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STRECKER REACTIONS OF CHIRAL *N*-ACYLHYDRAZONES

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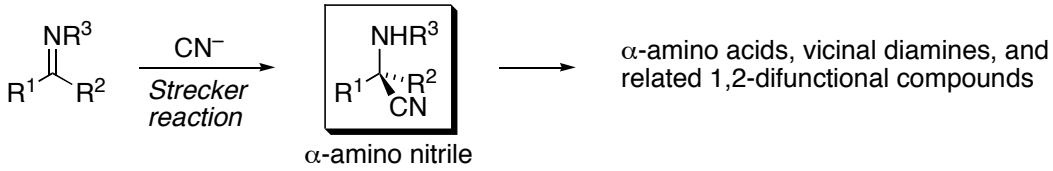
Abstract – Development of a method for addition of trimethylsilyl cyanide to chiral oxazolidinone-derived *N*-acylhydrazones is described. The diastereoselectivity was found to be highly dependent on the substituent of the oxazolidinone moiety; 4-phenyl-2-oxazolidinone achieved much higher stereocontrol than four other oxazolidinones screened. The reaction gives modest selectivity with aliphatic hydrazones and excellent selectivity with hydrazones prepared from aromatic aldehydes.

INTRODUCTION

Strecker-type cyanide addition to C=N bonds affords straightforward access to α-amino nitrile compounds, which offer a broad range of synthetic applications, mainly by hydrolysis, reduction or alkylation reactions of the nitrile group.[1] Recent interests on synthesis of unusual α-amino acids as key building blocks for pharmaceuticals have prompted intense investigation of the asymmetric Strecker-type reaction.[2] Highly efficient catalytic processes have been developed for asymmetric Strecker-type cyanation of imines; these have been based on organocatalysts,[3] phase transfer catalysts,[4] and metal Lewis acid catalysts.[5]

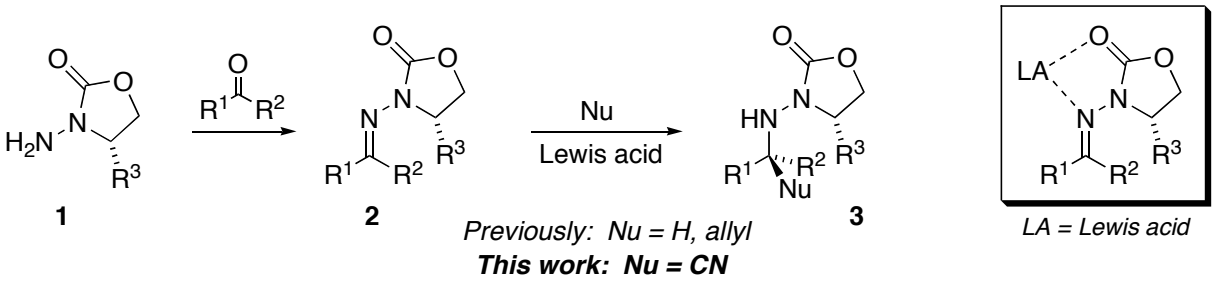


Scheme 1. The Strecker reaction and its utility

This paper is dedicated to Prof. Steven M. Weinreb on the occasion of his 65th birthday.

Use of enantiopure chiral auxiliaries offers a practical alternative wherein the intermediate diastereomer separation facilitates general access to rigorously enantiopure compounds, even in cases where the selectivity may not be optimal. Effective auxiliaries have been reviewed extensively,[1,2] and selected examples include α-substituted ethylamines,[6] 1,2-amino alcohols,[7] carbohydrate derivatives,[8] and sulfinimines.[9] Important biologically active α,α-dialkyl amino acids have been obtained with high selectivity using an acyloxy amino acid as a chiral auxiliary.[10] Diastereoselective Strecker reactions have also been accomplished by crystallization-induced asymmetric transformations of carbonyl compounds in the presence of chiral amines and cyanide donors.[11]

Among all the previous work noted above, there have been only sporadic reports regarding *N*-acylhydrazones as substrates for asymmetric Strecker-type cyanation. With their ease of preparation, increased air and hydrolytic stability, *N*-acylhydrazones are superior imine surrogates.[12] In 2004, Jacobsen reported asymmetric hydrocyanation to *N*-acylhydrazones catalyzed by lanthanide-PYBOX complexes.[13] Although good selectivity was observed for some aromatic and aliphatic aldehyde hydrazones, the scope is still limited to electron-rich hydrazones. More recently, Kobayashi has reported catalytic procedures for dual activation[14] in racemic cyanation of *N*-acylhydrazones.[15] Chiral *N*,*N*-dialkylhydrazones, prepared from (*S*)-1-amino-2-methoxymethylindoline (SAMI)[16] and (*S*)-1-amino-2-methoxymethyl-pyrrolidine (SAMP),[17] have also been used for Strecker-type reactions. However, the use of chiral *N*-acylhydrazones in Strecker reactions has not previously been reported.



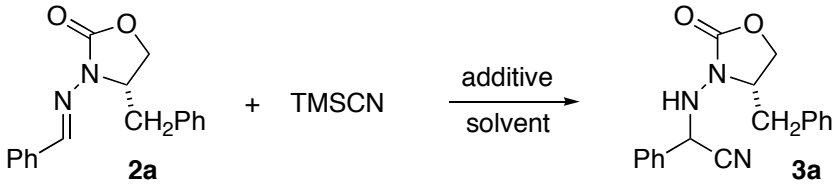
Scheme 2. General chiral *N*-acylhydrazone approach

Our recent studies have revealed *N*-acylhydrazones derived from chiral oxazolidinones[18] are excellent substrates for asymmetric nucleophilic additions of hydride[19] and allylsilane[20] reagents to C=N bonds.[21,22] The design of these chiral imino acceptors incorporates bidentate Lewis acid binding for efficient electrophilic activation and restriction of rotamer populations (Scheme 2). Following our initial studies, several applications of these chiral *N*-acylhydrazones to a variety of other addition reactions have been reported.[23] Inspired by the potential to build a general suite of reaction types around the general chiral *N*-acylhydrazone approach indicated in Scheme 2, we embarked on a study of their application in asymmetric Strecker-type reactions, and here we disclose the results of this methodology study.

RESULTS AND DISCUSSION

To initiate the study, the effects of Lewis acids on TMSCN addition were examined using prototype hydrazone (**2a**)[22] (Table 1). A control experiment established that **2a** does not react with TMSCN in the absence of Lewis acid (Entry 1). Based on the previous success with In(III) Lewis acids,[20,22b] several In(III) salts were screened. The hydrazone was indeed activated by $In(OTf)_3$, resulting in a good yield of α-amino nitrile (**3a**) (Entry 2). Comparison of In(III) halides showed that the counterion was important; $InCl_3$ was somewhat less active than the corresponding triflate, while InF_3 was inactive (Entries 3 and 4).[24] Nucleophilic activation of the TMSCN with tetrabutylammonium triphenyldifluorosilicate[25] (TBAT) as fluoride source also promoted the reaction in the presence of $In(OTf)_3$ (Entry 5), but the yield and diastereoselectivity were not competitive with $In(OTf)_3$ alone.

Table 1. Additions with variation of Lewis acid



Entry	Additives	Solvent	Conversion, %[a]	**3a**, %[b]	dr[c]
1	None	CH_2Cl_2	0	0	--
2	$In(OTf)_3$		86	77	67:33
3	$InCl_3$		62	48	55:45
4	InF_3		0	0	--
5	$In(OTf)_3$, TBAT[d]		91	59	63:37
6	$In(OTf)_3$	CH_3CN	91	78	52:48
7		THF	89	67	55:45
8		Et_2O	82	41	55:45
9		DMF	nd[e]	0	--

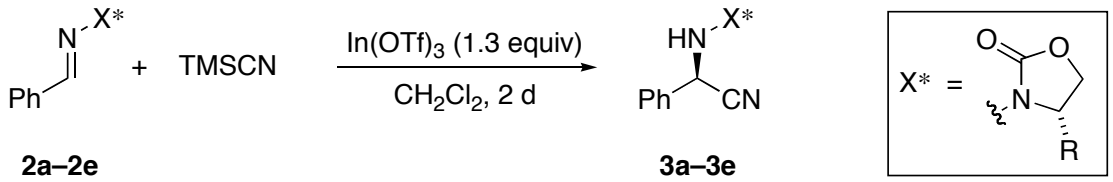
[a] Calculated from recovered hydrazone(**2a**). [b] Percent isolated yield of **3a**. [c] Diastereomer ratio, determined by ^1H NMR spectra prior to chromatography. [d] TBAT = tetrabutylammonium triphenyldifluorosilicate. [e] nd = not determined

Consistent with precedent,[8,17] a solvent dependence was also observed under these conditions (Entries 6–9). Decreased diastereomer ratios and moderate yields were observed in acetonitrile, diethyl ether and THF, whereas the reaction did not occur in DMF. A possible explanation is the interference with the two-point-binding complex (Scheme 2) by more polar solvents.

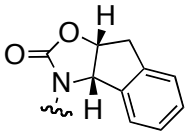
Based on the above results, the optimal conditions of (Table 1, Entry 2: 1.3 equiv $In(OTf)_3$ in CH_2Cl_2) were applied for screening of auxiliaries (Table 2). For most of the oxazolidinones, yields of cyanide adducts were in a useful range (up to 77%), but the diastereomeric ratios never exceeded 3:1. Beyond the point of attachment, it seems that the size of the substituent on the oxazolidinone moiety does not

affect selectivity (compare Entries 2 and 3). This is in sharp contrast to the observations with radical additions to a related series of hydrazones; in those reactions all of the auxiliaries were quite effective.

Table 2. Additions with variation of oxazolidinones



2a–2e **3a–3e**

Entry	Substrate	R of X*	Conversion, %[a]	Yield, %[b]	dr[c,d]
1	**2a**	CH_2Ph	86	77 (**3a**)	67:33
2	**2b**	*i*-Pr	87	65 (**3b**)	60:40
3	**2c**	$CHPh_2$	72	44 (**3c**)	67:33
4	**2d**	X* = 	93	72 (**3d**)	73:27
5	**2e**	Ph	77	46 (**3e**)	>99:1

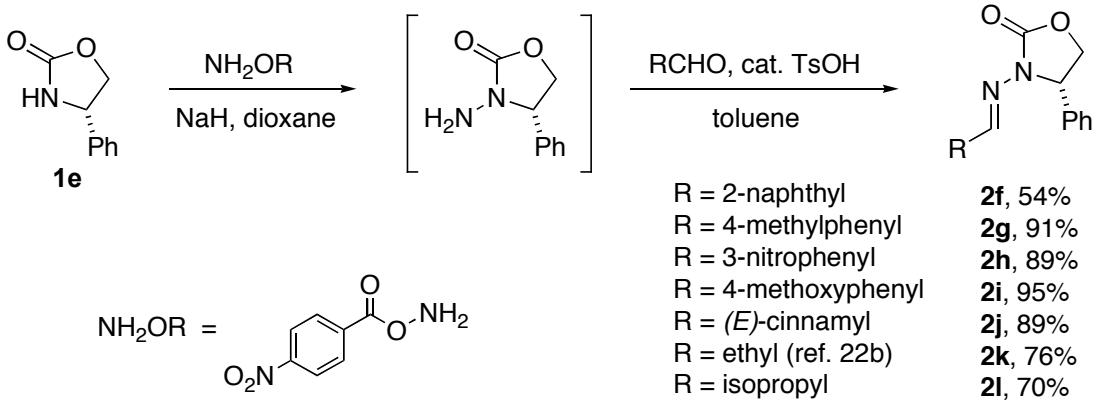
[a] Calculated based on recovered substrate. [b] Percent isolated yield. [c] Diastereomer ratio, determined by ^1H NMR spectra of product mixtures prior to chromatography. [d] Configurations assigned by analogy with **3l** (see eq 3).

Fortunately, there was a dramatic difference with the hydrazone (**2e**) derived from (*S*)-4-phenyl-2-oxazolidinone, which provided excellent diastereoselectivity (>99:1 dr, 2 days, Entry 5), albeit with moderate yield. Control experiments showed longer reaction time (7 days, 48% yield with 26% of hydrazone recovered) or increased TMSCN (10 equiv, 36% yield) did not improve the yields. A possible explanation for the anomalous stereoselectivity with **2e** is in the very small steric requirement of the linear CN^- anion, such that the sp^2-hybridized phenyl substituent of **2e** with unrestricted conformation (in comparison to **2d**) is the only one which can effectively block access to the imino carbon.

With outstanding stereoselectivity at hand, a survey of scope was undertaken using a series of hydrazones, which were prepared from the corresponding aldehydes in excellent yields for the two-step sequence by our standard procedure[26] (Scheme 3).

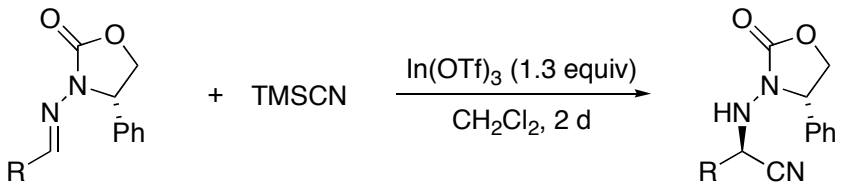
When subjected to the standard conditions, neutral or moderately electron-rich aromatic aldehyde hydrazones gave modest yields but excellent diastereoselectivities (Table 3, Entries 1-3). Electron-deficient *m*-nitrobenzaldehyde, the hydrazone of which has been previously found unreactive with TMSCN,[13] also participated in the reaction via hydrazone (**2h**) (Entry 4) to give a moderate yield of **3h**, but the selectivity dropped dramatically to 1.5:1. With a strong electron-donating group, there was very low isolated yield of **3i** (Entry 5), but this was in contrast to the good conversion detected by TLC,

suggesting the low yield may result from decomposition of the α-amino nitrile during purification. Interestingly, (*E*)-cinnamyl aldehyde hydrazone (**2j**) (Entry 6) was unreactive. On the other hand, aliphatic hydrazones (**2k**) and (**2l**) (Entries 7 and 8) participated in the reaction with modest diastereoselectivity. At –55 ˚C, selectivity of addition to **2l** improved slightly (not shown), but reaction rate at this temperature was too slow to be practical.



Scheme 3. Preparation of chiral *N*-acylhydrazones

Table 3. Scope of addition of TMSCN to chiral *N*-acylhydrazones

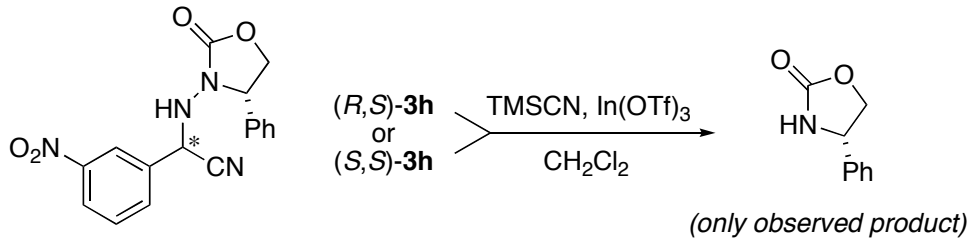


Entry	Hydrazone	R	Conversion, %[a]	Yield, %[b]	dr[c,d]
1	**2e**	Ph	77	46 (**3e**)	>99:1
2	**2f**	2-naphthyl	80	41 (**3f**)	>95:5
3	**2g**	4-methylphenyl	82	34 (**3g**)	>99:1
4	**2h**	3-nitrophenyl	100	53 (**3h**)	60:40
5	**2i**	4-methoxyphenyl	92	5 (**3i**)	>95:5
6	**2j**	*(E)*-cinnamyl	58	0 (**3j**)	--
7	**2k**	ethyl	100	37 (**3k**)	67:33
8	**2l**	isopropyl	100	73 (**3l**)	75:25

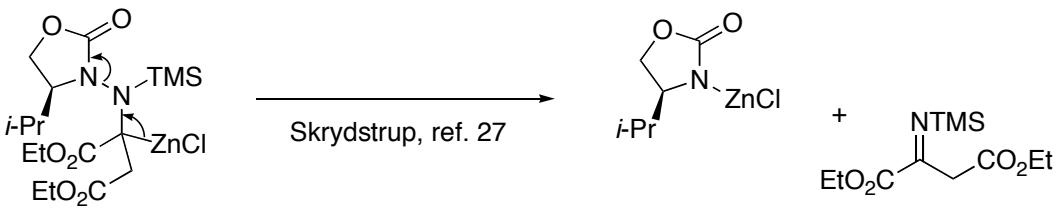
[a] Based on recovery of **2** after chromatography. [b] Isolated yield of **3**. [c] Diastereomer ratio of **3** measured by ^{1}H NMR spectrometry prior to chromatography. [d] Configurations assigned by analogy with **3l** (see eq 3).

The role of electronic properties in determining selectivity in the case of **2h** calls for further discussion. There are several reasonable explanations for the much lower selectivity in cyanation of the *m*-nitrobenzaldehyde hydrazone (**2h**). The strong electron-withdrawing effect of the nitro group would

be expected to lower the Lewis basicity of the substrate, interfering with chelation of $In(OTf)_3$. This may permit a greater proportion of the reaction to take place through an unchelated structure. Alternatives include equilibration through cyanide addition–elimination[11] or product epimerization through increased acidity at the α-carbon. To test these hypotheses, the two separable diastereomers of **3h** were resubmitted to the reaction conditions (eq 1). Surprisingly, cleavage of the N–N bond to form 4-phenyl-2-oxazolidinone was observed for both diastereomers,[27] and consequently no direct evidence of equilibration between the two diastereomers of **3h** was obtained. However, the N–N bond cleavage may be considered indirect evidence of enolization; Skrydstrup and we have reported a similar N–N bond cleavage of a related 2-hydrazinosuccinate initiated by enolization.[22b,23c] In that example, the hydrazine is attached at the α-carbon of an ester; deprotonation of the α-carbon was proposed to lead to N–N bond cleavage through β-elimination of the oxazolidinone anion (eq 2). The observed N–N bond cleavage of **3h** could occur through a similar pathway. The association of both N–N bond cleavage and low selectivity with the electron-deficient nitroaromatic therefore suggests that the addition to **2h** may be complicated by product epimerization.

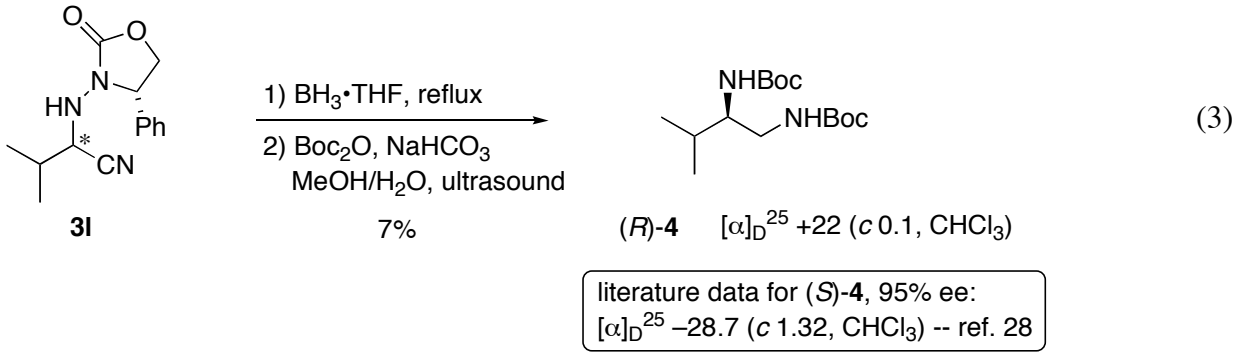


(1)



(2)

The absolute configuration of the newly formed stereocenter could be determined by chemical correlation to the known compound (*S*)-(**4**).[28] The separated major diastereomer of cyanation product (**3l**) was subjected to reductive N–N bond cleavage with borane (eq 3) and the crude product was treated with $(Boc)_2O$ to give 7% yield of a diamine (*R*)-(**4**). The *R* configuration was determined by comparison of optical rotation with the literature data for (*S*)-**4**. The low yield notwithstanding, these results confirmed the proposed configuration. This supported that the asymmetric Strecker addition to enantiopure *N*-acylhydrazones was controlled by a diastereofacial differentiation in the two-point binding complex as shown in Scheme 2.



(3)

In conclusion, examination of Strecker-type reaction of chiral *N*-acylhydrazones derived from various 2-oxazolidinones revealed an unusual dependence of diastereoselectivity on the oxazolidinone substituent. Using (*S*)-4-phenyl-2-oxazolidinone, excellent diastereomeric ratios favoring the (*R*)-aminonitrile were obtained for aromatic aldehyde hydrazones, with the exception of the hydrazone from 3-nitrobenzaldehyde. Aliphatic aldehyde hydrazones afforded modest diastereoselectivities. Improved yields are required for practical application, but this study achieves excellent stereocontrol in Strecker reactions of aromatic chiral *N*-acylhydrazones. From a broader perspective, this work extends the general utility of the chiral *N*-acylhydrazones and their application for acyclic stereocontrol.

EXPERIMENTAL

Known hydrazones (**2a**–**2e**)[18] and new hydrazones (**2f**–**2l**) were prepared according to General Procedure A from the appropriate substituted 3-amino-2-oxazolidinones.

Preparation of enantiopure *N*-acylhydrazones (General Procedure A): To a solution of the appropriate substituted (*S*)-3-amino-2-oxazolidinone (ca. 1 mmol) in toluene (ca. 0.1 M) was added $MgSO_4$ (200 mg), a catalytic amount of *p*-TsOH (ca. 5 mol %) and aldehyde (ca. 1.5 equiv). After heating at reflux for 10 min, concentration and flash chromatography (5:1 hexane/ethyl acetate) gave pure hydrazones.

(*S*)-3-(2-Naphthylmethylene)amino-4-phenyloxazolidin-2-one (2f). From 2-naphthaldehyde (0.19 g, 1.2 mmol) by General Procedure A was obtained **2f** (0.28 g, 88%) as a colorless solid; mp 234–236 °C; $[\alpha]_D^{25}$ +145 (*c* 0.15, $CHCl_3$); IR (film): 3041, 2988, 2923, 1765, 1752, 1457, 1405, 1311, 1225, 1098, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.78-7.72 (m, 4H), 7.45-7.34 (m, 7H), 5.33 (dd, *J* = 8.9, 5.8 Hz, 1H), 4.80 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.21 (dd, *J* = 8.7, 5.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 147.3, 137.1, 134.4, 133.0, 131.6, 129.7, 129.1, 128.3, 127.9, 127.1, 126.5, 126.0, 69.7, 59.5; MS (EI) *m/z* (relative intensity): 316 (M^+, 20%); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 76.00; H, 5.25; N, 8.66.

(*S*)-3-(4-Methylbenzylidene)amino-4-phenyloxazolidin-2-one (2g). From *p*-methylbenzaldehyde (0.23

g, 1.1 mmol) by General Procedure A was obtained **2g** (0.26 g, 91%) as a colorless solid; mp 156–158 °C; $[\alpha]_D^{25}$ +63 (*c* 0.19, $CHCl_3$); IR (film): 3034, 3001, 2916, 1770, 1752, 1560, 1456, 1401, 1320, 1303, 1208, 1096, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.45-7.08 (m, 9H), 5.28 (dd, *J* = 8.9, 5.7 Hz, 1H), 4.76 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.17 (dd, *J* = 8.8, 5.7 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$) δ 154.6, 147.5, 140.6, 137.2, 131.1, 129.6, 129.3, 129.0, 127.5, 126.0, 69.6, 59.4, 21.4; MS (EI) *m/z* (relative intensity): 280 (M^+, 73%); Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.23; H, 5.82; N, 9.64.

(*S*)-3-(3-Nitrobenzylidene)amino-4-phenyl-oxazolidin-2-one (2h). From *m*-nitrobenzaldehyde (0.168 g, 1.10 mmol) by General Procedure A was obtained **2h** (0.28 g, 89%) as a colorless solid; mp 124–126 °C; $[\alpha]_D^{23}$ +106 (*c* 0.14, $CHCl_3$); IR (film): 3089, 2917, 1771, 1617, 1532, 1473, 1400, 1209, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 4.4 Hz, 1H), 7.41-7.31 (m, 8H), 5.37 (dd, *J* = 8.8, 5.5 Hz, 1H), 4.84 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.21 (dd, *J* = 8.8, 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2, 148.5, 143.8, 136.6, 135.7, 132.6, 129.8, 129.6, 129.3, 126.0, 124.5, 122.2, 69.9, 59.3; MS (EI) *m/z* (relative intensity): 311 (M^+, 9%); Anal. Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.99; H, 4.42; N, 13.04.

(*S*)-3-(4-Methoxybenzylidene)amino-4-phenyloxazolidin-2-one (2i). From *p*-methoxybenzaldehyde (0.13 mL, 1.1 mmol) by General Procedure A was obtained **2i** (0.28 g, 95%) as a colorless solid; mp 162–164 °C; $[\alpha]_D^{25}$ +71 (*c* 0.5, $CHCl_3$); IR (film): 3034, 2975, 2916, 2844, 1760, 1607, 1514, 1405, 1253, 1171, 1089, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.45-7.30 (m, 6H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.27 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.76 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.16 (dd, *J* = 8.9, 5.9 Hz, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 154.7, 147.7, 137.3, 129.6, 129.1, 128.9, 126.6, 126.1, 114.0, 69.5, 59.7, 55.4; MS (CI) *m/z* (relative intensity): 297 ($[M+1]^+$, 100%); HRMS-FAB (*m/z*) $[M+H]^+$ Calcd for $C_{17}H_{17}N_2O_3$, 297.1239; found, 297.1239.

(*S*)-3-(3-Phenyl-2-(*E*)-propenylidene)amino-4-phenyloxazolidin-2-one (2j). From *trans*-cinnamaldehyde (0.13 mL, 1.0 mmol) by General Procedure A was obtained **2j** (0.26 g, 89%) as a colorless solid; mp 154–157 °C; $[\alpha]_D^{22}$ +106 (*c* 0.1, $CHCl_3$); IR (film): 3033, 2982, 2923, 1757, 1627, 1456, 1407, 1338, 1232, 1089, 1037, 978 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.43-7.26 (m, 10H), 6.89 (dd, *J* = 16.0, 9.0 Hz, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 5.24 (dd, *J* = 8.7, 5.6 Hz, 1H), 4.76 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.16 (dd, *J* = 8.7, 5.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 148.9, 139.8, 136.9, 135.7, 129.7, 129.1, 129.0, 128.8, 127.0, 125.9, 125.3, 69.8, 59.2; MS (EI) *m/z* (relative intensity): 292 (M^+, 7%); Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.50; H, 5.33; N, 9.55.

(*S*)-4-Phenyl-3-(propylideneamino)oxazolidin-2-one (2k). From propionaldehyde (0.09 mL, 1.2 mmol) by General Procedure A was obtained **2k** (0.14 g, 64%) as a colorless solid; mp 92–94 °C; $[\alpha]_D^{20}$ +112 (*c*

0.59, $CHCl_3$); IR (film): 2973, 2936, 1772, 1527, 1458, 1403, 1323, 1210, 1094, 1038, 917 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.12 (m, 6H), 5.13 (dd, *J* = 8.5, 5.9 Hz, 1H), 4.69 (dd, *J* = 8.8, 8.5 Hz, 1H), 4.08 (dd, *J* = 8.5, 5.9 Hz, 1H), 2.25-2.16 (m, 2H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9, 153.2, 137.0, 129.5, 128.9, 125.9, 69.6, 59.1, 26.2, 10.8; MS (CI) *m*/*z* (relative intensity): 219 ($[M+1]^+$, 100%); Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.96; H, 6.30; N, 12.77.

(*S*)-3-Isobutylideneamino-4-phenyloxazolidin-2-one (2l). From isobutyraldehyde (0.2 mL, 2.2 mmol) by General Procedure A was obtained **2l** (0.33 g, 70%) as a colorless solid; mp 110–112 °C; $[\alpha]_D^{23}$ +102 (*c* 0.24, $CHCl_3$); $[\alpha]_D^{20}$ +127 (*c* 0.62, $CHCl_3$); IR (film): 2967, 2873, 1767, 1529, 1483, 1460, 1399, 1220, 1104, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.22 (m, 4H), 6.96 (d, *J* = 5.8 Hz, 1H), 5.14 (dd, *J* = 8.4, 5.7 Hz, 1H), 4.69 (dd, *J* = 8.8, 8.8 Hz, 1H), 4.08 (dd, *J* = 8.8, 5.8 Hz, 1H), 2.50-2.41 (m, 1H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 154.9, 136.9, 126.5, 128.9, 126.0, 69.4, 59.1, 31.9, 19.77, 19.74; MS (EI) *m*/*z* (relative intensity): 232 (M^+, 31%); Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.44; H, 6.85; N, 11.85.

Strecker Reaction (General Procedure B): A mixture of the hydrazone (0.2 mmol) and $In(OTf)_3$ (0.26 mmol) in CH_2Cl_2 (2.5 mL) was stirred at ambient temperature for 4 h. To the resulting solution was added TMSCN (0.08 mL, 0.6 mmol) by syringe. After 2 d at ambient temperature the reaction was quenched by addition of saturated $NaHCO_3$ solution (2 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with brine, and dried over $MgSO_4$. Filtration, concentration and flash chromatography (hexane/EtOAc) gave α-hydrazinonitriles (**3a**–**3l**). Solid products were recrystallized from isopropanol to give colorless crystals. Infrared data for **3a**–**3l** showed very weak (sometimes undetected) absorbance in the region from 2210–2260 cm^{-1}, as expected for α-aminonitriles.[29]

2-[(*S*)-(4-Benzyl-2-oxooxazolidin-3-yl)amino]-2-phenylacetonitrile (3a). From **2a** (56 mg, 0.2 mmol) by General Procedure B was obtained **3a** as a colorless oil, inseparable 2:1 mixture of diastereomers; IR (film): 3273, 3030, 2912, 2252 (w), 1760, 1603, 1496, 1454, 1237, 1104, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.70-7.10 (m, 10H), 5.31 (d, *J* = 2.9 Hz, 0.33H), 5.25 (d, *J* = 2.9 Hz, 0.67H), 4.45-4.43 (m, 1H), 4.24 (dd, *J* = 8.0, 8.0 Hz, 0.67H), 4.20-4.14 (m, 0.67H), 4.09-4.01 (m, 1.33H), 3.73-3.66 (m, 0.33H), 3.48 (dd, *J* = 13.6, 3.7 Hz, 0.33H), 3.22 (dd, *J* = 13.6, 3.7 Hz, 0.67H), 2.76 (dd, *J* = 13.6, 9.8 Hz, 0.33H), 2.55 (dd, *J* = 13.6, 9.5 Hz, 0.67H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3 (minor), 158.1(major), 135.5 (minor), 135.3 (major), 131.9 (minor), 131.6 (major), 130.2, 129.4, 129.2, 129.0 (major), 128.9 (minor), 128.6 (minor), 128.5 (major), 127.3 (minor), 127.2 (major), 118.2 (major), 118.1 (minor), 67.5 (minor), 66.3 (major), 59.6 (minor), 58.8 (major), 55.8 (minor), 55.7 (major), 38.0 (minor), 36.7 (major); MS (EI) *m*/*z* (relative intensity): 307 (M^+, 1%).

2-[(*S*)-(4-Isopropyl-2-oxooxazolidin-3-yl)amino]-2-phenylacetonitrile (3b). From **2b** (44 mg, 0.19 mmol) by General Procedure B was obtained **3b** as a 1.5:1 mixture of diastereomers (32 mg, 65%, major diastereomer separable); **Major**: colorless oil. $[\alpha]_D^{20}$ –87 (*c* 0.35, $CHCl_3$); IR (film): 3272, 2964, 2877, 2250 (w), 1756, 1483, 1456, 1406, 1220, 1100 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 7.57-7.41 (m, 5H), 5.24 (d, *J* = 2.7 Hz, 1H), 4.35 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.25 (d, *J* = 2.4 Hz, 1H), 4.11 (dd, *J* = 9.1, 4.3 Hz, 1H), 3.98 (dd, *J* = 8.2, 4.0 Hz, 1H), 2.28-2.22 (m, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 131.5, 130.2, 129.4, 128.5, 118.4, 63.6, 61.4, 55.6, 28.9, 27.9, 17.6, 15.3; MS (EI) *m*/*z* (relative intensity): 259 (M^+, 3%); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 64.93; H, 6.62; N, 16.02.

2-[(*S*)-(4-Diphenylmethyl-2-oxooxazolidin-3-yl)amino]-2-phenylacetonitrile (3c). From **2c** (36 mg, 0.1 mmol) by General Procedure B was obtained **3c** (17 mg, 44%) as a colorless solid, inseparable 2:1 mixture of diastereomers; IR (film): 3283, 3060, 2922, 1759, 1652, 1593, 1494, 1216, 1102, 1023 cm^{-1}; **Major**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.11 (m, 15H), 4.97-4.93 (m, 1H), 4.85 (d, *J* = 4.8 Hz, 1H), 4.42-4.34 (m, 2H), 4.19-4.15 (m, 1H), 4.08-4.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 140.5, 139.3, 131.8, 131.1, 129.1, 129.0, 128.8, 128.6, 128.3, 127.6, 127.2, 126.9, 118.2, 65.9, 60.0, 55.3, 54.1; MS (EI) *m*/*z* (relative intensity): 383 (M^+, 4%); Anal. Calcd for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 75.08; H, 5.74; N, 10.61.

2-Hydrazino phenylacetonitrile (3d). From **2d** (56 mg, 0.2 mmol) by General Procedure B was obtained **3d** (44 mg, 72%) as a separable 2.7:1 mixture of diastereomers; **Major**: colorless oil; $[\alpha]_D^{20}$ +39 (*c* 0.1, $CHCl_3$); IR (film): 3276, 3071, 3031, 2932, 2248 (w), 1754, 1650, 1459, 1383, 1201, 1113, 1032 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 7.62-7.20 (m, 9H), 5.39-5.34 (m, 2H), 5.31 (d, *J* = 2.2 Hz, 1H), 4.29(s, 1H), 3.41-3.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.5, 140.0, 137.6, 131.4, 130.2, 129.8, 129.4, 128.5, 127.6, 126.1, 125.5, 118.5, 77.8, 65.3, 55.9, 38.3; MS (EI) *m*/*z* (relative intensity): 305 (M^+, 1%); Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.42; H, 5.01; N, 13.46. **Minor**: colorless oil; $[\alpha]_D^{20}$ +37 (*c* 0.04, $CHCl_3$); IR (film): 3275, 3034, 2924, 2248 (w), 1752, 1458, 1384, 1202, 1115, 1034 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.23 (m, 9H), 5.27 (d, *J* = 4.1 Hz, 1H), 5.08 (ddd, *J* = 7.1, 7.1, 2.2 Hz, 1H), 4.69 (d, *J* = 4.1 Hz, 1H), 4.62 (d, *J* = 7.0 Hz, 1H), 3.34-3.23 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4, 140.0, 137.4, 132.5, 130.1, 129.9, 129.3, 128.7, 127.6, 126.2, 125.5, 117.3, 77.5, 65.2, 54.4, 38.8; MS (EI) *m*/*z* (relative intensity): 305 (M^+, 2%); Anal. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.78; H, 5.01; N, 13.49.

2-[(*S*)-(2-Oxo-4-phenyloxazolidin-3-yl)amino]-2-phenylacetonitrile (3e). From **2e** (53 mg, 0.2 mmol) by General Procedure B was obtained **3e** (27 mg, 46%) as a colorless solid; mp 176–178 °C; $[\alpha]_D^{23}$ +60 (*c* 0.06, $CHCl_3$); IR (film): 3263, 2982, 2903, 2227 (w), 1756, 1495, 1456, 1103, 1025 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.30 (m, 10H), 5.02 (d, *J* = 4.9 Hz, 1H), 4.97 (dd, *J* = 8.2, 6.0 Hz, 1H), 4.68 (dd, *J* =

8.5, 8.5 Hz, 1H), 4.30-4.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 136.8, 131.3, 130.0, 129.4, 129.2, 128.3, 127.3, 118.3, 69.2, 62.1, 55.7; MS (EI) *m/z* (relative intensity): 293 (M^+, 2%); Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.73; H, 5.29; N, 14.32.

2-(Naphthalen-2-yl)-2-[(*S*)-(2-oxo-4-phenyloxazolidin-3-yl)amino]acetonitrile (3f). From **2f** (61 mg, 0.19 mmol) by General Procedure B was obtained **3f** (27 mg, 46%) as a colorless solid; mp 157–159 °C; $[\alpha]_D^{23}$ +49 (*c* 0.07, $CHCl_3$); IR (film): 3280, 3060, 2923, 2852, 2252 (w), 1761, 1458, 1398, 1212, 1100, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.82-7.29 (m, 11H), 5.18 (d, *J* = 4.7 Hz, 1H), 4.97 (dd, *J* = 8.1, 6.0 Hz, 1H), 4.68 (dd, *J* = 8.7, 8.7 Hz, 1H), 4.41 (d, *J* = 6.2 Hz, 1H), 4.29 (dd, *J* = 8.9, 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 143.9, 136.8, 133.7, 132.9, 129.4, 129.3, 129.2, 128.5, 128.3, 128.1, 127.7, 127.3, 127.0, 125.0, 118.3, 69.2, 62.2, 55.8; MS (EI) *m/z* (relative intensity): 343 (M^+, 3%); Anal. Calcd for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.68; H, 4.91; N, 12.19.

2-[(*S*)-(2-Oxo-4-phenyloxazolidin-3-yl)amino]-2-(*p*-tolyl)acetonitrile (3g). From **2g** (56 mg, 0.2 mmol) by General Procedure B was obtained **3g** (21 mg, 34%) as a colorless solid; mp 122–125 °C; $[\alpha]_D^{20}$ +48 (*c* 0.09, $CHCl_3$); IR (film): 3281, 3034, 2922, 2250 (w), 1762, 1608, 1528, 1458, 1399, 1358, 1264, 1100, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.30 (m, 7H), 7.14 (d, *J* = 7.6 Hz, 2H), 4.99-4.96 (m, 2H), 4.67 (dd, *J* = 8.9, 8.4 Hz, 1H), 4.28 (dd, *J* = 8.9, 5.9 Hz, 1H), 4.24 (d, *J* = 3.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 140.1, 136.9, 129.8, 129.3, 128.3, 128.2, 127.3, 118.5, 69.2, 62.1, 55.4, 21.2; MS (CI) *m/z* (relative intensity): 308 ($[M+1]^+$, 52%); Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.04; H, 5.83; N, 13.08.

2-(3-Nitrophenyl)-2-[(*S*)-(2-oxo-4-phenyloxazolidin-3-yl)amino]acetonitrile (3h). From **2h** (62 mg, 0.2 mmol) by General Procedure B was obtained **3h** (36 mg, dr = 1.5:1, 53%) as two separable diastereomers. **Major:** Colorless solid; mp 96–98 °C; $[\alpha]_D^{20}$ +58 (*c* 0.05, $CHCl_3$); IR (film): 3300, 3093, 2922, 2857, 2232 (w), 1752, 1532, 1351, 1241, 1099, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22-8.19 (m, 2H), 7.75 (d, *J* = 4.8 Hz, 1H), 7.76-7.21 (m, 6H), 5.10 (d, *J* = 5.2 Hz, 1H), 4.91 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.67 (dd, *J* = 8.8, 8.5 Hz, 1H), 4.58 (d, *J* = 5.1 Hz, 1H), 4.30 (dd, *J* = 9.0, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 148.6, 136.1, 134.2, 133.6, 130.3, 129.6, 129.4, 127.4, 124.9, 123.4, 117.0, 69.2, 62.6, 54.8; MS (CI) *m/z* (relative intensity): 312 ($[M-CN]^+$, 100%); Anal. Calcd for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.07; H, 4.35; N, 16.42. **Minor**: Colorless solid; mp 125-127 °C; $[\alpha]_D^{23}$ +237 (*c* 0.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, *J* = 1.9 Hz, 1H), 8.20 (d, *J* = 8.1 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.56 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.36-7.24 (m, 5H), 5.22 (d, *J* = 3.8 Hz, 1H), 4.67-4.62 (m, 2H), 4.53 (dd, *J* = 8.9, 8.4 Hz, 1H), 4.25 (dd, *J* = 9.0, 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 148.5, 135.5, 134.6, 134.1, 130.1, 129.7, 129.3, 127.7, 124.7, 123.4, 116.4, 69.2, 63.0, 54.3; MS (CI) *m/z* (relative intensity): 312 ($[M-CN]^+$, 100%); Anal. Calcd for $C_{17}H_{14}N_4O_4$: C, 60.35; H, 4.17; N, 16.56. Found: C, 60.58; H, 4.23; N, 16.38.

2-(4-Methoxyphenyl)-2-[(*S*)-(2-oxo-4-phenyloxazolidin-3-yl)amino]acetonitrile (3i). From **2i** (60 mg, 0.2 mmol) by General Procedure B was obtained **3i** (2 mg, 5%) as a colorless oil; $[\alpha]_D^{20}$ +22 (*c* 0.13, $CHCl_3$); IR (film): 3276, 2969, 2923, 2844, 2246, 1761, 1615, 1514, 1456, 1398, 1252, 1176, 1098, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.29 (m, 7H), 6.85 (d, *J* = 7.5 Hz, 2H), 5.02-4.97 (m, 2H), 4.68 (dd, *J* = 9.0, 8.4 Hz, 1H), 4.28 (dd, *J* = 9.0, 5.7 Hz, 1H), 4.24-4.20 (m, 1H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 158.1, 136.9, 129.7, 129.3, 127.3, 123.7, 118.5, 114.5, 69.2, 62.1, 55.4, 55.1; MS (CI) *m*/*z* (relative intensity): 324 ($[M+1]^+$, 36%); HRMS-FAB (*m*/*z*) $[M+H]^+$ Calcd for $C_{18}H_{18}N_3O_3$, 324.1348; found, 324.1356.

2-[(*S*)-(2-Oxo-4-phenyloxazolidin-3-yl)amino]butyronitrile (3k). From **2k** (43 mg, 0.2 mmol) by General Procedure B was obtained **3k** (18 mg, dr = 2:1, 37%) as a colorless oil, separable 2:1 mixture of diastereomers; **Major**: $[\alpha]_D^{20}$ +38 (*c* 0.65, $CHCl_3$); IR (film): 3283, 2975, 2929, 2877, 2252 (w), 1762, 1458, 1399, 1211, 1097, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47-7.33 (m, 5H), 4.98 (dd, *J* = 8.1, 6.2 Hz, 1H), 4.65 (dd, *J* = 8.8, 8.1 Hz, 1H), 4.27(dd, *J* = 8.8, 6.2 Hz, 1H), 4.15-4.10 (m, 1H), 3.81-3.79 (m, 1H), 1.69-1.61 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 136.8, 129.4, 129.3, 127.4, 119.2, 69.1, 62.2, 53.4, 24.4, 9.7; MS (CI) *m*/*z* (relative intensity): 246 ($[M+1]^+$, 43%); HRMS-FAB (*m*/*z*) $[M+H]^+$ Calcd for $C_{13}H_{16}N_3O_2$, 246.1243; found, 246.1234. **Minor**: $[\alpha]_D^{20}$ +53 (*c* 0.25, $CHCl_3$); IR (film): 3289, 2975, 2922, 2877, 2252 (w), 1762, 1453, 1394, 1212, 1091, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 4.89 (dd, *J* = 8.1, 6.2 Hz, 1H), 4.63 (dd, *J* = 8.8, 8.1 Hz, 1H), 4.30 (dd, *J* = 8.8, 6.2 Hz, 1H), 4.18 (br s, 1H), 3.88-3.78 (m, 1H), 1.79-1.71 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 136.1, 129.6, 129.4, 127.7, 118.7, 68.9, 62.2, 53.2, 24.9, 9.9; MS (CI) *m*/*z* (relative intensity): 246 ($[M+1]^+$, 32%); HRMS-FAB (*m*/*z*) $[M+H]^+$ Calcd for $C_{13}H_{16}N_3O_2$, 246.1243; found, 246.1241.**3-Methyl-2-[(*S*)-(2-oxo-4-phenyloxazolidin-3-yl)amino]butyronitrile (3l)**. From **2l** (46 mg, 0.2 mmol) by General Procedure B was obtained **3l** (38 mg, dr = 3:1, 73%) as separable diastereomers. **Major**: Colorless solid; mp 98–100 °C; $[\alpha]_D^{23}$ +52 (*c* 0.13, $CHCl_3$); IR (film): 3258, 2965, 2916, 2238 (w), 1758, 1459, 1408, 1364, 1245, 1106, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 4.96 (dd, *J* = 8.3, 6.1 Hz, 1H), 4.64 (dd, *J* = 8.8, 8.3 Hz, 1H), 4.28 (dd, *J* = 8.9, 6.1 Hz, 1H), 4.11 (d, *J* = 6.1 Hz, 1H), 3.69 (dd, *J* = 5.9, 5.9 Hz, 1H), 1.87-1.82 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 136.7, 129.4, 129.3, 127.4, 118.4, 69.0, 62.2, 58.4, 29.8, 19.1, 17.8; MS (EI) *m*/*z* (relative intensity): 259 (M^+, 7%); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 65.08; H, 6.47; N, 16.22. **Minor**: Colorless oil; $[\alpha]_D^{20}$ –15 (*c* 0.02, $CHCl_3$); IR (film): 3286, 2966, 2955, 2259 (w), 1762, 1497, 1458, 1397, 1211, 1100, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42-7.33 (m, 5H), 4.83 (dd, *J* = 8.2, 6.3 Hz, 1H), 4.61 (dd, *J* = 9.0, 8.2 Hz, 1H), 4.29 (dd, *J* = 8.2, 6.3 Hz, 1H), 4.21 (d, *J* = 4.8 Hz, 1H), 3.70 (dd, *J* = 5.8, 5.8 Hz, 1H), 1.99-1.93 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 136.1, 129.6, 129.3, 127.7,

117.6, 68.9, 62.3, 58.2, 29.8, 19.3, 17.8; MS (EI) *m/z* (relative intensity): 259 (M^+, 11%); Anal. Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.21. Found: C, 65.15; H, 6.75; N, 15.94.

Stereochemical Proof for Strecker Product (3l). The major product (**3l**) was subjected to reduction conditions: A mixture of **3l** (major diastereomer, 36 mg, 0.14 mmol) and BH_3•THF (4.2 mL, 1.0 M in THF, 4.2 mmol) in THF (3 mL) was heated to reflux. After 3 d, 3 M HCl (4 mL) was added to the mixture dropwise under ice-bath. The resulting mixture was stirred at 0 °C for 3 h, then at ambient temperature for 4 h. Solvent was removed and the residue was partitioned between basic brine and CH_2Cl_2. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. ^{1}H NMR showed that all **3l** had been consumed. To a solution of this crude mixture in MeOH (3 mL) was added $(Boc)_2O$ (250 mg, 1.1 mmol), $NaHCO_3$ (170 mg, 2.0 mmol) and water (0.3 mL). The mixture was sonicated for 90 min, stirred at ambient temperature overnight, filtered through celite, concentrated, and dried. Flash chromatography gave (*R*)-**4** (2 mg, 7% from **3l**) as a colorless oil; $[\alpha]_D^{25}$ +22 (*c* 0.1, $CHCl_3$) (Lit.,[28] value for (*S*)-**4**: $[\alpha]_D^{25}$ –28.7 (*c* 1.32, $CHCl_3$, 95% ee)). Spectral data matched the literature.[28]

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