylsilyl cyanide (Scheme 29, cycle A). However, the formation of a trimethylsilylimidazolium species **35**, which would transfer the cyano group more efficiently while regenerating the carbene, could also be proposed. Moreover, an alternative mechanism based on the initial attack of the carbene **33** on the imine was also invoked, as illustrated in the catalytic cycle B depicted in Scheme 29.

3.3. Amines and imines

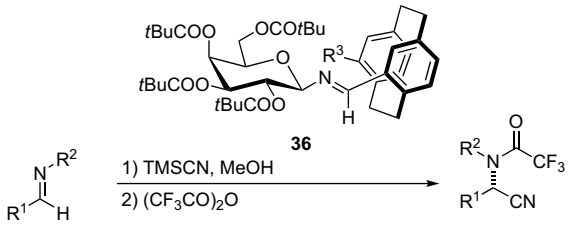
Kunz and co-workers[53] reported the catalytic effect exerted by *N*-galactosyl[2,2]paracyclophane carbaldimines **36** in the Strecker reaction (Scheme 30). Good-to-excellent enantioselectivities were obtained when the reaction was conducted in the presence of 5–10 mol % of **36**. The best results were obtained by using 10 mol % of catalyst. Actually, catalysts **36** neither display hydrogen-bonding interactions per se nor Brønsted acid properties.

The catalyst effect of **36** arose from the Lewis basic center cooperatively formed by the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group, which could trap the proton from the weak acid HCN formed in situ from trimethylsilyl cyanide and methanol, as shown in the model **37** (Fig. 6).

The direct Strecker reaction using trimethylsilyl cyanide as a cyanating agent in the absence of any solvent afforded α-amino nitriles in excellent yields.[54] It was considered that the active catalyst of the reaction was the amine employed in the three-component reaction (Scheme 31).

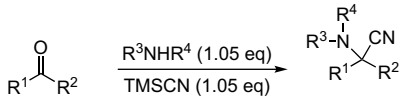


Scheme 29. Proposed organocatalytic cycles for carbenes.



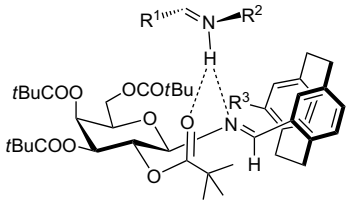
R^1	R^2	R^3	catalyst **77** (mol%)	*T* (°C)	t (h)	Yield (%)	ee (%)
Ph	allyl	CO_2Me	2	-50 to -20	20	55	71
4-Me-C_6H_4	allyl	H	10	-50 to -20	20	68	67
*i*Pr	allyl	CO_2Me	5	-50 to -20	30	20	96
cyclohexyl	$PhCH_2$	CO_2Me	5	-50 to -20	30	88	65
*i*Pr	allyl	CO_2Me	10	-50	24	89	96
cyclohexyl	$PhCH_2$	CO_2Me	10	-50	24	87	88
isoamyl	$PhCH_2$	CO_2Me	10	-50	24	84	99
4-MeO-C_6H_4	$PhCH_2$	CO_2Me	10	-50	24	87	82

Scheme 30. Strecker reaction catalyzed by cyclophane derivatives **77**.



R^1	R^2	R^3	R^4	t (min)	Yield (%)
Ph	H	Ph	H	3	99
Ph	H	4-MeO-C_6H_4	H	7	99
Ph	H	$PhCH_2$	H	3	99
Ph	H	allyl	H	3	99
Ph	H	$PhCH_2$	H	3	99
Ph	H	$PhCH_2$	$PhCH_2$	10	98
Ph	H	$PhCH_2$	Me	10	95
Ph	H	pyrrolidin-1-yl		5	98
4-Cl-C_6H_4	H	$PhCH_2$	$PhCH_2$	5	93
(*E*)-PhCH=CH	H	Ph	H	5	98
(*E*)-PhCH=CH	H	$PhCH_2$	H	3	99
(*E*)-PhCH=CH	H	$PhCH_2$	$PhCH_2$	12	90
(*E*)-Me$(CH_2)_4$CH=CH	H	$PhCH_2$	H	5	95
*i*Pr	H	Ph	H	3	99
*i*Pr	H	$PhCH_2$	H	3	99
*i*Pr	H	$PhCH_2$	$PhCH_2$	15	74
$PhCH_2CH_2$	H	$PhCH_2$	H	10	98
Ph	Me	$PhCH_2$	H	35	21
Et	Et	$PhCH_2$	H	18	77
-$(CH_2)_4$-		$PhCH_2$	H	13	98
-$(CH_2)_2C(t\text{Bu})(CH_2)_2$-		$PhCH_2$	H	12	97
-$(CH_2)O(CH_2)_2$-		$PhCH_2$	H	9	99
-$(CH_2)S(CH_2)_2$-		$PhCH_2$	H	11	98

Scheme 31. Strecker reaction under solvent-free conditions.

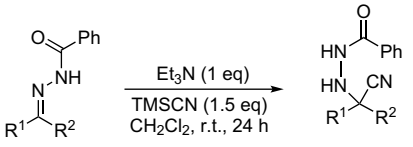


37

Figure 6. Proposed model **37** for catalytic effect of **36**.

As expected, aldehydes reacted faster than ketones. Indeed, only cyclic ketones afforded the corresponding α-amino nitriles under these conditions. The reaction showed a broad scope since both aromatic and aliphatic aldehydes were used as well as aromatic and aliphatic amines.

The cyanation of *N*-acylhydrazones with trimethylsilyl cyanide was reported by Kobayashi and co-workers, who used aliphatic amines as organic catalysts (Scheme 32).[55] The authors reported the use of stoichiometric amounts of amine, although it was reported in one case that 0.1 equiv of amine could also be used by increasing the reaction time to 168 h without significant loss of chemical yield.



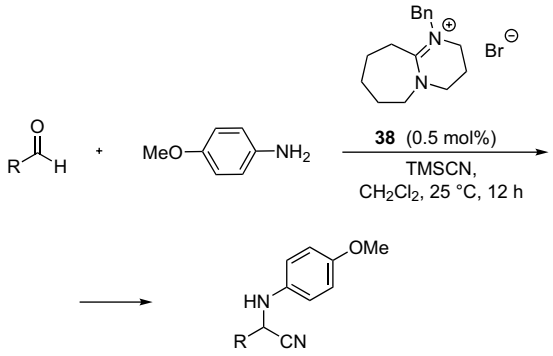
R^1	R^2	Yield (%)
$PhCH_2CH_2$	H	77
*n*heptyl	H	97
*i*Bu	H	87
*i*Pr	H	92
cyclohexyl	H	82
*t*Bu	H	62
$PhCH_2CH_2$	Me	60
$-(CH_2)_5-$		94
Ph	H	2
PhC≡C	H	nr
(*E*)-PhCH=CH	H	nr

nr: no reaction observed

Scheme 32. Hydrocyanation of hydrazones promoted by Et_3N.

Investigation of the substrate scope showed that aliphatic hydrazones reacted smoothly to afford the corresponding adducts in moderate-to-high yields. However, aromatic and α,β-unsaturated aldehyde-derived hydrazones remained almost intact resulting in the recovery of starting material.

Basic ammonium salts containing a tertiary amine in their structure, such as **38** are effective catalysts for the three-component Strecker reaction.[56] By using 0.5 mol % of **38** the corresponding α-amino nitriles are obtained from both aromatic and aliphatic aldehydes using *p*-anisidine and trimethylsilyl cyanide as nitrogen and cyanide sources, respectively (Scheme 33).

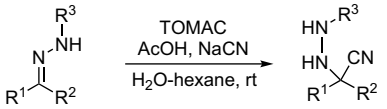


R	Yield (%)
Ph	77
4-MeO-C_6H_4	79
3,4-di-MeO-C_6H_3	67
$PhCH_2CH_2$	81
4-NO_2-C_6H_4	81
4-Cl-C_6H_4	69
3-NO_2-C_6H_4	72
3,4-methylenedioxyphenyl	68
$Me(CH_2)_3$	73
$Me(CH_2)_3$	83
$Me(CH_2)_3$	90

Scheme 33. Organocatalytic hydrocyanation catalyzed by basic ammonium salt **38**.

4. Phase-transfer catalysis

In 1990 Chiba and Okimoto highlighted the feasibility of applying phase-transfer catalysis to the addition of hydrogen cyanide to *N*-substituted hydrazones.[57] Ketone benzoyl-, tosyl-, and methoxycarbonyl-hydrazones added HCN generated in situ from sodium cyanide and acetic acid in a two-phase system in the presence of a catalytic amount of trioctylammonium chloride (TOMAC) (Scheme 34).

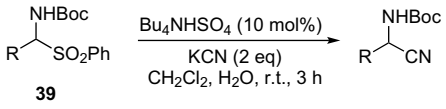


R^1	R^2	R^3	Catalyst (mol%)	time (h)	Yield (%)
*i*Bu	Me	COPh	10	2	92
*t*Bu	Me	COPh	20	6	79
*i*Pr	*i*Pr	COPh	40	21	79
$-(CH_2)_4-$		COPh	20	2	80
1-norbornanylene		COPh	10	5	94
*n*Pr	*n*Pr	Ts	10	2	80
*n*Pr	*n*Pr	CO_2Me	20	8	83
$-(CH_2)_5-$		CO_2Me	10	2	92
Ph	Me	COPh	40	21	92

Scheme 34. Phase-transfer-catalyzed hydrocyanation of hydrazones.

N-Boc imines generated in situ from *N*-Boc α-amido sulfones **39** underwent cyanide addition in 2-propanol or dichloromethane–water under phase-transfer conditions.[58] Tetrabutylammonium

hydrogen sulfate and benzyltriethyl-ammonium chloride were effective catalysts affording the corresponding *N*-Boc-α-amino nitriles in good yields (Scheme 35). Two equivalents of potassium cyanide were necessary, presumably because one equivalent acted as a base for generating the reactive intermediate *N*-Boc imine.

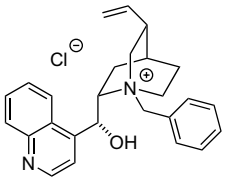


39

R	Yield (%)	R	Yield (%)
Ph	73	2-MeO- C_6H_4	74
4-Me-C_6H_4	82	1-naphthyl	80
4-*i*Pr- C_6H_4	79	2-furyl	84
4-*t*Bu- C_6H_4	78	2-thienyl	84
4-Cl- C_6H_4	84	*n*Pr	78
4-Br- C_6H_4	83	*i*Pr	81
3-OH- C_6H_4	81	*s*Bu	81
4-NO_2- C_6H_4	55	*n*pentyl	79
3-NO_2- C_6H_4	36	*n*undecyl	88
2-NO_2- C_6H_4	47	*t*Bu	82
4-CN- C_6H_4	42	$PhCH_2CH_2$	81
4-F- C_6H_4	83	$Ph(CH_2)_3$	82
4-MeO- C_6H_4	79	cyclohexyl	85
3-MeO- C_6H_4	82		

Scheme 35. Hydrocyanation of *N*-Boc-α-amido sulfones.

The reaction showed a broad scope since aromatic, aliphatic, and heteroaromatic compounds could be used giving in all cases good chemical yields. The same authors explored the asymmetric version of the reaction (for R=Ph) using 10 mol % of *N*-benzyl cinchonidinium chloride **40** as a catalyst. Unfortunately, the corresponding amino nitrile was obtained as a racemic mixture.[58]

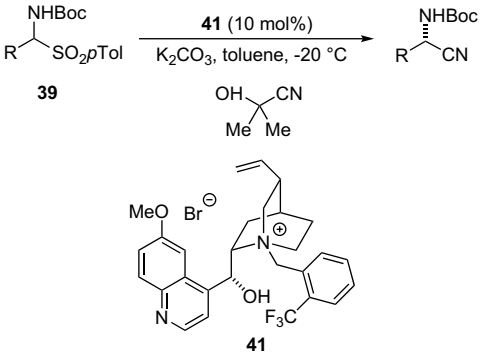


40

On the other hand, Ricci and Herrera[59] have exploited the modified quinidinium-type phase-transfer catalyst **41** in the catalytic asymmetric preparation of (*S*)-*N*-Boc amino nitriles in up to 88% ee (Scheme 36). These authors employed a cyanide source acetone cyanohydrins, which played a crucial role not only in cyanide transfer but also in generating the imine from precursor **39** at the interface.

According to this hypothesis the catalytic cycle illustrated in Scheme 37 was proposed. The conjugate base of the cyanohydrins might form with the chiral catalyst a lipophilic ion pair that released the first cyanide ion responsible for the imine formation (path A). In the presence of the imine the ion pair delivered a second cyanide ion to the imine carbon leading to the product of the reaction (path B).

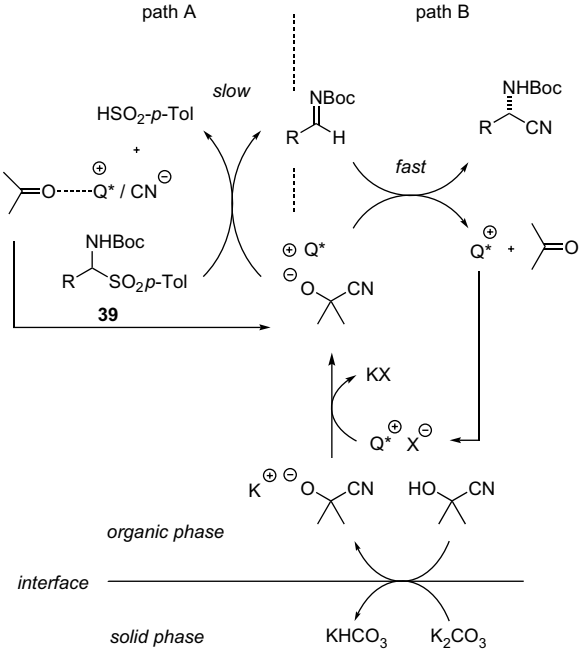
Maruoka and co-workers reported the asymmetric Strecker reaction of aldimines using aqueous potassium cyanide by the chiral quaternary ammonium salt **42** bearing a tetranaphthyl backbone.[60]



39 **41**

R	Yield (%)	ee (%)
$PhCH_2CH_2$	95	68
$PhCH_2$	95	79
Me	85	78
$MeCH_2$	88	80
*i*Pr	92	82
*t*Bu	85	88
$Me(CH_2)_5$	95	72
*i*Bu	90	68
cyclohexyl	95	50

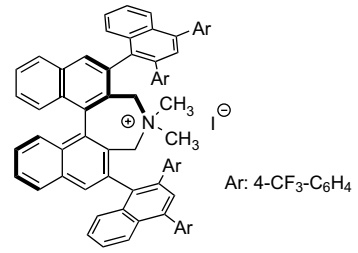
Scheme 36. Asymmetric phase-transfer-catalyzed synthesis of enantioenriched α-amino nitriles.

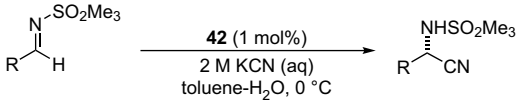


Scheme 37. Catalytic cycle for the phase-transfer-catalyzed Strecker reaction of α-amino sulfones and acetone cyanohydrins.

By using the catalyst **42** α-amino nitriles of (*S*)-configuration were obtained in excellent chemical yields and enantioselectivities with a catalyst loading of only 1 mol % (Scheme 38).

By using the same biphasic reaction conditions, *N*-arylsulfonyl-α-amino nitriles were obtained with excellent enantioselectivities from the corresponding α-amido sulfones, through a process involving the in situ generation of the reactive *N*-sulfonylimines.

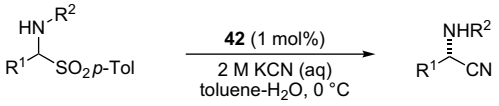




R	t (h)	Yield (%)	ee (%)
Cicloоctyl	2	88	97
*i*Pr	3	85	93
$PhCH_2CH_2$	2	81	90
*i*Bu	3	82	88
$Ph(Me)_2C$	3	94	94
adamantyl	8	95	98

Scheme 38. Asymmetric hydrocyanation of α-amido sulfones via phase-transfer catalysis using catalyst **42**.

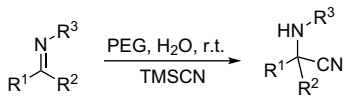
Both mesitylenesulfonyl (Mts) and 4-methoxy-2,3,6-trimethylbenzenesulfonyl (Mtr) groups were evaluated as suitable protecting groups. In both cases, very good results were obtained with primary and secondary alkyl substituents (Scheme 39).[60]



R^1	R^2	t (h)	Yield (%)	ee (%)
cyclohexyl	Mts	1.5	99	97
cyclooctyl	Mts	2	99	98
*i*Pr	Mts	1.5	99	97
N-Cbz-piperidin-4-yl	Mts	1	99	99
$PhCH_2CH_2$	Mts	1	99	94
$(Me)_2CHCH_2$	Mts	1	96	91
$Me(CH_2)_5CH_2$	Mts	1	96	84
$PhCH_2$	Mts	1	93	85
$PhCH_2CH_2$	Mtr	1	98	96
$(Me)_2CHCH_2$	Mtr	1	99	93
$Me(CH_2)_5CH_2$	Mtr	1	96	89
$PhCH_2$	Mtr	1	86	86

Scheme 39. Hydrocyanation of *N*-sulfonylimines generated in situ.

The direct trimethylsilyl cyanide addition to imines in water was catalyzed by polyethylene glycol (PEG), which acted as thermally stable and recoverable medium for phase-transfer catalysis (Scheme 40).[61] The reaction showed a wide scope since both aromatic and aliphatic imines were prepared and the catalyst could be recovered and reutilized. With high chemical yields, the reaction is a good example of the use of an environmentally friendly process.



R^1	R^2	R^3	t (h)	Yield (%)
Ph	H	Ph	3	94
Ph	H	4-F-C_6H_4	3	94
Ph	H	2-Me-C_6H_4	5	88
4-Br-C_6H_4	H	Ph	3	92
4-Cl-C_6H_4	H	4-F-C_6H_4	3	94
4-Me-C_6H_4	H	Ph	3	90
4-Me-C_6H_4	H	Tosyl	3	90
2,4,6-tri-Me-C_6H_2	H	Ph	3.5	88
4-MeO-C_6H_4	H	Ph	3	90
2,4-di-MeO-C_6H_4	H	Ph	3.5	86
4-allyloxy-C_6H_4	H	Ph	3.5	90
4-NO_2-C_6H_4	H	Ph	5	84
(*E*)-PhCH =CH	H	Ph	5	82
2-naphthyl	H	Ph	3	90
$C_{10}H_{21}$	H	Ph	5	85
Ph	Me	Ph	4	88
4-Me-C_6H_4	Me	Ph	4.5	86

Scheme 40. Addition of TMSCN to imines catalyzed by PEG.

5. Conclusions

The increasing interest in highly enantioselective synthetic strategies observed over the past years has needed effective methods for securing the production of enantiomerically pure molecules through environmentally friendly approaches. In this respect the renewed interest in organic catalysis is beyond any doubt. A large number of organic reactions are catalyzed by small organic molecules and the Strecker reaction represents a good example of the various possibilities offered by organocatalysis including catalysis by organic Brønsted acids, Lewis bases, and phase-transfer catalysis. A number of organocatalyzed syntheses of α-amino nitriles through the Strecker reaction have been developed in recent years. Optically active α-amino nitriles are useful intermediates for preparing α-amino acids and their utility is illustrated in numerous reports. As seen in some of the examples described herein, the various approaches can be considered complementary, e.g., between aromatic and aliphatic substrates, but subtle changes in the catalyst can significantly affect the stereochemical outcome of the reaction. Because of this, it is expected that the design and synthesis of new catalysts in the future will be more efficient in both reactivity and selectivity. Indeed, although in several instances organic catalysts could be used in substoichiometric amounts (e.g., 20–30 mol %), several examples illustrated in this compilation demonstrated that it is also possible to achieve good results with loadings of 1 mol %. Given the already high number of successful applications of organocatalysis we are sure that new highly efficient organic catalysts will be developed for the Strecker reaction.

Acknowledgements

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Biographical sketch

Pedro Merino was born in Zaragoza in 1962 and graduated with an honors M.Sc. degree in chemistry from the University of Zaragoza in 1986. After earning a Ph.D. in organic chemistry from the same university in 1989 under the guidance of Professor Enrique Melendez, he spent two years as a postdoctoral fellow with Professor Alessandro Dondoni at the University of Ferrara (Italy), working on thiazole chemistry applied to asymmetric synthesis. In 1992 he returned to the University of Zaragoza as an Assistant Professor, where he started his independent research. In 1994 he was promoted to Associate Professor and in 2005 he obtained his habilitation as a full professor in organic chemistry. In 2006 he was awarded a Chair in organic chemistry at the Department of Organic Chemistry, University of Zaragoza. His research interests span the areas of asymmetric synthesis, target-oriented synthesis, organometallic chemistry, and asymmetric metal-assisted and organic catalysis.

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Raquel P. Herrera was born in Alicante, Spain in 1977. She received her B.S. degree from the University of Alicante in 1999 and her M.S. degree from the same University in 2000. From 1999 to 2003, she completed her Ph.D. under the supervision of Professor Albert Guijarro and Professor Miguel Yus at the University of Alicante. She then took up a European postdoctoral contract with Professor Ricci (University of Bologna, Italy) in the Industrial Chemistry Faculty until March 2006, at which time she joined Dr. Jose M. Lassaletta's group at the IIQ-CSIC (Seville, Spain). She was appointed to her present position at ICMA (Instituto de Ciencia de Materiales de Aragón) CSIC-University of Zaragoza in January 2008. Her research interests focus on asymmetric organocatalysis and its applications.