Synthesis N. Vagkidis et al. Paper

Evaluation of Amino Nitriles and an Amino Imidate as Organocatalysts in Aldol Reactions

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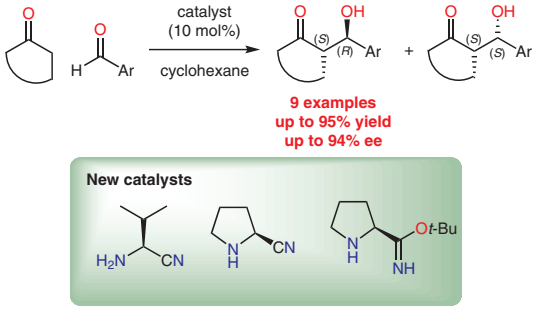

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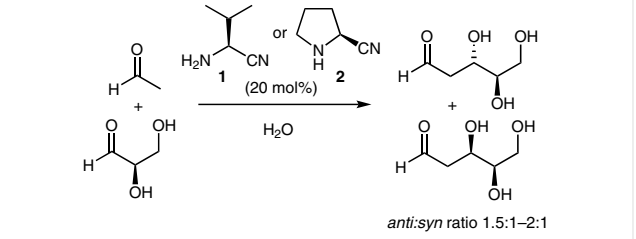
Abstract The efficiency of L-valine and L-proline nitriles and a *tert*-butyl L-proline imidate as organocatalysts for the aldol reaction have been evaluated. L-Valine nitrile was found to be a *syn*-selective catalyst, while L-proline nitrile was found to be *anti*-selective, and gave products in modest to good enantioselectivities. *tert*-Butyl L-proline imidate was found to be a very efficient catalyst in terms of conversion of starting reagents to products, and gave good *anti*-selectivity. The enantioselectivity of the *tert*-butyl L-proline imidate was found to be good to excellent, with products being formed in up to 94% enantiomeric excess.

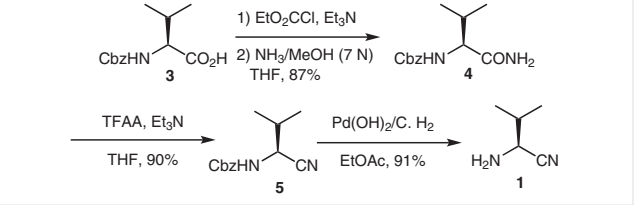
Key words asymmetric synthesis, organocatalysis, aldol reaction, amino nitrile, amino imidate

The synthesis and evaluation of new small molecules as organocatalysts has become an important endeavour.[1] From the initial development of proline as a catalyst for the aldol reaction by List and Barbas,[2] and the imidazolidinones by MacMillan for the Diels–Alder reaction,[3] many novel contributions have been made. The pyrrolidine ring of proline is still by far the most abundant scaffold for these catalysts, with the carboxylic acid being replaced with tetrazoles,[4] silyl ethers of tertiary alcohols,[5] esters,[6] and amides,[7] all of which bring subtle changes in catalytic ability and the type of transformation which can be catalysed. Recently, we reported the use of amino nitriles as catalysts for the formation of 2-deoxy-D-ribose under aqueous, potentially prebiotic conditions (Scheme 1).[8] The ability of amino nitriles to catalyse this reaction inspired us to evaluate them as more general aldol catalysts in organic solvents under more conventional reaction conditions.

Amino nitriles **1** and **2** were prepared from the parent carbamate-protected amino acids (Schemes 2 and 3). Cbz-L-valine was converted to the primary amide in 87% yield by formation of the mixed anhydride and treatment with methanolic ammonia. Dehydration of the amide to the nitrile was achieved in 90% yield using TFAA and Et_3N. Finally the Cbz-group was removed in 91% yield by hydrogenation over a $Pd(OH)_2/C$ catalyst in EtOAc to give **1** (Scheme 2).



Scheme 1 Amino nitrile-catalysed formation of 2-deoxy-D-ribose



Scheme 2 Synthesis of L-valine nitrile **1**

Boc-L-proline was converted to the primary amide in 85% yield by formation of the mixed anhydride and treatment with methanolic ammonia. Dehydration of the amide to the nitrile was achieved in 89% yield using TFAA and Et_3N. Removal of the Boc-group was achieved by treatment with TFA in CH_2Cl_2 at 0 °C to generate the TFA salt of **2** in a 93% yield. The amine was free-based immediately before use by stirring with solid $NaHCO_3$ in CH_2Cl_2 (Scheme 3).

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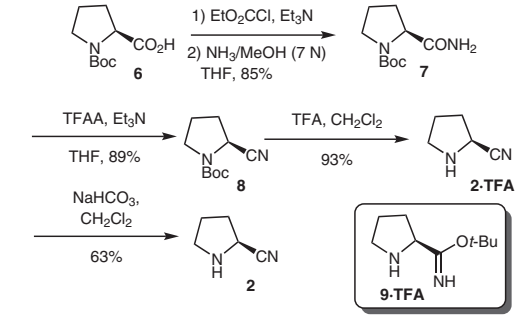
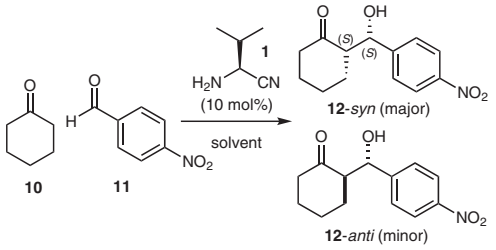


Scheme 3 Synthesis of L-proline nitrile **2**

However, the Boc-deprotection of **8** was more challenging than expected, as the clean formation of **2·TFA** was dependent on the batch of TFA used. Some batches of TFA generated **2·TFA** cleanly, while other batches also generated a side product, which was identified by ^{1}H NMR and MS as the imidate **9·TFA**.[9] We rationalised that if the TFA was wet, water could intercept the *t*-Bu-cation to form *t*-BuOH, which then underwent an acid-catalysed addition to the nitrile **2·TFA** to form imidate **9·TFA**. Conducting the TFA-mediated deprotection in the presence of *t*-BuOH provided a reliable method for the synthesis of imidate **9·TFA**, and also provided us with an additional new catalyst class to study.

The first reaction which was investigated was the standard test reaction for any new organocatalyst: the aldol reaction of cyclohexanone with substituted benzaldehydes (Scheme 4).[4,7,10] All reactions used 10 mol% of catalyst, with 5 equivalents of cyclohexanone to 1 equivalent of 4-nitrobenzaldehyde in a range of solvents. When L-valine nitrile **1** was used conversion to the aldol adduct was <15% for a wide range of solvents covering both dipolar aprotic and non-polar solvents. However, very interestingly the *syn*:*anti* ratio of the products favoured the *syn*-isomer in all cases (CH_2Cl_2 4.5:1; DMF 2.3:1; 1.4-dioxane 1.3:1; THF 3.8:1; toluene 5.3:1; cyclohexane 3.0:1; cyclohexanone 5.3:1) with the highest ratio being in EtOAc >25:1. Due to the low conversions the enantioselectivity of these reactions were not determined. It was rationalised that one possibility for the low conversions was that the amino nitrile catalyst was being trapped as the 4-nitrobenzaldehyde imine. In order to try and hydrolyse any imine back to 4-nitrobenzaldehyde and amino nitrile, water (10 mol%) was added to the reaction in toluene, which had provided the greatest conversion. This had the marked effect on increasing the *syn*:*anti* ratio from 5.3:1 to >25:1, but had no effect on the conversion. The introduction of water (10 mol%) and TsOH (10 mol%) to this system did not improve the conversion and gave products in a *syn*:*anti* ratio of >25:1. In this instance, the enantioselectivity of the reaction was determined by HPLC and the *syn*-product **12**-*syn* was found to have a 34% ee. The absolute stereochemistry of **12**-*syn* was determined to be *S*,*S*, by comparison to the literature.[10a]

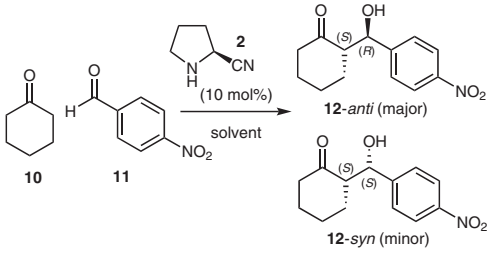


Scheme 4 Aldol reactions catalysed by H_2N-L-Val-CN **1**

While it was disappointing that L-valine nitrile **1** was not a better catalyst, it was very interesting that the *syn*-diastereomer **12**-*syn* was the major product under all conditions studied. The formation of the *syn*-diastereomer as the major product is most unusual in organocatalytic aldol reactions which proceed via enamine catalysis, as the *anti*-diastereomer usually dominates.[11] In order to determine if this diasteroeselectivity was a general feature of amino nitrile catalysis L-proline nitrile **2** was investigated. It was also rationalised that any formation of a L-proline nitrile **2**/4-nitrobenzaldehyde adduct would be less problematic due to it being an iminium species rather than an imine and so it would be slower to form and more easily hydrolysed.

Reactions were conducted with 10 mol% of catalyst **2**, with 5 equivalents of cyclohexanone to 1 equivalent of 4-nitrobenzaldehyde in a range of solvents (Table 1).

Table 1 Aldol Reactions Catalysed by HN-L-Pro-CN **2**



Entry	Solvent	Conversion (%)[a]	*anti*:*syn*[a]	% ee[b] *anti*	% ee[b] *syn*
1	CH_2Cl_2	43	4.0:1	13	11
2	DMF	7	2.5:1	20	18
3	1,4-dioxane	55	4.8:1	11	11
4	MeCN	11	2.9:1	20	20
5	DMSO	3	1.7:1	–[c]	–[c]
6	THF	39	3.9:1	40	12
7	EtOAc	51	3.9:1	23	15
8	toluene	75	4.8:1	20	6
9	cyclohexane	75	4.0:1	13	0

[a] Determined by 400 MHz ^{1}H NMR analysis, by integration of the aldehyde proton and the carbinol protons of the aldol products.
[b] Determined by HPLC chiralpak IB column (see Supporting Information).
[c] Not determined.

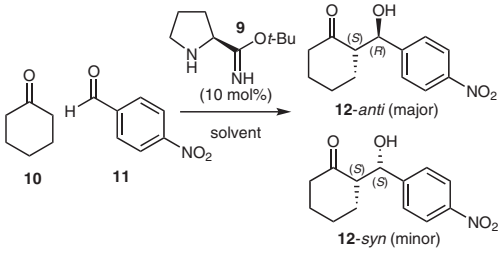
The results in Table 1 show that L-proline nitrile **2** is a much more efficient catalyst than L-valine nitrile **1** in terms of converting starting materials into products. Conversions of 75% were reached in non-polar hydrocarbon solvents such as toluene and cyclohexane (Table 1, entries 8 and 9). The increased conversion is attributed to the greater catalytic ability of the secondary amine of **2** compared to the primary amine of **1**, for the reasons mentioned earlier. Interestingly, the *anti*-diastereomer **12**-*anti* was the major adduct formed in all cases, showing that it is not the amino nitrile function alone which was responsible for the switch to the *syn*-diastereomer for L-valine nitrile **1**. The difference in the major diastereomer is probably down to the conformation adopted by the enamine and its attack trajectory on the aldehyde, to minimise steric interactions. The enantioselectivity of the reaction remained reasonably constant in all solvents studies (~10–20%) with the exception of THF (entry 6), which generated **12**-*anti* product in 40% ee. In general, the % ee of the *anti*-diastereomer was slightly greater than that of the *syn*-diastereomer. The absolute stereochemistry of the aldol products was determined as (*S*,*R*)-**12**-*anti* and (*S*,*S*)-**12**-*syn* by comparison with literature data.[10a]

Disappointingly it seems that the amino nitriles studied are not useful catalysts for the formation of aldol products. This is probably due to the lack of functionality, which can allow for the controlled association or organisation of the reagents via hydrogen bonding (as in the case of proline) or large steric buttresses (as in the case of diaryl proline silyl ethers) to control the facial selectivity of the attack.

tert-Butyl proline imidate **9**, however, does contain both a potential hydrogen bond donor in the form of the imidate NH, and a sterically bulky *t*-Bu group and so this catalyst could provide higher levels of enantioselectivity in the aldol reaction. *t*-Bu-proline imidate **9** was initially screened using our standard conditions: 10 mol% of catalyst, 5 equivalents of cyclohexanone to 1 equivalent of 4-nitrobenzaldehyde in several solvents (Table 2).

Pleasingly, amino imidate **9** is a much better catalyst than amino nitrile **2** for the promotion of aldol reactions. As can be seen from Table 2 the conversions are all substantially better, with hydrocarbon solvents like toluene (Table 2, entry 3) and cyclohexane (entry 4) providing 85% and 100% conversion of starting material to aldol product. The *anti*:*syn* ratio is modest and very similar irrespective of the solvent used, with the *anti*-diastereomer **12**-*anti* being the major product in all cases. Significantly, the enantioselectivities were also much higher when amino imidate **9** was used as a catalyst, with the highest for both the *anti*- and *syn*-diastereomers (at 76% ee and 51% ee, respectively) when the reaction was run in cyclohexane (entry 4). With these encouraging results it was decided to screen a number of different aldehydes in the amino imidate **9**-catalysed reaction (Table 3).

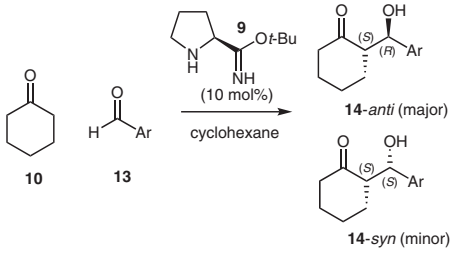
Table 2 Aldol Reactions Catalysed by *tert*-Butyl Proline Imidate **9**



Entry	Solvent	Conversion (%)[a]	*anti*:*syn*[a]	% ee[b] *anti*	% ee[b] *syn*
1	CH_2Cl_2	61	5.6:1	69	45
2	THF	57	5.8:1	46	36
3	toluene	85	4.6:1	58	27
4	cyclohexane	100	5.3:1	76	51

[a] Determined by 400 MHz ^{1}H NMR analysis, by integration of the aldehyde proton and the carbinol protons of the aldol products.
[b] Determined by HPLC chiralpak IB column (see Supporting Information).

Table 3 Amino Imidate **9**-Catalysed Aldol Reactions



Entry	**13** Ar	Conversion[a] (%)	**14** *anti*:*syn*[a]	% ee[b] *anti*
a	2-$NO_2C_6H_4$	100	4.7:1	75
b	3-$NO_2C_6H_4$	100	3.0:1	63
c	2-ClC_6H_4	98	5.0:1	76
d	3-ClC_6H_4	96	3.0:1	67
e	4-ClC_6H_4	94	2.7:1	57
f	2-BrC_6H_4	100	7.0:1	69
g	3-BrC_6H_4	99	2.5:1	71
h	4-BrC_6H_4	90	3.0:1	61
i	Ph	69	3.5:1	67
j	4-$MeOC_6H_4$	0	–	–

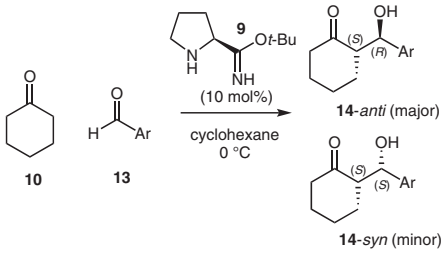
[a] Determined by 400 MHz ^{1}H NMR analysis, by integration of the aldehyde proton and the carbinol protons of the aldol products.
[b] Determined by HPLC chiralpak IB column (see Supporting Information).

As can be seen from Table 3, amino imidate **9** was able to efficiently catalyse the aldol reaction of cyclohexanone with a number of differently substituted aryl aldehydes **13a–i** to afford the aldol products **14a–i**. Excellent conversions were obtained regardless of whether the aldehyde was substituted in the 2, 3, or 4-positions with an electron-

withdrawing substituent (Table 3, entries **a**–**h**). However, no reaction was observed when electron-donating 4-MeO group was introduced (entry **j**). Unsubstituted, electronically neutral, benzaldehyde had the lowest conversion of those aldehydes that underwent reaction at only 69% (entry **i**) compared to the +90% conversions of the other aldehydes. The reaction was modestly *anti*-selective in all cases, while the enantioselectivities were modest to good with the highest being 75% ee (entry **a**) and 76% ee (entry **c**). In general, higher enantioselectivities were seen for aldehydes with 2-substitution than for 3- or 4-substitution (compare entries **a** and **b**, entries **c**, **d**, and **e**), and with the exception of 4-chlorobenzaldehyde (entry **e**) were all above 60% ee.

In order to determine if the enantioselectivity could be increased further, the reactions were run at 0 °C. The reaction of cyclohexanone, 4-nitrobenzaldeyde in cyclohexane at 0 °C, catalysed by **9** proceeded with a conversion of 40% and a *anti*:*syn* ratio of 5.7:1. However, the enantioselectivity of the *anti*-product **12**-*anti* was found to be 94% ee. Encouraged by this significant increase in enantioselectivity the use of other aldehydes was investigated. These results can be seen in Table 4.

Table 4 Amino Imidate **9**-Catalysed Aldol Reactions at 0 °C

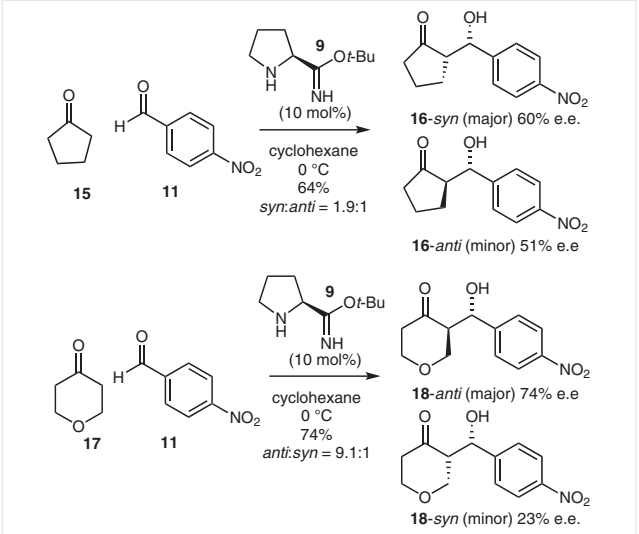


Entry	**13** Ar	Conversion (%)[a]	**14** *anti*:*syn*[a]	% ee[b] *anti*
a	2-$NO_2C_6H_4$	87	4.8:1	82
b	3-$NO_2C_6H_4$	80	5.7:1	51
c	2-ClC_6H_4	46	6.8:1	79
d	3-ClC_6H_4	39	5.3:1	72
e	4-ClC_6H_4	47	4.8:1	77
f	2-BrC_6H_4	47	6.6:1	69
g	3-BrC_6H_4	54	4.8:1	74
h	4-BrC_6H_4	57	5.8:1	76
i	Ph	10	3.8	73

[a] Determined by 400 MHz ^{1}H NMR analysis, by integration of the aldehyde proton and the carbinol protons of the aldol products.
[b] Determined by HPLC chiralpak IA, IBN-5, and IC columns (see Supporting Information).

Reducing the temperature of the reaction to 0 °C does have a beneficial effect on % ee in almost all cases, raising it by as much as 18% in the case of aldehyde **11**. It also has a beneficial effect on the *anti*:*syn* ratio, increasing the proportion of *anti*-product formed in the reaction. However, the reduced rate of reaction at 0 °C, does lead to a reduced conversion to adduct over the same period of time.

The final investigation focused on the use of cyclopentanone (**15**) and pyran-4-one (**17**) in the amino imidate **9**-promoted reaction with 4-nitrobenzaldehyde (**11**) (Scheme 5).



Scheme 5 Aldol reaction of cyclopentanone and pyran-4-one with 4-nitrobenzaldehyde catalysed by amino imidate **9**

Cyclopentanone (**15**) underwent aldol condensation to generate aldol adducts **16**-*syn* and **16**-*anti*, with the *syn*-diastereomer dominating. The major product **16**-*syn* was formed in 60% ee, while the minor product **16**-*anti* was formed in 51% ee. The use of pyran-4-one (**17**) as the aldol donor resulted in the formation of **18**-*anti* as the major diastereomer in 74% ee, while the minor **18**-*syn*-diastereomer was formed in 23% ee. The ratio of *anti*:*syn* was a good 9.1:1.

An investigation has been conducted into the catalytic efficiency of amino nitriles and an amino imidate for aldol condensations. L-Valine nitrile **1** was not efficient as a catalyst in terms of reaction yields and enantioselectivity, although it did exhibit unusual *syn*-diastereomer selectivity. L-Proline nitrile **2** was more efficient in terms of both conversion and the enantioselectivity of the products, with the major *anti*-diastereomer being formed in up to 76% ee, when cyclohexane was used as the reaction solvent. However, the serendipitous discovery of L-proline imidate **9**, and its use as an organocatalyst led to synthetically useful conversions and *anti*:*syn* ratios of products in line with other organocatalysts. The enantioselectivities of the major *anti*-products were good (60–75%). The enantioselectivity of the L-proline imidate-catalysed reaction and the *anti*:*syn* ratio of the products could be increased further when the reaction was run at 0 °C, with the *anti*-product being formed in

as high as 94% ee. These enantioselectivities are on a par with other common proline-derived catalysts, which have been used in similar aldol reactions. Proline amides gave products with % ees in the mid-70% to high 90% range, depending on the amine used.[12] Proline tetrazole gave % ees up to the low 90% range,[4] whereas ring-substituted prolines with parent carboxylic acid gave products with % ees up to the high 90% range.[12] Amino imidates based on proline are a new class of organocatalyst, which have the potential to be efficient and highly enantioselective aldol catalysts. Further work is underway to modify the proline imidate in order to increase the enantioselectivity further.

Unless otherwise noted, all compounds were bought from commercial suppliers and used without further purification. NMR spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: $CDCl_3$ 7.26 ppm for ^{1}H NMR; $CDCl_3$ 77.0 ppm for ^{13}C NMR. Coupling constants (*J*) are quoted in Hertz. IR absorbances were recorded on a PerkinElmer UATR Two FT-IR spectrometer using NaCl plates. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1}. TLC was performed on aluminum sheets coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, basic aq $KMnO_4$ or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich. Anhydrous solvents were acquired from a PureSolv PS-MD7 solvent tower. High-performance liquid chromatography (HPLC) was performed using an Agilent 1200 series instrument using the chiral columns indicated and a range of wavelengths from 210–280 nm for detection.

Cbz-L-Valine-Amide 4

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Cbz-L-valine **3** (2.0 g, 7.96 mmol) was added to the flask. To this flask Et_3N (1.2 mL, 1.1 equiv) and anhyd THF (40 mL) were added. The solution was cooled at 0 °C and stirred. After 10 mins, ethyl chloroformate (0.8 mL, 1 equiv) was added and the reaction was continued to be stirred at 0 °C. After 1 h, NH_3 in MeOH (7 N) was added (1.66 mL, 1.5 equiv) and the mixture was continued to be stirred at 0 °C for another 1 h. After 1 h, the reaction was allowed to warm at r.t. and was continued to be stirred. After a further 17 h, the reaction was deemed complete by TLC (90:10 DCM/MeOH) and the stirring was stopped. The solvent was removed in vacuo and the white precipitate was filtered and washed with ice cold H_2O to give the pure Cbz-protected amide **4** as a white solid; yield: 1.73 g (87%, 6.92 mmol); mp 206–209 °C (Lit.[13] mp 205–208 °C); $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) +24.7 (*c* 1.0 g cm^{-3} in DMF) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[8] +25.0 (*c* 1.0 g cm^{-3} in DMF)}.

IR (ATR): 3374, 3315 (N–H), 3201, 3030, 2972, 2958, 2895, 2872 (C–H), 1681, 1654 (C=O), 1243 cm^{-1} (C–O).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.38–7.28 (6 H, m), 7.16 (1 H, d, *J* = 8.9 Hz), 7.03 (1 H, br s), 5.03 (2 H, s), 3.80 (1 H, dd, *J* = 8.9, 6.6 Hz), 1.99–1.28 (1 H, app oct, *J* = 6.6 Hz), 0.86 (3 H, d, *J* = 6.6 Hz), 0.83 (3 H, d, *J* = 6.6 Hz).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 173.2, 156.2, 137.2, 128.4, 127.8, 127.3, 65.4, 60.1, 30.2, 19.4, 18.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}N_2O_3Na$: 273.1210; found: 273.1210.

Spectroscopic data are identical to that reported in the literature.[8]

Cbz-L-Valine Nitrile 5

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Cbz-L-valine amide **4** (1.75 g, 7.00 mmol), dissolved in anhyd THF (30 mL) was added to the flask. The flask was cooled at 0 °C, and Et_3N (2.18 mL, 2.2 equiv) was added and the solution was stirred. After 30 min, TFAA (1.50 mL, 10.5 equiv) was added and the reaction was continued to be stirred at 0 °C for 1 h and a further 17 h at r.t. The reaction was deemed complete by TLC (90:10 DCM/MeOH) and the stirring was stopped. The solvent was removed in vacuo and the crude oil was re-dissolved in EtOAc. The crude mixture was washed with aq 2 M HCl and extracted with EtOAc (3 × 10 mL). The organic layers were combined and washed with sat. aq $NaHCO_3$ (3 × 10 mL), then washed with brine. The aq brine layer was extracted with EtOAc (1 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and the solution was concentrated in vacuo to give the crude product as a red translucent oil. The crude product was then further purified by column chromatography (90:10 hexane/EtOAc) to afford the pure Cbz-protected amino nitrile **5** as a red solid; yield: 1.47 g (90%, 6.30 mmol); mp 49–51 °C (Lit.[14] mp 53 °C); $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) –43.07 (*c* 1.0 g cm^{-3} in MeOH) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[8] –37.3 (*c* 0.97 g cm^{-3} in MeOH)}.

IR (ATR): 3298 (N–H),3064, 3032, 2970, 2930, 2877 (C–H), 2459 (CN), 1686 (C=O), 1213 (C–N), 1176 cm^{-1} (C–O).

^{1}H NMR (400 MHz DMSO-d_6): δ = 8.22 (1 H, br d, *J* = 8.0 Hz), 7.39–7.31 (5 H, m), 5.09 (2 H, s), 4.40 (1 H, app t, *J* = 8.0 Hz), 1.98 (1 H, m), 1.00 (3 H, d, *J* = 6.8 Hz), 0.94 (3 H, d, *J* = 6.8 Hz).

^{13}C NMR (400 MHz, DMSO-d_6): δ = 155.5, 135.7, 128.8, 128.6, 128.4, 117.8, 67.9, 49.1, 31.9, 18.7, 18.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_2Na$: 255.1104; found: 255.1105.

Spectroscopic data are identical to that reported in the literature.[8]

L-Valine Nitrile 1

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Cbz-L-valine nitrile **5** (200 mg, 0.86 mmol) in EtOAc (7.5 mL) and Pearlman's reagent (20% b.w., 60 mg, 0.1 equiv) were placed in the flask and the flask was evacuated. Then the flask was placed under a H_2 atmosphere (60 psi) and the reaction was stirred. After 1.5 h of stirring, the reaction was deemed complete by TLC (95:5 DCM/MeOH) and the stirring was stopped. The mixture was filtered through a pad of Celite and the Celite was washed thoroughly with EtOAc (50 mL). Aq 4 M HCl in 1,4-dioxane (1.0 mL) was added and the mixture was stirred for 30 min turning the solution cloudy. Upon evaporation, the salt of the amine was isolated as a white-yellow solid. The free amine **1** was liberated by dissolving the salt in DCM and stirring over $NaHCO_3$ for 30 min before filtering and concentrating in vacuo, as a yellow oil; yield: 76 mg (91%, 0.78 mmol); $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) –6.37 (*c* 1.0 g cm^{-3} in DCM) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[8] –8.3 (*c* 0.83 g cm^{-3} in DCM)}.

IR (ATR): 3384 (N–H), 2228 (CN), 1098 cm^{-1} (C–N).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (1 H, d, *J* = 5.6 Hz), 1.93 (1 H, dspt, *J* = 6.8, 5.6 Hz), 1.64 (2 H, br s), 1.07 (3 H, d, *J* = 6.8 Hz), 1.06 (3 H, d, *J* = 6.8 Hz).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 121.1, 49.7, 32.8, 18.8, 17.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{11}N_2$: 99.0917; found: 99.0919.

Spectroscopic data are identical to that reported in the literature.[8]

Boc-L-Proline Amide 7

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Boc-L-proline **6** (2.0 g, 9.2 mmol) and anhyd THF (30 mL) were added to the flask. To this flask, Et_3N (1.43 mL, 1.1 equiv) was added and the solution was stirred at r.t. After 15 min, ethyl chloroformate (0.86 mL, 1 equiv) was added and the reaction was continued to be stirred at r.t. After 1 h, NH_3 in MeOH (7 N, 2 mL), was added and the reaction was continued to be stirred for a further 14 h. After that, the reaction was deemed complete by TLC (70:30 hexane/EtOAc) and the stirring was stopped. The solvent was removed in vacuo and the solution was washed with H_2O (10 mL) and extracted with DCM (5 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solution was concentrated in vacuo to give the title compound **7** as a white solid; yield: 1.67 g (85%, 7.8 mmol); $[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) –44.7 (*c* 1.0 g cm^{-3} in MeOH) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[15] –42.4 (*c* 1.0 g cm^{-3} in MeOH)}.

IR (ATR): 3344 (N–H), 1676 (C=O), 1164 cm^{-1} (C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (1 H, s), 5.40–6.10 (1 H, m), 4.35–4.15 (1 H, m), 3.55–3.25 (2 H, m), 2.40–1.80 (4 H, m), 1.45 (9 H, s).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}N_2O_3Na$: 237.1210; found: 237.1209.

Spectroscopic data are in agreement with the literature.[8]

Boc-L-Proline Nitrile 8

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Boc-L-proline amide **7** (625 mg, 2.92 mmol) in anhyd THF (20 mL) and Et_3N (0.9 mL, 2.2 equiv) were added to the flask. The flask was cooled at 0 °C and stirred. After 30 min of stirring, anhyd TFAA kept in a dry ampule (1.0 g, 1.5 equiv) was added and the reaction was continued to be stirred at 0 °C. After 2 h, the reaction was warmed at r.t. and was continued to be stirred. After a further 16 h, the reaction was deemed complete by TLC (90:10 DCM/MeOH) and the stirring was stopped. The solvent was removed in vacuo. The crude yellow oil was re-dissolved in EtOAc and was washed with aq 2 M HCl and extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with sat. aq $NaHCO_3$ and the aqueous layers were extracted with EtOAc (3 × 10 mL). The organic layers were combined, washed with brine and the aq brine layer was extracted with EtOAc (3 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and filtered. The solution was concentrated in vacuo to give the crude product as an orange oil. The crude oil was further purified by column chromatography (20:80 EtOAc/hexane) to give the title compound **8** as a pale yellow oil; yield: 508 mg (89%, 2.60 mmol); $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) –91.15 (*c* 1.3 g cm^{-3} in MeOH) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[15] –95.5 (*c* 1.3 g cm^{-3} in MeOH).

IR (ATR): 2976, 2239 (CN), 1797, 1692 cm^{-1} (C=O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.60–4.40 (1 H, m), 3.58–3.25 (2 H, m), 2.30–1.95 (4 H, m), 1.50–1.45 (9 H, m).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 153.1, 119.3, 81.6, 47.3, 45.8, 31.8, 28.4, 23.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{16}N_2O_2Na$: 219.1104; found: 219.1105.

Spectroscopic data are in agreement with the literature.[8]

L-Proline Nitrile Trifluoroacetate Salt (2·TFA)

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Boc-L-proline nitrile **8** (364 mg, 1.7 mmol) and TFA (3.6 mL, 25 equiv) in anhyd DCM (5 mL) were added to the flask and the flask was cooled at 0 °C. The solution was stirred until the reaction was deemed complete by TLC (90:10 DCM/MeOH). The stirring was stopped and solvent was removed in vacuo. Trituration with Et_2O provided the pure TFA salt of L-proline nitrile **2·TFA**; yield: 318 mg (93%, 1.58 mmol); mp 90–92 °C (Lit.[16] mp 92–94 °C); $[\alpha]_D^{20}$ (deg cm^3 g^{-1} dm^{-1}) –11.6 (*c* 1.0 g cm^{-3} in MeOH) {$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) Lit.[8] –16.7 (*c* 1.0 g cm^{-3} in MeOH)}.

IR (ATR): 3323 (N–H), 2943, 2831, 2269 (CN), 1665 cm^{-1} (C=O).

^{1}H NMR (400 MHz, CD_3OD): δ = 4.60 (1 H, t, *J* = 7.4 Hz), 3.62–3.43 (2 H, m), 2.58–2.47 (1 H, m), 2.27–1.97 (3 H, m).

^{13}C NMR (400 MHz, CD_3OD): δ = 161.8 (q, *J* = 34.7 Hz, CF_3), 115.2, 46.8, 45.8, 29.9, 23.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_9N_2$: 97.0760; found: 97.0759.

Spectroscopic data are in agreement with the literature.[8]

The free amine **2** was liberated by dissolving the salt in DCM and stirring over $NaHCO_3$ for 30 min before filtering and concentrating in vacuo; yield: 90 mg (63%, 1.07 mmol).

^{1}H NMR (400 MHz, CD_3OD): δ = 4.07 (1 H, dd, *J* = 7.9, 4.7 Hz), 3.10–2.85 (2 H, m), 2.15 (1 H, m), 2.07–1.74 (3 H, m).

L-Proline Imidate Trifluoroacetate Salt (9·TFA)

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Boc-L-proline nitrile **8** (200 mg, 1.02 mmol) dissolved in TFA (3.55 mL, 45 equiv) was added to this flask and the flask was cooled at 0 °C. Upon consumption of the starting material (TLC check), *t*-BuOH (0.2 mL, 2 equiv) was added and the reaction was allowed to warm at r.t. The reaction was left stirring overnight. Stirring was stopped and the solvent was removed in vacuo. Trituration with hot diisopropyl ether provided the TFA salt of the L-proline imidate **9·TFA**; yield: 217.5 mg (75%, 0.77 mmol); mp 88–90 °C; $[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) –47.23 (*c* 1.0 g cm^{-3} in DCM).

IR (ATR): 3300 (N–H), 2967, 2872, 1658 cm^{-1} (C=N).

^{1}H NMR (400 MHz, CD_3OD): δ = 8.00 (1 H, br s), 4.15 (1 H, dd, *J* = 8.4, 6.8 Hz), 3.44–3.32 (2 H, m), 2.48–2.34 (1 H, m), 2.09–1.89 (3 H, m), 1.36 (9 H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 167.2, 59.9, 51.4, 51.2, 46.1, 30.1, 29.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O$: 171.1492; found: 171.1491.

The free L-proline imidate **9** was liberated by dissolving the salt in DCM and stirring over $NaHCO_3$ for 30 min before filtering and concentrating in vacuo; yield: 31 mg (55%, 0.18 mmol).

IR (ATR): 3300 (N–H), 2967, 2872, 1658 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (1 H, br s), 3.69 (1 H, dd, *J* = 8.8, 5.6 Hz), 3.10–2.86 (3 H, m) 2.18–2.05 (1 H, ddt, *J* = 12.6, 8.8, 7.1 Hz), 1.92–1.81 (1 H, m), 1.78–1.64 (1 H, m), 1.33 (9 H, s).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 173.5, 61.1, 50.4, 47.2, 30.8, 28.8, 26.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{19}N_2O$: 171.1492; found: 171.1491,

Aldol Reaction Catalysed by L-Proline Imidate; General Procedure

A flask was flame dried and was allowed to cool at r.t. under a N_2 atmosphere. Ketone (1.25 mmol) was added to this flask. The catalyst **9·TFA** (0.025 mmol, 0.1 equiv) was dissolved in cyclohexane (1 mL)

and was added to the flask. Solid $NaHCO_3$ (0.025 equiv) was then added to the flask and the contents of the flask were stirred. After 5 min, aldehyde (0.25 mmol) was added and the reaction was continued to be stirred for a further 24 h. The stirring stopped after 24 h and the reaction was quenched with aq NH_4Cl and the solvent was removed in vacuo at r.t. The crude product was re-dissolved in DCM and washed with H_2O (5 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and filtered. The solution was then concentrated in vacuo. The conversion of the reaction was determined by integrating the ^1H NMR of the crude reaction mixture using the aldehyde peak as a reference. *Syn*/*anti* ratio was determined by integrating the ^1H NMR of the crude reaction mixture and by comparing the two C*H*OH peaks. The enantiomeric excess of the crude product was analysed by HPLC using a chiralpak IA, IBN-5, IC, IB, and AD-H column. Representative data for **12**-*syn* and **12**-*anti* are given below. See Supporting Information for data on **14a–i**, **16**, and **18**.

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (12-*syn* and 12-*anti*)

Yield: 89%, yellow oil; diastereomeric ratio: *anti*/*syn*: 5.3:1; 76% *anti* ee.

12-*syn* Diastereomer

IR (ATR): 3517, 2940, 1700, 1516, 1346 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (2 H, m), 7.49 (2 H, m), 5.49 (1 H, br s), 3.18 (1 H, br s), 2.66–2.59 (1 H, m), 2.52–2.46 (1 H, m), 2.45–2.35 (1 H, m), 2.15–2.08 (1 H, m), 1.89–1.82 (1 H, m), 1.76–1.65 (2 H, m), 1.63–1.47 (2 H, m).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 214.0, 149.1, 147.1, 126.7, 123.8, 70.2, 56.9, 42.7, 28.0, 26.0, 25.0.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}NO_4Na$: 272.0893; found: 272.0875.

12-*anti* Diastereoisomer

IR (ATR): 3510, 2939, 1693, 1520, 1346 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (2 H, m), 7.51 (2 H, m), 4.89 (1 H, dd, *J* = 3.2, 8.35 Hz), 4.08 (1 H, d, *J* = 3.2 Hz), 2.64–2.54 (1 H, m), 2.53–2.46 (1 H, m), 2.42–2.31 (1 H, m), 2.15–2.08 (1 H, m), 1.89–1.79 (1 H, m), 1.74–1.64 (1 H, m), 1.63–1.47 (2 H, m), 1.45–1.34 (1 H, m).

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{15}NO_4Na$: 272.0893; found: 272.0879.

Spectroscopic data are in agreement with the literature.[10a]

Retention times for the *syn* and *anti* stereoisomers: *syn*-diastereomer: minor enantiomer t_R = 27.7 min, major enantiomer t_R = 30.0 min; *anti* diastereomer: major enantiomer t_R = 34.6 min, minor enantiomer t_R = 43.0 min.

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Supporting Information

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