A General Catalyst for the Asymmetric Strecker Reaction**

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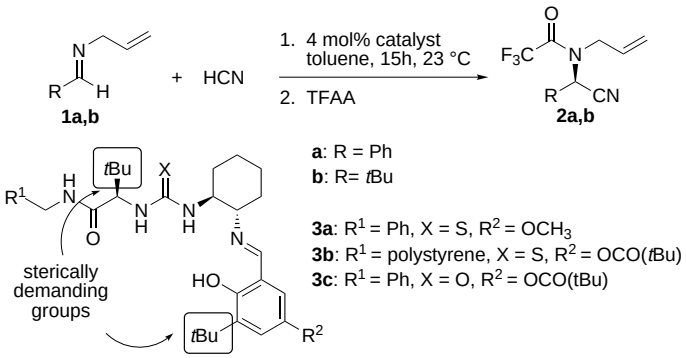
α-Amino acid derivatives are broadly useful chiral building blocks, with especially important applications in complex natural product and combinatorial syntheses. Substantial progress has been made toward the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potential.[1, 2] One of the most attractive strategies amenable to asymmetric catalysis is the addition of hydrogen cyanide to imines (the Strecker reaction, Scheme 1),[3] and promising enantioselective variants of this reaction have been uncovered very recently.[4] Here we report new catalysts for the Strecker reaction that display high enantioselectivity and broad substrate scope for both aromatic and aliphatic imines. These catalysts can be used either in solution or covalently linked to polystyrene resin, with the latter retaining full reactivity and enantioselectivity after repeated recycling.



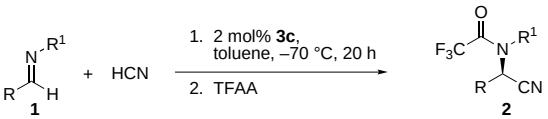
Scheme 1. Asymmetric Strecker reaction with catalysts **3**.

The discovery and optimization of catalysts for the asymmetric Strecker reaction was approached by screening parallel synthetic libraries of resin-bound catalyst candidates and validating the most enantioselective library members by the preparation of soluble analogues.[5] In previous work,[4c] simple Schiff base libraries with the general structure shown in Scheme 1 were identified as effective catalysts for the asymmetric hydrocyanation of aromatic imine **1a**. The key elements responsible for high enantioselectivity were the presence of bulky substituents at both the amino acid position and at the 3-position of the salicylimine moiety, with **3a** emerging from the preliminary screens as an enantioselective catalyst with promising generality (Scheme 1). On the basis of these encouraging results, we have constructed a new optimization library of 70 compounds incorporating seven amino acids with large α-substituents and ten new salicylaldehyde derivatives. Each library member was evaluated for enantioselectivity in the Strecker reaction of aliphatic imine **1b** at 23 °C, and the 5-pivaloyl-substituted Schiff base **3b** proved to be the superior catalyst.[6, 7]

A soluble analogue of **3b** was prepared (**3c**) and evaluated.[8] At −78 °C, 2 mol % of **3c** catalyzed the formation of the Strecker adduct **2b** in 75 % yield (isolated product) and 95 % *ee*. This constitutes a substantial improvement over results obtained with catalyst **3a** (85 % *ee*).[4c] Benzaldimine **1a** also underwent hydrocyanation with improved enantioselectivity (95 % *ee* with catalyst **3c** vs. 91 % *ee* with **3a**).

The scope of the asymmetric Strecker reaction catalyzed by **3c** proved to be remarkably broad (Table 1). Aryl imines (entries 1, 3–12) are excellent substrates, undergoing hydrocyanation in generally high enantioselectivities and yields. The bromo-substituted products **2i**–**k** are particularly versatile intermediates, as these can be elaborated further by using cross-coupling or Heck reactions, thereby providing access to a wide variety of arylglycine derivatives. While all of the aryl imine substrates **1a**, **c**–**l** exist predominantly or exclusively as the *E* isomers, this does not appear to be a requirement for high enantioselectivity. The cyclic *Z*-imine 3,4-dihydroisoquinoline (**1v**) underwent hydrocyanation with **3c** in 91 % *ee*,

Table 1. Asymmetric catalytic Strecker reactions with catalyst **3c**.



Entry		Imine **1** R	Imine **1** R^1	Yield [%]	*ee* [%][a]
1	**a**	C_6H_5	allyl	74	95
2	**b**	*tert*-butyl	allyl	75	95 (91)
3	**c**	*p*-$OCH_3C_6H_4$	allyl	98	95
4	**d**	*m*-$OCH_3C_6H_4$	allyl	99	93
5	**e**	*o*-$OCH_3C_6H_4$	allyl	93	77
6	**f**	*p*-$CH_3C_6H_4$	allyl	99	95
7	**g**	*m*-$CH_3C_6H_4$	allyl	97	96
8	**h**	*o*-$CH_3C_6H_4$	allyl	96	95
9	**i**	*p*-BrC_6H_4	allyl	89	89
10	**j**	*m*-BrC_6H_4	allyl	87	90
11	**k**	*o*-BrC_6H_4	allyl	88[b]	95
12	**l**	*p*-$(CH_3)_3CC_6H_4$	allyl	89	97
13	**m**	*tert*-butyl	benzyl	88	96 (93)
14	**n**	cyclohexyl	benzyl	85	87
15	**o**	cyclohexyl	allyl	88	86
16	**p**	1-cyclohexenyl	benzyl	90	91 (87)
17	**q**	$(CH_3)_3CCH_2$	benzyl	85	90 (87)
18	**r**	$CH_3(CH_2)_4$	benzyl	69	78
19	**s**	$(CH_3)_2CH$	benzyl	74	79
20	**t**	cyclopropyl	benzyl	89	91
21	**u**	cyclooctyl	allyl	65	90

[a] Values of *ee* in parentheses were obtained with resin-bound catalyst **3b**. [b] Reaction time was 36 h.

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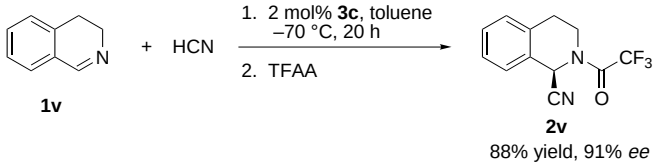
with the same sense of stereoinduction with respect to the benzylic center as the acyclic *E*-imines [Eq. (1)].[9]

Catalyst **3c** also proved very effective for the hydrocyanation of a variety of aliphatic substrates (Table 1, entries 2, 13–20). Either *N*-benzyl or allyl imines could be used with no significant differences in the results obtained (entries 2 and 13, and 14 and 15). The size of the aliphatic group appears to dictate the level of enantioselectivity with these substrates, with the largest groups affording the highest *ee* values (e.g., entry 12). Given the results described above for 3,4-dihydroisoquinoline (**1v**), it appears unlikely that the lower *ee* values obtained with unhindered imines are due to the increased amount of *Z* isomer present in these substrates.

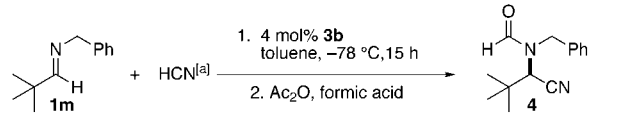


(1)

In general, the soluble catalyst **3c** effected hydrocyanation of imines with 2–4% higher *ee* values than the resin-bound analogue **3b** (Table 1, entries 2 and 13, 16 and 17). On the other hand, while all of the reactions summarized in Table 1 led to quantitative product formation with no detectable by-products, some losses were incurred upon product isolation as a result of the need to separate the catalyst chromatographically. In that respect, the polymer supported catalyst **3b**—which is easily removed from the reaction mixtures by simple filtration—holds practical advantages compared to the solution-phase analogue, despite the slightly lower enantioselectivity it displays. To assess the practical potential of the resin-bound catalyst, the Strecker reaction of pivalaldimine **1m** was examined under preparative conditions. Clean hydrocyanation of **1m** was observed with only a slight reduction in enantioselectivity (96% to 93% *ee*) by using **3b** (Table 1, entry 13). The product was isolated in nearly quantitative yield after catalyst removal by filtration, and no loss of catalyst reactivity or product enantioselectivity was observed after ten catalyst recycles (Table 2).

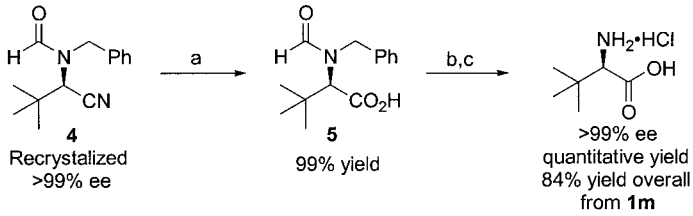
As noted above, one of the most important applications of the asymmetric Strecker reaction is toward the synthesis of enantiomerically enriched amino acids. We selected D-*tert*-leucine as a target because of its considerable utility as a chiral building block and its high current commercial cost ($>\$100\,g^{-1}$). Attempts to hydrolyze the amino nitrile product of the Strecker reaction of **1m** required fairly harsh conditions (concentrated acid, $>90\,^{\circ}C$) and resulted in considerable decomposition. This problem was circumvented by first protecting the amino nitrile as the formamide **4**, and this allowed facile recrystallization to give enantiomerically pure material in 85% overall yield. Complete and clean hydrolysis of **4** and deformylation was accomplished in one pot (Scheme 2) by using concentrated HCl at 70 °C, although some racemization was observed (99% *ee* to 93% *ee*). In contrast, selective hydrolysis of the nitrile to the acid **5** with concentrated sulfuric acid at 45 °C for 20 h occurs with no

Table 2. Preparative Strecker reactions with resin-bound catalyst **3b**.[a]



Cycle[b]	Yield [%][c]	*ee* [%]
1	97	92
2	98	93
3	98	93
4	97	93
5	97	92
6	96	93
7	98	93
8	97	93
9	98	93
10	98	93

[a] Either HCN or equimolar quantities of TMSCN (TMS = trimethylsilyl) and MeOH were employed with identical results (1.3 equiv). The scale of the reaction was 1.07 g (6.1 mmol) in all cases. [b] Catalyst was removed by filtration from the previous reaction mixture and rinsed with toluene prior to reuse. [c] Yield of isolated **2** bearing no detectable impurities as determined by ^{1}H NMR spectroscopy.



Scheme 2. Hydrolysis and deformylation of **4**. a) 65% (w/v) H_2SO_4, 45 °C, 20 h; b) HCl (conc.), 70 °C, 12 h; c) H_2, Pd/C, MeOH.

racemization. Deformylation was then effected in quantitative yield by using concentrated HCl to yield the benzyl-protected amino acid; removal of the benzyl group with Pd/C under 1 atm of H_2 gas afforded *tert*-leucine in >99% *ee* and 84% overall yield from imine **1m**.

In summary, the asymmetric Strecker reaction catalyzed by nonmetal catalysts **3b** and **3c** provides direct access to a diverse range of unnatural aliphatic and aromatic substituted amino acid precursors in high enantiomeric excess. The catalysts are easy to prepare in solution or on solid phase. The use of the resin-bound catalyst **3b** allows Strecker product purification by simple filtration and solvent removal, and the catalyst can be reused indefinitely without loss of either activity or enantioselectivity. Preliminary kinetic experiments indicate that the reaction follows Michaelis–Menten kinetics consistent with reversible binding of imine followed by rate-limiting addition of HCN. Consistent with the notion that these catalysts are enzyme-like, all structural components of **3c** have been shown to be vital for both reactivity and enantioselectivity and thus appear to function cooperatively. Experiments to ascertain the precise mechanism of catalysis and the application of this catalyst class to other types of enantioselective reactions of imines and related electrophiles are currently under investigation.

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[6] Full details of the parallel library synthesis and evaluation are provided as Supporting Information.
[7] HCN was generated by the method of Ziegler. Alternatively, generation of HCN in situ by reaction of TMSCN and MeOH afforded identical results. K. Ziegler in *Organic Synth. Coll. Vol. 1* (Eds.: H. Gilman, A. H. Blatt), Wiley, New York, **1932**, p. 314. **Caution**: Hydrogen cyanide is a highly toxic and volatile compound that should be handled with extreme care to avoid inhalation.
[8] Whereas the thiourea derivatives proved slightly more enantioselective than the urea derivatives in the resin-bound catalysts, there was no significant difference between them in the solution analogues. On the other hand, the urea-containing catalyst **3c** proved easier to synthesize in solution than the thiourea analogue (see Supporting Information).
[9] The stereochemical assignment is based on comparison of CD spectra of **2v** with those of compounds **2f**, **g**, **i**, and **p** (see Supporting Information).

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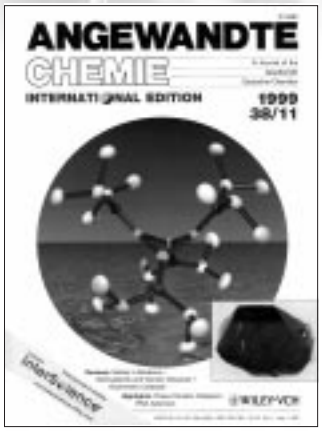

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