Synthesis and evaluation of guanidinyl pyrrolidines as bifunctional catalysts for enantioselective conjugate additions to cyclic enones†

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Guanidinyl pyrrolidines derived from '*S*'-proline are effective catalysts for the enantioselective conjugate addition of malonate, nitroalkane and other carbon and heteroatom nucleophiles to cyclohexenone and cyclopentenone in the absence of basic additives. The stereoselectivity is strongly dependant on catalyst loading as well as reaction concentration.

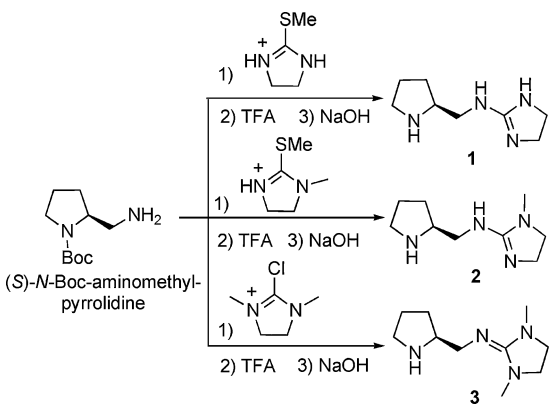
Introduction

The organocatalytic Michael addition of carbon nucleophiles to a variety of acceptors has been extensively investigated in recent years.[1] One particular class of these reactions, the conjugate addition of carbon nucleophiles to α,β-unsaturated ketones, is of special interest. The ready availability of starting materials, the simplicity of the process, and the synthetic versatility of the Michael adducts have all contributed to the notable interest in the asymmetric catalysis of this reaction. Remarkable progress in the enamine-mediated[2] and the iminium ion[3] mediated conjugate addition reactions has been witnessed in recent years. However, the organocatalytic conjugate addition of malonates and nitroalkanes to cyclic and acyclic enones is an enduring challenge and the search for new and efficient organocatalysts for these reactions continues.[4–9] Herein, we report preliminary results on the application of pyrrolidinyl guanidines as catalysts for the malonate-enone and nitroalkane-enone conjugate addition reactions.

Studies on the iminium ion mediated organocatalytic conjugate addition of malonates to enones have employed catalysts based on functionalized imidazolidinones[4] and modified prolines.[5] Moderate to good enantioselectivities are obtained, but reactions with the imidazolidinone catalysts are sluggish and are often conducted with malonate as the solvent. The proline-based catalysts usually require amine additives for optimum performance. Similarly, modified prolines/amine additives,[6] peptides/amine additives[7] and imidazolidinone catalyst systems[8] have been examined for the asymmetric conjugate addition of nitroalkanes to enones. The imidazolidinone catalysts provide better stereoselectivities in these reactions but often require a large excess of the nitroalkane. A few organocatalysts that do not rely on iminium ion formation have also been examined for malonate and nitroalkane conjugate additions.[9]

Considering that proline and peptide based catalysts work best with amine additives, we reasoned that an efficient catalyst system could probably be developed by appending a basic moiety to the pyrrolidine framework. In addition, it seemed plausible that a base-containing catalyst would enhance the reaction rate by assisting in the deprotonation of the nucleophile. This would potentially offer some improvements over catalyst systems which require a large excess of malonate and prolonged reaction times for appreciable turnover. A cursory examination of the acidity of carbon nucleophiles suggested that a guanidine moiety[10] would be well suited as the base for deprotonation of malonate and nitroalkane nucleophiles. Hence, we chose to prepare the guanidinyl pyrrolidines **1–3** as catalyst candidates for this study. It may be noted that relatively few studies[10] have examined chiral guanidines as bases in conjugate addition reactions in general and even fewer studies have investigated guanidine-catalyzed conjugate additions of malonates to enones.[10h,i]

The synthesis of catalysts **1–3** is readily achieved by reaction of (*S*)-*N*-Boc-aminomethylpyrrolidine with the appropriate imidazolium species followed by deprotection of the pyrrolidine (Scheme 1).



Scheme 1

Preliminary experiments involved screening of the guanidinyl pyrrolidines **1–3** for efficacy in the conjugate addition of dibenzyl malonate to cyclohexenone in a variety of solvents to provide (*S*)-**4a**[4] (Table 1).

Amino-guanidines **1**,**2** and **3** catalyzed the conjugate addition of dibenzyl malonate to cyclohexenone in substoichiometric amounts (15 mol%), to provide **4** in good to moderate yield. Although reasonable yields were obtained with catalysts **1** and **3** the enantiomeric excess was negligible (0–12%, Table 1, entries 1–6). In contrast, catalyst **2** provided (*S*)-**4a** with higher enantioselectivity

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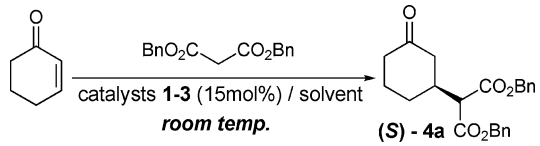
Table 1 Addition of dibenzyl malonate to cyclohexenone



Entry[a]	Catalyst	Solvent	Time (h)	Yield (%)	Ee(%)[b]
1	**1**	toluene	168	94	4
2	**1**	CH_2Cl_2	92	91	12
3	**1**	DMF	168	82	6
4	**3**	toluene	36	41	5
5	**3**	$CHCl_3$	36	35	3
6	**3**	DMF	36	75	< 1
7	**2**	—	20	99	4
8	**2**	DMF	48	56	21
9	**2**	toluene	48	68	36
10	**2**	$CHCl_3$	48	46	49
11	**2**	THF	48	84	50
12	**2**	DCE	48	70	58
13	**2**	**CH_2Cl_2**	**48**	**41**	**61**
14	**2**	***t*-BuOH**	**48**	**45**	**63**

[a] 1.2 eq. malonate. [b] Chiral HPLC analysis.

in 1,2-dichloroethane, dichloromethane and *t*-butyl alcohol (Table 1, entries 12–14). Also, with **2** as the catalyst, dibenzyl malonate provided higher enantioselectivity compared to its dimethyl[5b] (**4b**, 59% ee) and diethyl[5b] (**4c**, 52% ee) congeners whereas di-*t*-butyl malonate failed to react. Interestingly, the enantioselectivity was negligible (4%, entry 7, Table 1) when dibenzyl malonate was used as the solvent. These observations clearly indicated an important role for the solvent as well as the concentration of the reactants. We therefore conducted an optimization study with dibenzyl malonate, cyclohexenone and catalyst **2**. The effect of catalyst loading and reaction concentration was examined in this study (Table 2).

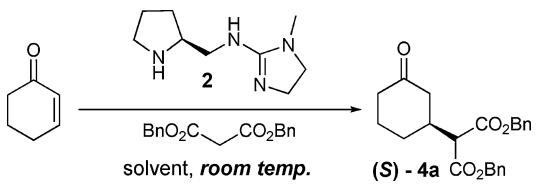
Although *tert*-butyl alcohol had provided the highest enantioselectivity in the solvent screening study, it was immediately apparent that dilution was not an option with this solvent (Table 2, entry 1, 31% ee). Experiments in dichloromethane and 1,2-dichloroethane (DCE) were more fruitful and diluting the reaction mixture had a significant, positive effect on enantioselection in these solvents. For example, doubling the dilution in dichloromethane with 15 mol% of **2**, increased the enantioselectivity from 61% to 82% (entries 2 and 5, Table 2). Further dilution and a concomitant decrease in catalyst loading improved the enantioselectivity to 86% (Table 2, entry 6) but at the expense of the yield. A similar effect of dilution was also observed in 1,2-dichloroethane but, in this case, decreasing the catalyst loading was less detrimental to the overall yield. Consequently, 1,2-dichloroethane was the solvent of choice and under the optimized conditions, **4a** was obtained in 64% yield and 86% ee (Table 2, entry 12).

The precise reasons for the effect of dilution on the enantioselection are not clear at this time. We hypothesize that at higher reaction concentrations, deprotonation of the malonate by **2** is faster than iminium ion formation and this results in a direct conjugate addition of malonate anion to cyclohexenone with low enantioselectivity. The poor enantioselectivity observed in malonate as the reaction medium supports this proposal. As the effective concentration of malonate is lowered, the rate of malonate deprotonation by free catalyst **2** is sufficiently reduced to allow iminium ion formation, and conjugate addition to an iminium species involving **2** proceeds with higher enantioselectivity. These observations suggest a bifunctional role for guanidinyl pyrrolidine **2**, namely, iminium ion formation and malonate deprotonation. It is also plausible that dilution favours double hydrogen bonding between the malonate anion and the guanidinium ion, which results in a directed addition of the malonate.

We next investigated the conjugate addition of nitroalkanes to cyclohexenone and cyclopentenone. These results are summarized in Table 3.

The guanidinyl pyrrolidine **2** was again the catalyst of choice in these reactions and a small excess (2–5 eq.) of the nitroalkane was beneficial for enantioselectivity. Compared with the malonate

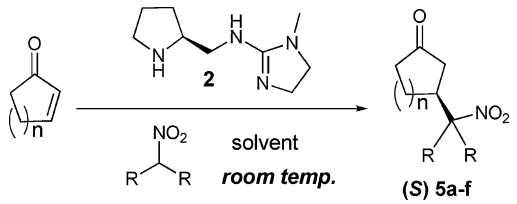
Table 2 Optimization studies with catalyst **2**



Entry[a]	Cat. (mol%)	Solvent	Vol. (mL)	Malonate (M)	Time (h)	Yield (%)	Ee (%)[b]
1	15	*t*-BuOH	2	0.3	48	88	31
2	15	CH_2Cl_2	1	0.6	48	41	61
3	5	CH_2Cl_2	2	0.3	90	16	74
4	10	CH_2Cl_2	2	0.3	120	50	82
5	15	CH_2Cl_2	2	0.3	90	61	82
6	**10**	**CH_2Cl_2**	**4**	**0.15**	**156**	**27**	**86**
7	15	DCE	2	0.3	48	92	73
8	20	DCE	5	0.12	164	99	79
9	20	DCE	7	0.09	185	87	81
10	10	DCE	2	0.3	140	78	84
11	10	DCE	4	0.15	156	47	86
12	**10**	**DCE**	**3**	**0.2**	**140**	**64**	**86**

[a] 0.5 mmol cyclohexenone, 1.2 eq. malonate. [b] By chiral HPLC.

Table 3 Asymmetric conjugate additions of nitroalkanes to cycloalkenones



Entry[a]	5[b]	n	R	Cat. (mol%)	Vol. (mL)	Nitroalkane (M)	Time (h)	Yield (%)	Ee (%)[c]
1	**a**	**2**	**H**	**15**	**2**	**1.25**	**120**	**31**	**72**
2			H	5	1	2.5	192	15	72
3			H	15	3	0.8	168	97	56
4			H	10	3	0.8	164	54	66
5	**b**	**2**	**CH_3**	**10**	**4**	**0.25**	**156**	**43**	**65**
6			CH_3	15	2	0.5	120	52	58
7	**c**	2	$(CH_2)_4$	10	4	0.6	240	44	41
8	**d**	2	$(CH_2)_5$	10	4	0.25	192	42	45
9	**e**	1	H	15	2	1.5	96	50	50[d]
10	**f**	1	CH_3	10	4	0.3	96	88	26

[a] CH_2Cl_2 as solvent, DCE for entries 4, 5 and 9. [b] 5 eq. of nitroalkane 2 eq. for entries 5, 6 and 8. [c] Chiral HPLC. [d] ^{13}C NMR of ketal with (2*R*,3*R*)-2,3-butanediol.

study, the trend in stereoselection was less predictable and lowering catalyst loading and increasing dilution did not always increase enantioselectivity. (**5a**, entries 1, 3 and 4). Curiously, increasing the size of the nitroalkane did not result in an increase in enantioselectivity as has been observed in some studies and the enantioselectivity with nitrocyclopentane and nitrocyclohexane is lower than the acyclic nitroalkanes.[11] It is also noteworthy that an increase in catalyst loading and reaction time for the nitromethane/cyclohexenone reaction provided **5a** in excellent yield (97%, Table 3, entry 3). This suggests that **5a** is stable under the reaction conditions and may not be reacting further as indicated in studies with the tetrazolyl proline catalyst.[6d] Significantly, all of the malonate and the nitroalkane addition products have the '*S*' configuration whereas the earlier proline-derived catalysts[4,5b,6–8] provide the '*R*' products in the majority of cases. A possible explanation of this observation is initial iminium ion formation followed by addition of malonate or nitronate that is hydrogen-bonded to the protonated guanidine[12] as shown in Fig. 1.

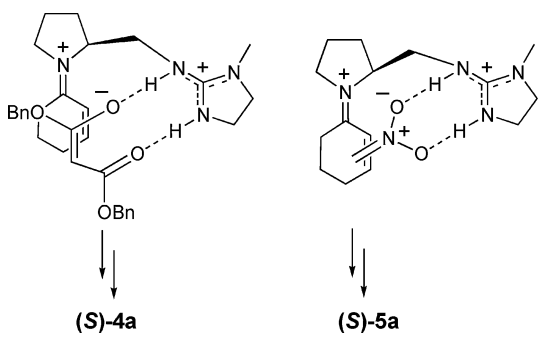


Fig. 1 Proposed model for the origin of stereoselectivity with amino guanidine catalyst **2**.

The conjugate addition of other carbon and heteroatom nucleophiles such as dibenzoylmethane,[13] malononitrile,[14] and naphthalene-2-thiol[15] was also effectively catalyzed with amino guanidine **2** to provide the conjugate addition products **6–8** respectively (Fig. 2). The stereoselectivities for these reactions were strongly dependant on the amount of catalyst employed and low catalyst loading was necessary for appreciable enantioselection. This observation highlights the basicity of the guanidine pendant in catalyst **2**. Presumably, these nucleophiles are rapidly deprotonated due to their higher acidity, and the non-iminium ion mediated conjugate addition pathway predominates as the catalyst loading increases. Low catalyst loading increases enantioselection but reduces the product yield. For example, the triketone **6** (Fig. 2) was obtained in 99% yield and 39% ee when 15 mol% of catalyst **2** were employed. A similar reaction with 1 mol% of **2** provided **6** with 80% ee but reduced yield (12%) in spite of a longer reaction period. While this highlights the inherent potential in **2** for asymmetric induction, a balance between iminium ion forming ability and basicity seems necessary, especially when nucleophiles with low pK_a values are employed.

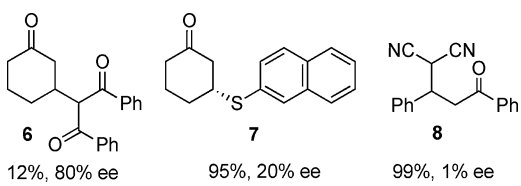


Fig. 2 Results with other nucleophiles.

In conclusion, new organocatalysts incorporating iminium ion forming (pyrrolidine) and strongly basic (guanidine) functionalities were prepared and examined in the conjugate addition reactions of cyclohexenone and cyclopentenone with a variety of nucleophiles. The enantioselectivity for the addition of dibenzyl malonate to cyclohexenone (86% ee) is, to the best of our knowledge, the highest reported for the organocatalytic variant of this reaction in the absence of an externally added base.[16] It is also noteworthy that the malonate conjugate additions do not require a large excess of the malonate and good yields

of the products with cyclohexenone are obtained in reasonable time (Table 2, 1.2 eq. of malonate, average time 115 h, average yield 63%). Qualitatively, this implies an increased reaction rate compared to the functionalized imidazolidinone catalysts[4] used for this reaction (malonate as reaction medium (8 eq.), 78% yield, 150 h). The observations from this study provide some insight into the reactivity of amine-guanidine bifunctional catalyst motifs and lay the foundation for designing second generation catalysts with modulated nucleophilic and basic character. Current efforts focus on reactions of other nucleophiles and enones catalyzed by **2** and related amino-guanidines.

Experimental section

General

All commercially available reagents and solvents were used without purification. Commercial precoated silica gel (Merck 60F-254) plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are uncorrected. IR spectra were recorded on a Bruker TENSOR 27 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE-500 instrument. Coupling constants (J) are given in Hz. Mass spectra were obtained on an Agilent 1100 series LC/MSD chromatographic system. High-resolution mass spectra were obtained on a Waters GCT Premier Micromass mass spectrometer. Optical rotations were measured at the sodium D line on a JASCO-DIP 370 digital polarimeter at ambient temperature.

4,5-Dihydro-*N*-(((*S*)-pyrrolidin-2-yl)methyl)-1H-imidazol-2-amine (1)

To a solution of (*S*)-*N*-Boc-2-aminomethyl pyrrolidine[17] (1.25 g, 6.25 mmol) in isopropanol (50 mL) was added 2-methylthio-2-imidazoline hydroiodide ((prepared from ethylenediamine by conversion to imidazolidine-2-thione and subsequent reaction with iodomethane), 1.53 g, 6.25 mmol) at room temperature and the solution was heated to reflux at 95 °C for 2 days. The solution was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (dichloromethane/methanol 98/2) to provide 1.40 g, (57%) of (*S*)-*tert*-butyl 2-((4,5-dihydro-1H-imidazol-2-ylamino)methyl)pyrrolidine-1-carboxylate hydroiodide (**1a**) as a white foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H, N*H*), 8.36 (s, 1H, N*H*), 7.59 (s, 1H, N*H*), 3.77 (s, 4H, NCH_2CH_2N), 3.68-3.65 (br m, 1H, C*H*N), 3.39-3.34 (m, 1H, CH_2NCO), 3.34-3.29 (dd, 1H, J = 6, 15 CHCH_2N), 3.23-3.12 (m, 2H, CH_2NCO, CHCH_2N), 2.02-1.87 (m, 4H, CH_2CH_2), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.1 (N*C*O), 156.3 (N*C*N), 81.4 (*C*(CH$_3$)$_3$, 57.6 (*C*HN), 47.2 (*C*H_2NCO), 46.5 (*C*H_2N), 43.6 (*C*H_2N), 43.3 (*C*H_2N), 30.4 (*C*H_2CH$_2$), 28.8 (C(*C*H$_3$)$_3$), 23.8 (CH$_2$*C*H$_2$); MS (APCI): m/z 269.2 ((M − HI) + 1, 100); IR: (neat) 2960, 1663, 1291, 1199, 1175, 1127 cm^{-1}; HRMS (CI): m/z 268.1897 (268.1899 calc. for $C_{13}H_{24}N_4O_2$ (M − HI)).

To a stirred solution of the above hydroiodide (0.25 g, 0.63 mmol) in dry CH_2Cl_2 (3 mL), was added trifluoroacetic acid (1.5 mL) at 0 °C. The solution was brought to room temperature after 30 min., stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was extracted with water (2 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 50 mg (47%) of **1** as a colourless oil. This material was directly used further.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.50 (s, 4H, NCH_2CH_2N), 3.28-3.23 (m, 1H, C*H*N), 3.20-3.16 (dd, 1H, J = 3.5, 13.5 CHCH_2N), 2.98-2.93 (dd, 1H, J = 8.2, 13.5 CHCH_2N), 2.88-2.83 (m, 1H, CH_2N), 2.77-2.72 (m, 1H, CH_2N), 1.84-1.71 (m, 2H, CH_2CH$_2$), 1.63-1.56 (m, 1H, CH_2CH_2), 1.40-1.31 (m, 1H, CH_2CH$_2$); visible peaks for tautomer: 3.73-3.7 (m); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 163.4 (NCN), 59.0 (N*C*H$_2$CH$_2$N), 48.5 (br, N*C*H), 46.8 (br, 2 x N*C*H$_2$), 29.4 (br, *C*H$_2$CH$_2$), 26.4 (br, CH$_2$*C*H$_2$); visible peaks for minor tautomer: δ 63.9, 49.5, 46.5, 41.9, 31.9; MS (APCI): m/z 169.2 (M + 1, 100); IR: (neat): 3261, 2960, 1608, 1559, 1456, 1263, 1199 cm^{-1}; HRMS (CI): m/z 169.1454 (169.1453 calc. for $C_8H_{17}N_4$ (M + H)); $[\alpha]_D^{23} = -33.2$ (c 1, $CHCl_3$).

4,5-Dihydro-1-methyl-*N*-(((*S*)-pyrrolidin-2-yl)methyl)-1H-imidazol-2-amine (2)

To a solution of (*S*)-*N*-Boc-2-aminomethyl pyrrolidine[17] (3 g, 15 mmol) in isopropanol (50 mL) was added 4,5-dihydro-1-methyl-2-(methylthio)-1H-imidazole hydroiodide ((prepared from *N*-methyl ethylenediamine by conversion to 1-methyl imidazolidin-2-thione and subsequent reaction with iodomethane), 3.87 g, 15 mmol) at room temperature and the solution was heated to reflux at 95 °C for 2 days. The solution was concentrated under reduced pressure to provide 6.13 g (99%) of (*S*)-*tert*-butyl 2-((4,5-dihydro-1-methyl-1H-imidazol-2-ylamino)methyl)pyrrolidine-1-carboxylate hydroiodide (**2a**) as a pale yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (s, 1H, N*H*), 8.54 (s, 1H, N*H*), 3.84-3.83 (m, 1H, C*H*N), 3.80-3.76 (m, 2H, CH_2NCO), 3.68-3.59 (m, 3H, NCH_2CH_2N, CHCH_2N), 3.42-3.35 (m, 2H, NCH_2CH_2N), 3.27-3.24 (m, 1H, CHCH_2N), 3.14 (s, 3H, NCH_3), 2.26 (m, 1H, CH_2CH_2), 2.04-1.89 (m, 2H, CH_2CH_2), 1.89-1.85 (m, 1H, CH_2CH_2), 1.47 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.5 (N*C*O), 156.9 (N*C*N), 81 (O*C*(CH$_3$)$_3$, 56.9 (*C*HN), 50.3 (*C*H$_2$NCO), 48.2 (CH*C*H$_2$N), 47.1 (*C*H$_2$N), 41.4 (N*C*H$_3$), 33.2 (*C*H$_2$N), 29.7 (*C*H$_2$CH$_2$), 28.4 (C(*C*H$_3$)$_3$), 23.7 (CH$_2$*C*H$_2$); MS (APCI): m/z 283.3 (M + 1, 100); IR (neat): 3199, 2967, 2228, 2024, 1669, 1405 cm^{-1}; HRMS (CI): m/z 282.2054 (282.2056 calc. for $C_{14}H_{26}N_4O_2$ (M − HI)).

To a stirred solution of the above hydroiodide (1.5 g, 3.61 mmol) in dry CH_2Cl_2 (5 mL), was added trifluoroacetic acid (5 mL) at 0 °C. The solution was brought to room temperature after 30 min., stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was extracted with water (2 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give 624 mg (93%) of **2** as a colourless oil. This was directly used further.

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.45–3.41 (m, 2H, NCH_2CH_2N), 3.33-3.28 (m, 1H, C*H*N), 3.27-3.21 (m, 3H, CHCH_2N, NCH_2CH_2N), 3.04-3.00 (dd, 1H, J = 8.3, 12.7,

CHCH_2N), 2.93-2.85 (m, 2H, CH_2N), 2.73 (m, 3H, CH_3N), 1.87-1.79 (m, 1H, CH_2CH_2), 1.77-1.73 (m, 1H, CH_2CH_2), 1.70-1.62 (m, 1H, CH_2CH_2), 1.45-1.38 (m, 1H, CH_2CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 161.8 (N*C*N), 59.5 (*C*HN), 51.4 (N*C*H_3), 48.1 (CH*C*H_2N), 46.5 (NCH_2*C*H_2N), 41.7 (N*C*H_2CH_2N), 33.7 (*C*H_2N), 29.2 (*C*H_2CH_2), 26.8 (CH_2*C*H_2); MS (APCI): *m/z* 183.1 (M + 1, 100); IR (neat): 2958, 2024, 1655, 1409, 1262, 1031 cm^{-1}; HRMS (CI): *m/z* 183.1605 (183.1610 calc. for $C_9H_{19}N_4$ (M + H)); $[\alpha]_D^{23} = -50.4$ (c 1, $CHCl_3$).

N-(1,3-Dimethylimidazolidin-2-ylidene)((*S*)-pyrrolidin-2-yl)methanamine (3)

To a solution of (*S*)-*N*-Boc-2-aminomethyl pyrrolidine[17] (1.38 g, 6.9 mmol) in acetonitrile (25 mL) was added commercially available 2-chloro-1,3-dimethylimidazolinium chloride (1.17 g, 6.9 mmol) and potassium carbonate (2.86 g, 21 mmol) at room temperature and the solution was stirred at room temperature for 2 days. The undissolved solids were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (dichloromethane/methanol 90/10) to provide 0.78 g (34%) of (*S*)-*tert*-butyl-2-((1,3-dimethylimidazolidin-2-ylideneamino)methyl)pyrrolidine-1-carboxylate hydrochloride (**3a**) as a white, gummy foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.6 (s,1H, N*H*), 3.94-3.93 (br m, 1H, C*H*N), 3.75-3.72 (m, 1H, CHCH_2N), 3.64 (s, 4H, NCH_2CH_2N), 3.52-3.48 (m, 1H, CHCH_2N), 3.37-3.32 (m, 2H, CH_2NCO), 3.28 (s, 6H, NCH_3), 2.33-2.29 (m, 1H, CH_2CH_2), 2.11-2.09 (1H, m, CH_2CH_2), 1.93-1.83 (m, 2H, CH_2CH_2), 1.45 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.9 (N*C*O), 156.1 (N=*C*N), 80.2 (O*C*(CH$_3$)$_3$), 57.1 (*C*HN), 49.7 (CH*C*H_2N, N*C*H_2CH_2N), 47.3 (N*C*H_3), 46.1 (N*C*H_3), 35.3 (*C*H_2NC(O)), 29.5 (C(*C*H_3)$_3$), 28.4 (NCH_2CH_2(pyrrolidine)), 23.7 (NCH_2 (pyrrolidine)). Visible peaks for isomeric salt: δ 157.3, 81.09, 56.1, 53.6, 47.8, 45.6, 30.9; MS (APCI): *m/z* 297.2 ((M – HI) + 1, 100); IR (neat): 2972, 1684, 1632, 1392, 1166, 1109 cm^{-1}; HRMS (CI): *m/z* 296.2203 (296.2212 calc. for $C_{15}H_{28}N_4O_2$ (M – HI)).

To a stirred solution of the above hydrochloride (0.320 g, 0.96 mmol) in dry CH_2Cl_2 (3 mL) was added trifluoroacetic acid (1.5 mL) at 0 °C. The solution was brought to room temperature after 30 min., stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in ethyl acetate (5 mL) and the solution was extracted with water (2 mL). The aqueous phase was cooled (<5 °C), basified with NaOH pellets and the basic solution was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give 138 mg (73%) of **3** as a pale yellow gum.

^{1}H NMR (500 MHz, $CDCl_3$): 3.96-3.92 (m, 1H, C*H*N), 3.84-3.8 (dd, 1H, *J* = 9.2, 13, CHCH_2N), 3.5-3.45 (m, 1H, CH_2N), 3.4-3.37 (dd, 1H, *J* = 5.7, 13, CHCH_2N), 3.24-3.14 (m, 3H, CH_2N, NCH_2CH_2N), 2.87 (s, 3H, CH_3N), 2.82 (br s, 1H, N*H*), 2.81-2.76 (m, 3H, N*H*), 2.45 (s, 3H, CH_3N), 1.96-1.9 (m, 1H, CH_2CH_2), 1.82-1.74 (m, 2H, CH_2CH_2), 1.54-1.47 (m, 1H, CH_2CH_2); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 167.7 (N*C*N), 64.2 (*C*HN), 58.6 (CH*C*H_2N), 51.3 (*C*H_2N), 51.1 (NCH_2*C*H_2N), 49.4 (N*C*H_2CH$_2$N), 36.9 (N*C*H_3), 36.7 (N*C*H_3) 32.4 (*C*H_2CH$_2$), 26.1 (CH$_2$*C*H$_2$); MS (APCI): *m/z* 197.1 (M + 1, 100); IR (neat): 2937, 2231, 2024, 1652, 1603, 1447, 1403, 1288, 1263, 1114 cm^{-1}; HRMS (CI): *m/z* 197.1774 (197.1766 calc. for $C_{10}H_{21}N_4$ (M + H)); $[\alpha]_D^{23} = -54.6$ (c 1, $CHCl_3$).

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