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

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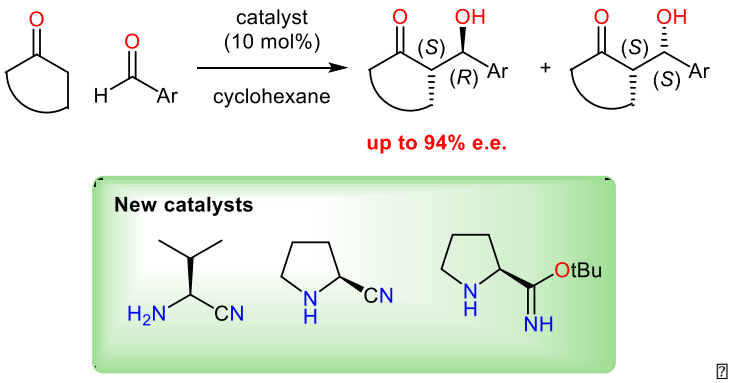

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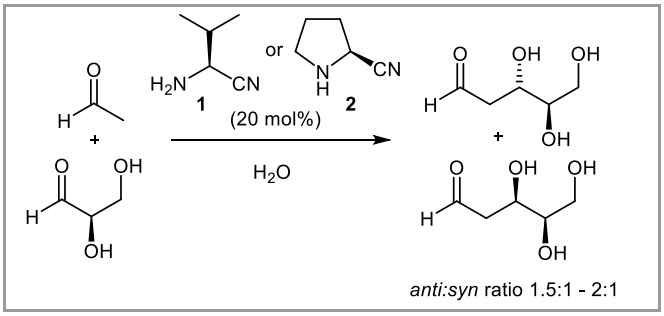
Abstract The efficiency of *L*-valine and *L*-proline nitriles and a *tert*-butyl *L*-proline imidate as organocatalysts for the aldol reaction have been evaluated. *L*-Valine nitrile was found to be a *syn*-selective catalyst, while *L*-proline nitrile was found to be *anti*-selective, and gave products 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.

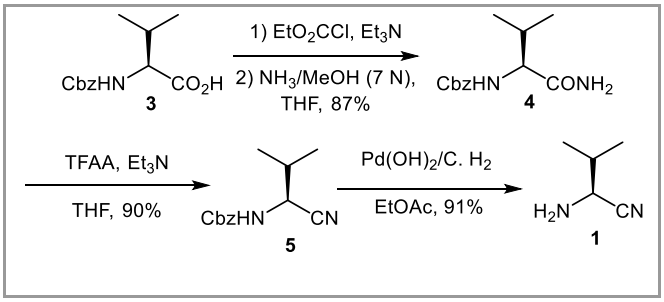
Key words asymmetric synthesis, organocatalysis, aldol reaction, amino nitrile, amino imidate.

The synthesis and evaluation of new small molecules as organocatalysts has become an important endeavor.[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 catalyzed. 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 catalyze 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).



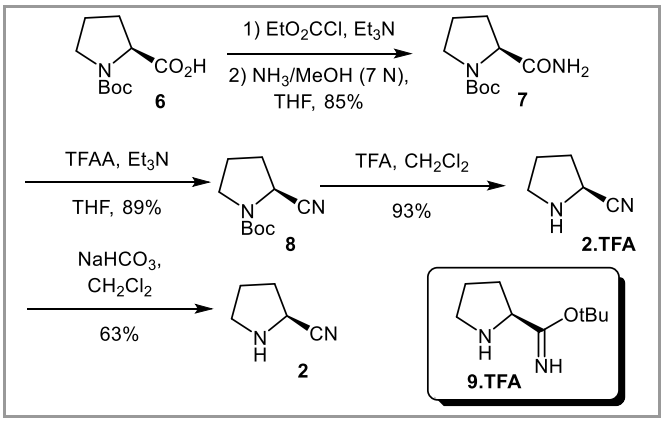
Scheme 1. Amino nitrile catalysed formation of 2-deoxy-D-ribose



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

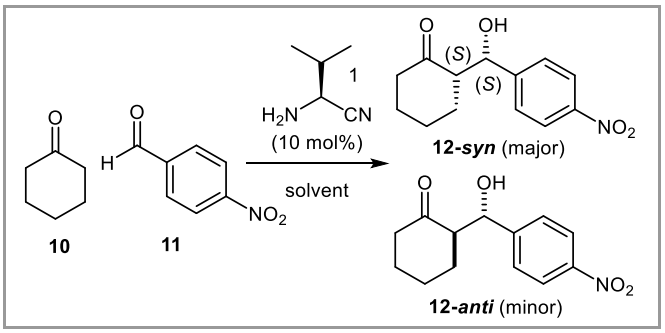
free-based immediately before use by stirring with solid $NaHCO_3$ in CH_2Cl_2 (Scheme 3).



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** was dependent on the batch of TFA used. Some batches of TFA generated **2** 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 tBuOH 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 equiv. of cyclohexanone to 1 equiv. 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; Dioxane 1.3:1; THF 3.8:1; PhMe 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 PhMe, 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% e.e. The absolute stereochemistry of **12-*syn*** was determined to be (*S*), (*S*), by comparison to the literature.[10a]

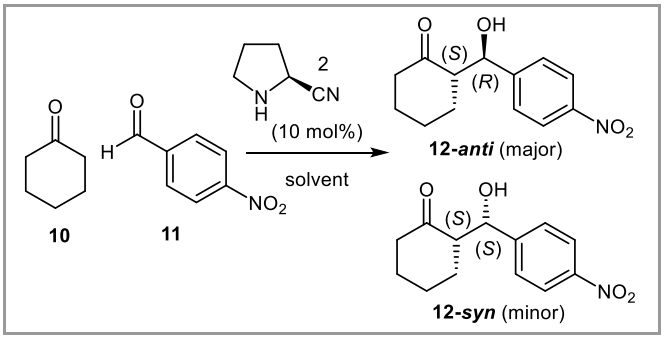


Scheme 4. Aldol reactions catalysed by H_2N-*L*-Val-CN **1**

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 equiv. of cyclohexanone to 1 equiv. 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]	% e.e[b] *anti*	% e.e[b] *syn*
1	CH_2Cl_2	43	4.0:1	13	11
2	DMF	7	2.5:1	20	18
3	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	PhMe	75	4.8:1	20	6

9	Cyclohexane	75	4.0:1	13	0

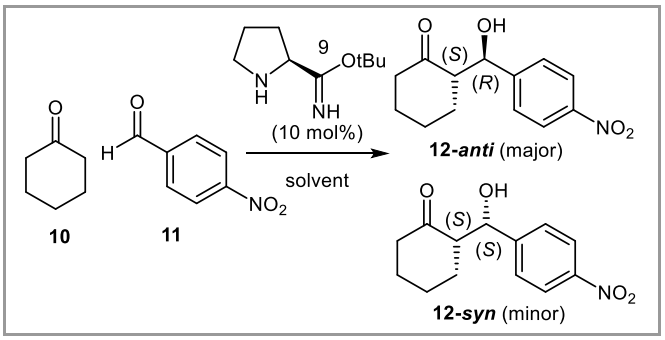
[a] Determined by 400 MHz ^{1}H NMR, by integration of the aldehyde proton and the carbinol protons of the aldol products. [b] Determined by HPLC chiralpak IB column (see supporting information). [c] Not determined.

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 PhMe and cyclohexane (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 reasonable constant in all solvents studies (~ 10-20%) with the exception of THF (Entry 6), which generated **12-*anti*** product in 40% e.e. In general the % e.e. of the *anti*-diastereomer was slightly greater than that of the *syn*-diastereomer. The absolute stereochemistry of the aldol products was determined as **12-*anti*** (*S*), (*R*) and **12-*syn*** (*S*), (*S*) 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.

*t*Bu-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 equiv. of cyclohexanone to 1 equiv. of 4-nitrobenzaldehyde in several solvents (Table 2).

Table 2. Aldol reactions catalysed by *t*Bu-Proline imidate **9**

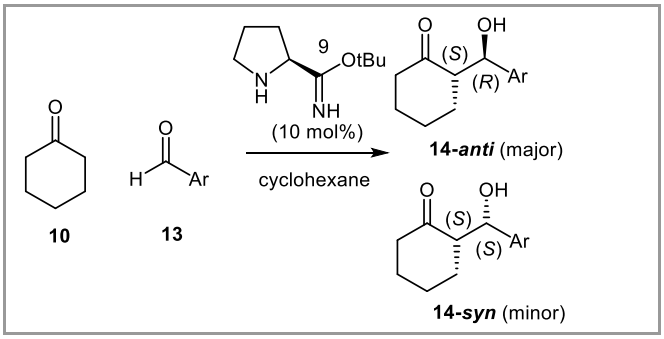


Entry	Solvent	Conversion[a] (%)	*anti:syn*[a]	% e.e[b] *anti*	% e.e[b] *syn*
1	CH_2Cl_2	61	5.6:1	69	45
2	THF	57	5.8:1	46	36
3	PhMe	85	4.6:1	58	27
4	Cyclohexane	100	5.3:1	76	51

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

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 3 the conversions are all substantially better, with hydrocarbon solvents like PhMe (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% e.e. and 51% e.e. 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 3. Amino imidate **9** catalysed aldol reactions



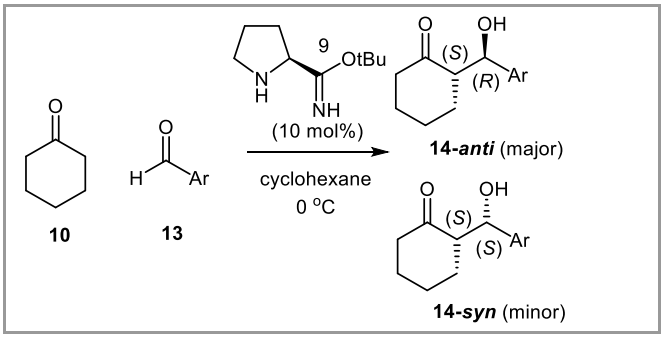
Entry	13 (Ar)	Conversion[a] (%)	14 *anti:syn*[a]	% e.e[b] *anti*
a	2-NO_2-C_6H_5	100	4.7:1	75
b	3-NO_2-C_6H_5	100	3.0:1	63
c	2-Cl-C_6H_5	98	5.0:1	76
d	3-Cl-C_6H_5	96	3.0:1	67
e	4-Cl-C_6H_5	94	2.7:1	57
f	2-Br-C_6H_5	100	7.0:1	69
g	3-Br-C_6H_5	99	2.5:1	71
h	4-Br-C_6H_5	90	3.0:1	61
i	C_6H_5	69	3.5:1	67
j	4-MeO-C_6H_4	0	-	-

[a] Determined by 400 MHz ^{1}H NMR, 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 **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 (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% e.e. (Entry a) and 76% e.e (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% e.e.

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, catalyzed 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% e.e. 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

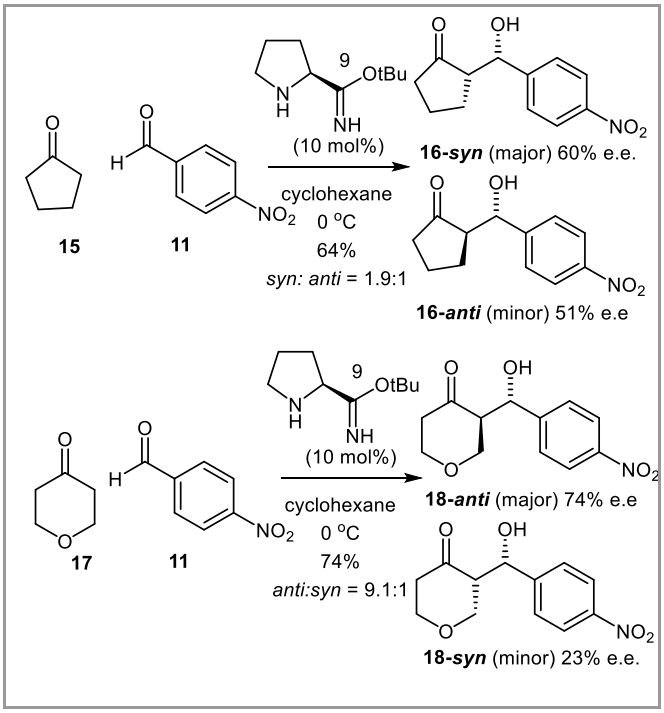


Entry	13 (Ar)	Conversion[a] (%)	14 *anti:syn*[a]	% e.e[b] *anti*
a	2-NO_2-C_6H_5	87	4.8:1	82
b	3-NO_2-C_6H_5	80	5.7:1	51
c	2-Cl-C_6H_5	46	6.8:1	79
d	3-Cl-C_6H_5	39	5.3:1	72
e	4-Cl-C_6H_5	47	4.8:1	77
f	2-Br-C_6H_5	47	6.6:1	69
g	3-Br-C_6H_5	54	4.8:1	74
h	4-Br-C_6H_5	57	5.8:1	76
i	C_6H_5	10	3.8	73

[a] Determined by 400 MHz ^{1}H NMR, 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 % e.e. 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% e.e., while the minor product **16-*anti*** was formed in 51% e.e. The use of pyran-4-one **17** as the aldol donor resulted in the formation of **18-*anti*** as the major diastereomer ion 74% e.e., while the minor **18-*syn***-diastereomer was formed in 23% e.e. 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% e.e., 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 catalyzed 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% e.e. 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 %e.e.s in the mid-70% to high 90% range, depending on the amine used.[16] Proline tetrazole gave %e.e.s upto the low 90% range,[4] whereas ring substituted prolines with parent carboxylic acid gave products with %e.e.s upto the high 90% range.[16] 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.

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Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Nuclear magnetic resonance 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: chloroform-d, 7.26 ppm for 1H NMR; chloroform-d, 77.0 ppm for 13C NMR. Coupling constants (J) are quoted in Hertz. Infra-red 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 [α]D values are given in 10- 1 deg.cm2.g-1. Thin layer chromatography was performed on aluminium sheets coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, basic aqueous potassium permanganate 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. Dry 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.

Procedures

Cbz-*L*-Valine-Amide (4)

A flask was flame dried and was allowed to cool at room temperature under a nitrogen 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 eq.) and dry THF (40 mL) was added. The solution was cooled at 0 °C and was stirred. After 10 minutes, ethyl chloroformate (0.8 mL, 1 eq.) 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 eq.) and the reaction was continued to be stirred at 0 °C for another 1 h. After 1 h, the reaction was allowed to warm at room temperature and was continued to be stirred. After a further 17 hours, the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed *in vacuo* and the white precipitate was filtered and washed with ice cold water to give the pure Cbz-protected amide **4** as a white solid in 87% yield (1.73 g, 6.92 mmol). Data identical to that reported in the literature.[8]

Melting Point: 206-209 °C, literature 205-208 °C.[12]

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

$[\alpha]_D^{20}$ (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}) literature +25.0 (c=1.0 g cm^{-3} in DMF).[40]

^{1}H NMR (400 MHz, *DMSO-d*$_6$) δ ppm: 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, apparent 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 ppm: 173.2, 156.2, 137.2, 128.4, 127.8, 127.3, 65.4, 60.1, 30.2, 19.4, 18.0.

HRMS (ESI): $[M+Na]^+$ HRMS found 273.1210, $C_{13}H_{18}N_2O_3$ required 273.1210.

Cbz-*L*-Valine Nitrile (5)

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Cbz-*L*-Valine amide **4** (1.75 g, 7.00 mmol), dissolved in dry THF (30 mL), and was added to the flask. The flask was cooled at 0 °C, and Et_3N (2.18 mL, 2.2 eq.) was added and the solution was stirred. After 30 minutes, TFAA (1.50 mL, 10.5 eq.) was added and the reaction was continued to be stirred at 0 °C for 1 hour and a further 17 hours at room temperature. The reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed in *vacuo* and the crude oil was re-dissolved in EtOAc. The crude mixture was washed with 2 M HCl and extracted with EtOAc (3 x 10 mL), organic layers combined and washed with saturated $NaHCO_3$ (3 x 10 mL), then washed with brine and extracted (1 x 10 mL). The organic extracts were combined, dried over magnesium sulfate, filtered and the solution was concentrated *in vacuo* to give the crude product as red translucent oil. The crude product was then, further purified by column chromatography (90:10 hexane: EtOAc) and gave the pure Cbz-protected aminonitrile **5** as a red solid in a 90 % yield (1.47 g, 6.30 mmol). Data identical to that reported in the literature.[8]

Melting Point: 49-51 °C, literature 53 °C.[13]

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

$[\alpha]_D^{20}$ (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}) literature -37.3 (c = 0.97 g cm^{-3} in MeOH).[8]

^{1}H NMR (400 MHz *DMSO d*^{6}): δ ppm 8.22 (1H, br. d, J= 8.0 Hz), 7.39-7.31 (5H, m), 5.09 (2H, s), 4.40 (1H, apparent t, J= 8.0), 1.98, (1H, m), 1.00 (3H, d, J= 6.8 Hz), 0.94 (3H, d, J= 6.8 Hz).

^{13}C NMR (400 MHz, *DMSO-d*$_6$) δ ppm: 155.5, 135.7, 128.8, 128.6, 128.4, 117.8, 67.9, 49.1, 31.9, 18.7, 18.0.

HRMS (ESI): $[M+Na]^+$ HRMS found 255.1105, $C_{13}H_{16}N_2O_2Na$ required 255.1104.

***L*-Valine Nitrile (1)**

A flask was flame dried and was allowed to cool at room temperature under a nitrogen 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 eq.) were placed in the flask and the flask was evacuated. Then the flask was placed under a hydrogen atmosphere (60 psi) and was stirred. After 1.5 h of stirring the reaction was deemed complete by TLC (95:5 DCM:MeOH) and the stirring stopped. The mixture was filtered through a pad of celite and the celite was washed thoroughly with EtOAc (50 mL). 4 M HCl in dioxane (1.0 mL) was added and the reaction was stirred for 30 minutes 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 sodium bicarbonate for 30 mins before filtering and concentrating in *vacuo*, as yellow oil in a 91% yield (76 mg, 0.78 mmol). Data identical to that reported in the literature.[8]

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

$[\alpha]_D^{20}$ (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}) literature -8.3 (c = 0.83 g cm^{-3} in DCM).[8]

^{1}H NMR (400 MHz, *CDCl*$_3$) δ ppm: 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): $[M+H]^+$ HRMS found 99.0919, $C_5H_{11}N_2$ required 99.0917.

Boc-*L*-Proline Amide (7)

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-*L*-Proline **6** (2.0 g, 9.2 mmol) and dry THF (30 mL) were added to the flask. To this flask, Et_3N (1.43 mL, 1.1 eq.) was added and the solution was stirred, at room temperature. After 15 minutes, ethyl chloroformate (0.86 mL, 1 eq.) was added and the reaction was continued to be stirred at room temperature. 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 hours. After that, the reaction was deemed complete by TLC (70:30 hexane:EtOAc) and the stirring stopped. The solvent was removed *in vacuo* and the solution was washed with water (10 mL) and extracted with DCM (5 x 10 mL). The combined organic layers dried over magnesium sulfate and the solution was concentrated in vacuo to give the title compound **7** as a white solid in an 85% yield (1.67 g, 7.8 mmol). Spectroscopic data are in agreement with the literature.[8]

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

$[\alpha]_D^{25}$ (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}) literature -42.4 (c=1.0 g cm^{-3} in MeOH).[14]

^{1}H NMR (400 MHz, *CDCl₃*) δ ppm: 6.85 (1H, s), 5.40-6.10 (1H, m), 4.35-4.15 (1H, m), 3.55-3.25 (2H, m), 2.40-1.80 (4H, m), 1.45 (9H, s).

HRMS (ESI): $[M+Na]^+$ HRMS found 237.1209, $C_{10}H_{18}N_2O_3Na$ required 237.1210.

Boc-*L*-Proline Nitrile (8)

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-*L*-Proline amide **7** (625 mg, 2.92 mmol) in dry THF (20 mL) and Et_3N (0.9 mL, 2.2 eq.) were added to the flask. The flask was cooled at 0 °C and stirred. After 30 minutes of stirring, TFAA in a dry ampule (1.0 g, 1.5 eq.) was added and the reaction was continued to be stirred at 0 °C. After 2 hours the reaction was warmed at room temperature and was continued to be stirred. After a further 16 hours the reaction was deemed complete by TLC (90:10 DCM:MeOH) and the stirring stopped. The solvent was removed in *vacuo*. The crude yellow oil was re-dissolved in EtOAc and was washed with 2 M HCl and extracted with EtOAc (3 x 10 mL). Organic layers were combined, washed with saturated $NaHCO_3$ and extracted (3 x 10 mL). Organic layers again, were combined, washed with brine and extracted (3 x 10 mL). Organic layers were combined, dried over magnesium sulfate 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 in a 89% yield (508 mg, 2.60 mmol). Data identical to that reported in the literature.[8]

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

$[\alpha]_D^{20}$ (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}) literature -95.5 (c= 1.3 g cm^{-3} in MeOH).[14]

^{1}H NMR (400 MHz, *CDCl₃*) δ ppm: 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, *CDCl₃*) δ ppm: 153.1, 119.3, 81.6, 47.3, 45.8, 31.8, 28.4, 23.9.

HRMS (ESI) $[M+Na]^+$ HRMS found 219.1105, $C_{10}H_{16}N_2O_2Na$ required 219.1104.

***L*-Proline Nitrile Trifluoroacetate Salt (2.TFA)**

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere. Boc-*L*-Proline nitrile **8** (364 mg, 1.7 mmol) and TFA (3.6 mL, 25 eq.) in dry 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** in a 93% yield (318 mg, 1.58 mmol). Spectroscopic data are in agreement with the literature.[8]

Melting Point 90-92 °C; literature 92-94 °C.[15]

IR (ATR): 3323 (N-H stretch), 2943, 2831, 2269 (CN), 1665 (C=O).

$[\alpha]_D^{20}$ (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}) literature -16.7 (c= 1.0 g cm^{-3} in MeOH).[8]

^{1}H NMR (400 MHz, *MeOD d⁴*) δ ppm: 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, *MeOD d⁴*) δ ppm: 161.8 (q, J=34.7 Hz, C-F_3), 115.2, 46.8, 45.8, 29.9 , 23.2.

HRMS (ESI) $[M+H]^+$ HRMS found 97.0759 $C_5H_9N_2$ required 97.0760.

The free amine **2** was liberated by dissolving the salt in DCM and stirring over sodium bicarbonate for 30 mins before filtering and concentrating in *vacuo* in a 63% yield (90 mg, 1.07 mmol).

^{1}H NMR (400 MHz, *MeOD* d⁴) δ ppm: 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 room temperature under a nitrogen atmosphere. Boc-*L*-Proline nitrile **8** (200 mg, 1.02 mmol) dissolved in TFA (3.55 mL, 45 eq.) were 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 eq.) was added and the reaction was allowed to warm at room temperature. The reaction was left stirring overnight. Stirring was stopped and the solvent was removed *in vacuo*. Trituration with hot isopropyl ether provided the TFA salt of the *L*-proline imidate **9.TFA** in a 75% yield (217.5 mg, 0.77 mmol).

Melting Point 88-90 °C.

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

$[\alpha]_D^{25}$ (deg cm^3 g^{-1} dm^{-1}) -47.23 (c= 1.0 g cm^{-3} in DCM),

^{1}H NMR (400 MHz, *MeOD*) δ ppm: 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, *CDCl₃*) δ ppm: 167.2, 59.9, 51.4, 51.2, 46.1, 30.1, 29.7,

HRMS (ESI) $[M+H]^+$ HRMS found 171.1491, $C_9H_{19}N_2O$ required 171.1492.

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

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

^{1}H NMR (400 MHz, *CDCl₃*) δ ppm: 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, *CDCl₃*) δ ppm: 173.5, 61.1, 50.4, 47.2, 30.8, 28.8, 26.1.

HRMS (ESI) $[M+H]^+$ HRMS found 171.1491, $C_9H_{19}N_2O$ required 171.1492.

General Procedure for the Aldol Reaction Catalysed by L-Proline Imidate

A flask was flame dried and was allowed to cool at room temperature under a nitrogen atmosphere, ketone (1.25 mmol) was added to this flask. The catalyst **9.TFA** (0.025 mmol, 0.1 eq.) was dissolved in 1 mL of cyclohexane and was added to the flask. Solid sodium bicarbonate (0.025 eq.) was then added to the flask and the flask was stirred. After 5 minutes, 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 NH_4Cl and the solvent was removed *in vacuo* at room temperature. The crude product was re-dissolved in DCM and washed with water (5 mL) and extracted with DCM (3 x 10 mL). Organic layer was dried over sodium sulfate and filtered. The solution was then concentrated *in vacuo*. The conversion of the reaction was determined by integrating the ^{1}H NMR of the crude reaction mixture

using the aldehyde peak as a reference. *Syn/anti* ratio was determined by integrating the ^{1}H NMR of the crude reaction mixture and by comparing the two C*H*-OH peaks. The enantiomeric excess of the crude product was analysed, via HPLC using a chiralpak IA, IBN-5, IC, IB and AD-H column. Representative data for **12-*syn*** and **12-*anti*** is given below. See supporting information for data on **14a-i**, **16** and **18**.

2-(hydroxy((4-nitrophenyl)methyl)cyclohexanone (12-*syn* and 12-*anti*)

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

^{1}H NMR (400 MHz, *CDCl$_3$)* δ ppm: 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 (1H, m), 1.76-1.65 (2 H, m), 1.63-1.47 (2 H, m).

^{13}C NMR (400 MHz, *CDCl$_3$*) δ ppm: 214.0, 149.1, 147.1, 126.7, 123.8, 70.2, 56.9, 42.7, 28.0, 26.0, 25.0.

HRMS (ESI) HRMS found 272.0875, $C_{13}H_{15}NNaO_4$ required 272.0893.

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

^{1}H NMR (400 MHz, *CDCl$_3$)* δ ppm: 8.21 (2 H, m), 7.51 (2 H, m), 4.89 (1H, dd, J=3.2 Hz, 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) HRMS found 272.0879, $C_{13}H_{15}NNaO_4$ required 272.0893. 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

YES (this text will be updated with links prior to publication)

Primary Data

Reference spectroscopic and reaction data can be found at DOI: 10.15124/2da4946b-3c7d-4a0e-ac03-9eaa672d8da8

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