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C_2-Symmetric Amino Acid Amide-Derived Organocatalysts †

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† Dedicated to the staff and students of the Department of Chemistry, University College of North Wales, 18 October 1884–31 July 2022.

Abstract: *N*-alkylated C_2-symmetric amino acid amide derivatives were shown to catalyse the Michael addition of 2-hydroxy-1,4-napthoquinone to β-nitrostyrene, achieving a maximum ee of 44%. The corresponding trifluoroacetic acid salts also catalysed the aldol reaction between 4-nitrobenzaldehyde and hydroxyacetone, leading to the formation of predominantly *syn*-aldol products in up to 55% ee. Aspects of the solvent dependence of the aldol reaction and the H-bonding of the catalyst were investigated.

Keywords: organocatalysis; amino acids; Michael additions; aldol reactions

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Citation: Al-Taie, Z.S.; Coles, S.J.; Congreve, A.; Ford, D.; Green, L.; Horton, P.N.; Jones, L.F.; Kett, P.; Kraehenbuehl, R.; Murphy, P.J.; et al. C_2-Symmetric Amino Acid Amide-Derived Organocatalysts. *Reactions* **2024**, *5*, 567–586. https://doi.org/10.3390/reactions5030027

Academic Editor: Dmitry Yu. Murzin

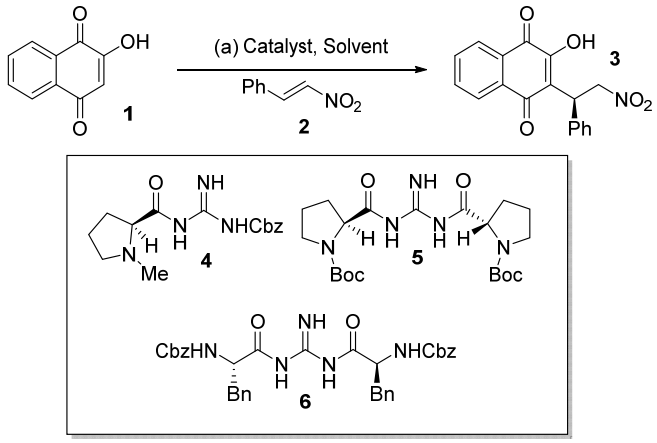
Received: 6 June 2024
Revised: 31 July 2024
Accepted: 16 August 2024
Published: 24 August 2024

1. Introduction

Organocatalysis of organic reactions continues to be of significant interest, particularly the design and application of novel catalysts to asymmetric C–C bond formation [1–10]. We recently reported [11,12] the preparation of a range of amino acid-derived guanidines which were shown to have some potential as asymmetric organocatalysts in the Michael reaction. It was, however, apparent that several problems were associated with this work. Our initial L-proline-derived catalysts (for example **4**) gave, at best, a modest 56% ee for the formation of the Michael adduct **3** from the addition of 2-hydroxy-1,4-napthoquinone **1** to β-nitrostyrene **2**. These catalysts were found to be difficult to prepare as the intermediates in their synthesis were prone to racemization. We also investigated several *N*-protected C_2-symmetric amino acid-derived catalysts including **5** (18–22% ee over three solvents) and **6** (15–26% ee over two solvents). These were not as successful as catalyst **4** and gave very slow rates of conversion due to low basicity (Scheme 1).

We were able to deduce from crystallographic studies that these catalysts took part in strong intramolecular H-bonding, which may be preventing the desired intermolecular interaction of catalyst with substrate. Our overall goal in this research was to develop a catalyst that takes part in strong associative interactions with the reactants. The various modifications made to our catalyst structures did not lead to any improvement in ee, and it was apparent from X-ray studies that the H-bonding patterns observed are not predictable. This suggested that the ability of the guanidine to form multiple strong H-bonds is not a favorable one and our original goal [11,12] to employ a simplified range

of base catalysts might be more advantageous [13–15]. This proposition was supported by an investigation in the solid state demonstrating extensive intra- and intermolecular H-bonding abilities of the proline, guanidine, and/or amide functional groups within these organic moieties. Based on these observations, we have investigated the simpler *N*,*N*-dimethylated C_2-symmetric amides of general structure **7** (Figure 1), which should have less capability for strong intramolecular H-bonding.



Scheme 1. Catalytic Michael addition: Catalyst (0.1 equiv.), −20 °C, 48 h.

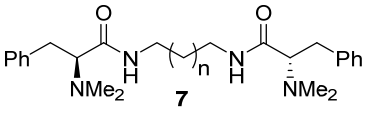


Figure 1. Generalised catalyst structure (n = 0–5).

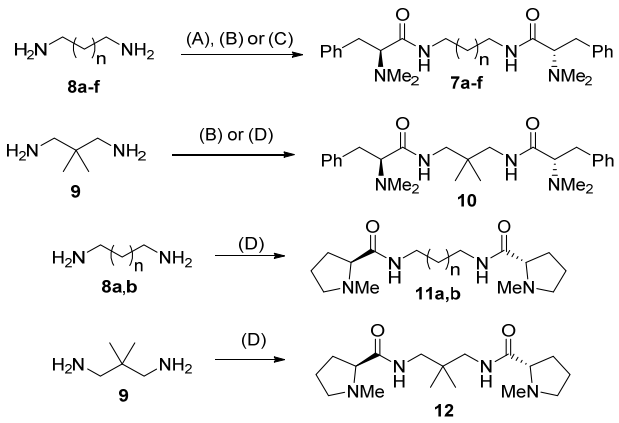
2. Preparation of Michael Catalysts

The catalysts **7a–e** were prepared by reaction of the required diamine **8a–e** with a 2-fold excess of *N*,*N*-dimethylphenylalanine [16], which had been activated by treatment with CDI in DMF (Method A). This gave the required catalysts but in consistently low yield (21–33% over 5 examples), and unfortunately, the catalysts were consistently contaminated with unidentified by-products and required repetitive chromatography to achieve high purity. An alternative method (Method B) was attempted for compound **7f,** which reversed the coupling and methylation steps. Thus, the diamine **8f** (n = 5) was coupled with a 2-fold excess of Z-L-Phe-OH activated using CDI, following which the intermediate bis-Cbz-protected amine was simultaneously deprotected and methylated in situ using Pd/C in the presence of methanolic formaldehyde solution. This gave **7f** in an excellent 76% yield, and the method was next applied to the most successful (vide infra) catalysts **7a** and **7b**. Unfortunately, the method was not applicable to these compounds as they were insoluble in most of the solvents we employed. Even on prolonged reaction times (7–10 days), the deprotection was slow at 1 atm of hydrogen, and low yields were obtained. Despite this, after simple chromatography, the compounds were obtained in high purity. In order to improve this process for catalyst **7c,** the corresponding bis-Cbz-protected amine was deprotected using HBr/AcOH, and the diamine formed methylated in situ using Pd/C in the presence of methanolic formaldehyde solution (Method C). This gave catalyst **7c** in 80% yield (4.0 g scale) after a simple work-up (Entry 2(c), Table 1). We also attempted to prepare the dimethyl-substituted base **10** from Cbz-L-Phe-OH by Method B and had some measure of success (Entry 7(b), Table 1), obtaining a 63% yield. However, the reaction was capricious, and repetition of the hydrogenation step led to varied results. We repeated the reaction using hydrogenation in the presence of formaldehyde over Raney Ni and obtained a better result and found purification was easier, leading to **10** in 73% yield from the intermediate diamine (Method D, entry 7(d)). This method was utilized for the proline-derived catalysts

11a, **11b**, and **12**, giving them in 65%, 59%, and 38% yield from the intermediate diamines (Scheme 2, Table 1).

Table 1. Preparation of catalysts **7a–f** and **10**.

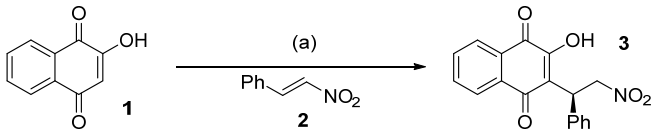
Entry	Catalyst	n	A/%	B/%	C/%	D/%
1	**7a**	0	27	30	---	---
2	**7b**	1	23	13	80	---
3	**7c**	2	33	---	---	---
4	**7d**	3	32	---	---	---
5	**7e**	4	31	---	---	---
6	**7f**	5	---	76	---	---
7	**10**	---	---	63	---	73
8	**11a**	0	---	---	---	65
9	**11b**	1	---	---	---	59
10	**12**	---	---	---	---	38



Scheme 2. Method A: N,N-dimethyl-L-phenylalanine (2.1 equiv.), CDI (2.3 equiv.), DMF, 1 h. then amine **8a–f** (1 equiv.), 24 h. Method B: (i) Cbz-L-Phe-OH (2.1 equiv.), CDI (2.3 equiv.), CH_2Cl_2, 10 min, then amine **8a–f** (1 equiv.), 16 h. (ii) CH_2O (aq. 37%, 13 equiv.), H_2/Pd/C, MeOH, 48 h. Method C: Cbz-L-Phe-OH (2.1 equiv.), CDI (2.3 equiv.), CH_2Cl_2, 10 min, then **9** (1 equiv.), 16 h. (ii) HBr in AcOH (33%, excess) then NaOH (aq). (iii) CH_2O (aq. 37%, 13 equiv.), H_2/Pd/C, MeOH, 48 h. Method D: (i) Boc-L-Phe-OH or Boc-L-Pro-OH or Cbz-L-Pro-OH (2.1 equiv.), CDI (2.3 equiv.), CH_2Cl_2, 10 min, then **8a,b** or **9** (1 equiv.), 16 h. (ii) $CF_3CO_2H/CHCl_3$ (1:2, excess) then NaOH (aq) or HBr in AcOH (33%, excess) then NaOH (aq). (iii) CH_2O (aq. 37%, 13 equiv.), H_2/Raney Ni, MeOH, 96 h. (n = 0–5).

3. Michael Reaction—Catalytic Studies

We initially investigated our previously studied reaction [11,12] of 2-hydroxy-1,4-napthoquinone **1** to β-nitrostyrene **2** leading to the Michael product **3** (Scheme 3, Table 2).



Scheme 3. Catalytic studies: Conditions: See Table 2, catalyst (0.1 equiv.), −20 °C, CH_2Cl_2.

Table 2. Catalysed Michael reaction between **1** and **2**.

Entry	Cat.	n	Time/d	ee	Yield/%
1	**7a**	0	4	26	89
2	**7b**	1	4	44	70
3	**7c**	2	4	36	77
4	**7d**	3	4	44	92
5	**7e**	4	4	27	96
6	**7f**	5	4	19	92
7	**10**	-	4	38	85
8	**11a**	0	4	10	39
9	**11a**	0	14	15	87
10	**11b**	1	4	9	98
11	**12**	-	4	15	69

The catalysts **7a–f** were all successful in this reaction, with the catalysts **7b** and **7d** both giving 44% ee (Table 2, entries 1–6); however, there was no clear relationship between the proximity of the amides and any improvement in ee. We next tried the dimethyl-substituted catalyst **10**, hoping for an improvement [17]; however, there was no appreciable increase in ee (Table 2, entry 7). The reactions involving the three proline-derived catalysts (Table 2, entries 8–11) gave very poor ees (9–15%) in comparison to the previous catalysts. Interestingly, compound **11a** gave poor conversion over the standard reaction time (Table 2, entry 8) and required 14 days to achieve comparable yields to the other catalysts (Table 2, entry 9). Additionally, despite numerous efforts to obtain suitable crystals of all the catalysts employed, catalyst **11a** was the only compound that gave crystals suitable for X-ray analysis, which were obtained on standing from a dichloromethane solution and were found to crystallise in the orthorhombic $P2_12_12$ space group (see Table 3 for crystallographic details). There was disorder of the entire bridging diamide units, which was best modelled over two sites (split in 65:35 occupancy). Intramolecular hydrogen bonding is observed between the proline N atoms (N2 and s.e.) and nearby amide NH functional groups at distances of 2.39(4) Å (N1(H1)$\cdots$N2) and 2.47(7) Å (N1B(H1BA)$\cdots$N2; Figure 1). Intermolecular H-bonding is also found between the carbonyl O atoms (O1 and O1B and s.e.) and neighbouring diamide nitrogen protons (H1′ and H1BA′; where ′ = x, y, 1 + z) at distances of 2.06(4) Å (O1$\cdots$N1′(H1); Figure 1) and 2.06(6) Å (O1B$\cdots$N1B′(H1BA′)). These intermolecular interactions allow the superimposable alignment of the individual units of **11a** along the *c* unit cell direction (Figures 2 and 3). The 1D hydrogen-bonded rows pack efficiently in three dimensions using the common brickwork motif.

Two points of note from the X-ray structure of **11a** are, firstly, the disorder present in the -CH_2CH_2- linker. It is likely this disorder will be present in the longer chain analogue, and this might explain the lower ees achieved by these catalysts. Secondly, the intramolecular H-bonds between N1(H1)$\cdots$N2 of 2.39(4) Å represent a relatively strong interaction and might be expected to be preserved in solution [18,19]. If reactions involving these catalysts are determined by the breaking of this bond, then this might be a significant factor in determining ee and the relatively slow progress of the reaction.

Following this work, we investigated the reaction of β-nitrostyrene **2** with dimethyl malonate using the catalysts **7b** and **7f** and found that the catalysts were ineffective in this reaction. Both **7b** and **7f** were able to catalyse the Michael addition of acetylacetone and 1,3-diphenylpropane-1,3-dione to β-nitrostyrene **2**; however, the ees for this process were low (15% and 11%, respectively); full details are given in the supplementary information.

Table 3. X-ray crystallographic data obtained from **11a**.

	11a
Formula	$C_{14}H_{26}N_4O_2$
M_W	282.388
Crystal System	Orthorhombic
Space group	$P2_12_12$
a/Å	13.7087(5)
b/Å	11.6393(4)
c/Å	5.0039(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	798.42(5)
Z	2
T/K	100(2)
λ/Å	1.54178
D_c/g cm^{-3}	1.175
μ(Mo-Ka)/mm^{-1}	0.645
Meas./indep.(R_{int}) refl.	7332/1497 (0.0350)
Restraints, Parameters	0.109
wR2 (all data)	0.1843
R1	0.0867
Goodness of fit on F^2	1.042

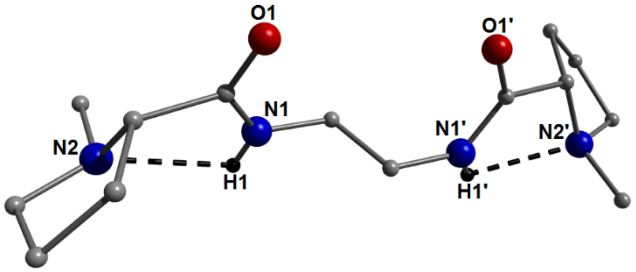


Figure 2. Crystal structure of **11a**. The colour codes used throughout this work are Grey (C), Red (O), Blue (N) and black (H). The majority of H-atoms have been omitted for clarity. Only one form of the disordered connecting diamide bridges is shown. The dashed lines represent intramolecular H-bonds (N1(H1)$\cdots$N2 = 2.39(4) Å ($'$ = 1 − x, 1 − y, z).

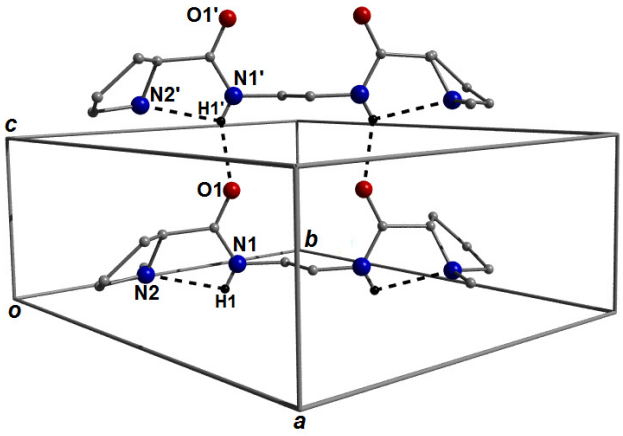


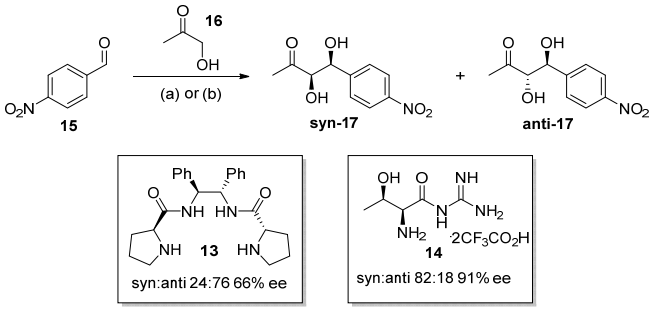
Figure 3. Packing arrangement of **11a** as viewed along the *ab* plane of the unit cell. The dashed lines represent intermolecular H-bonding interactions at a distance of O1$\cdots$N1′(H1′) = 2.06(4) Å ($'$ = x, y, 1 + z; $''$ = x, y, −1 + x). Only one form of the disordered connecting diamide bridges is shown.

4. Conclusions on Michael Additions

We can conclude from these reactions that the dimethylamine/amide-linked catalysts are catalysts for this process, but the ees obtained are only modest and do not achieve levels of asymmetric induction achieved by other catalysts [1,2]. There is possibly a strong intramolecular H-bond, based on previous studies on guanidine-based catalysts, which might need to be broken to allow the reaction to proceed with efficiency [11,12,20]. The shorter chain length catalysts (**7a** to **7d**) appear to give better results. With the catalyst precursors in hand, we next went on to study an aldol-type reaction.

5. Aldol Reactions

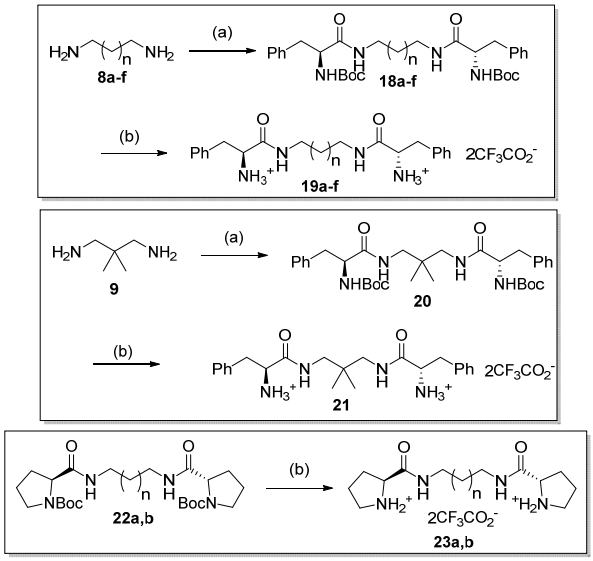
We were interested in other potential applications of these catalysts and were intrigued by the work of Zhao and co-workers [21] and the more recent work of Jimeno [22], who reported that the catalysts **13** and **14** catalysed the biomimetic aldol reaction [23,24] between aldehyde **15** and hydroxyacetone **16**, leading to the formation of *syn*-**17** and *anti*-**17**. Interestingly, the free amine catalyst **13** leads to predominantly *anti*-**17**, whilst the salt **14** leads to the *syn*-**17** product. (Scheme 4)



Scheme 4. Aldol reaction catalysed by **13** or **14**. (a) Catalyst **13** (10 mol%), THF; 38% yield. (b) Catalyst **14** (20 mol%), DMF; 75% conversion.

6. Preparation of Aldol Catalysts

The required diamine trifluoroacetate catalysts **19a–f**, **21** and **23a,b** were prepared from the diamines **8a–f** and **9** via the Boc-protected intermediates **18a–f** [25–27], **20** and **22a,b**, [28,29] by treatment with trifluoroacetic acid in chloroform, followed by drying under vacuum for 24 h (Scheme 5).



Scheme 5. (a) Boc-L-Phe-OH (2.10 equiv.), CDI (2.60 equiv.), CH_2Cl_2, 10 min, then **8a–f** (1.00 equiv.), 16 h. (b) $CF_3CO_2H/CHCl_3$ (1:2, excess), 4 h. (c) Cbz-L-Pro-OH (2.10 equiv.), CDI (2.60 equiv.), CH_2Cl_2, 10 min, then **9** (1.00 equiv.), 16 h. (n = 0–5).

7. Aldol Reaction—Catalytic Studies

The initial study was the reaction between **15** and **16** (Scheme 4) and employed catalysts **19a–f** and **21** and intended to study the relationship between the de (*syn*- to *anti*-ratio), ee, and the chain length within the catalysts. A standard set of conditions was employed in the initial reactions, and the results are shown in Table 4 (entries 1–7). It was apparent from these results that all 7 catalysts studied gave very similar *syn*- to *anti*-ratios, with the *syn*-**17** product as the major diastereoisomer (Table 4, entries 1–7). It was found that the shortest chain length catalyst **19a** gave the best levels of conversion and the highest ee, with a 50% ee for *syn*-**17** and a 72% ee for the *anti*-**17** product (entry 1). The ee decreases as the chain length increases, becoming fairly constant at a chain length of 4 or more carbons (Table 4, entries 3–6). The most successful catalysts, **19a**, **19b**, and **21**, were investigated further by increasing the concentration of the reaction and reaction time (Table 4, entries 8–10). This led to an increased conversion; however, the *syn*:*anti* selectivity was lower in all cases, as were the ees. We also investigated the effect of increasing the number of equivalents of hydroxyacetone **16** (Table 4, entries 11–13) at the higher reaction concentration. This gave increased conversion (72–86% over the three reactions). In the case of **19a** and **19b** (Table 4, entries 11 and 12), the *syn*:*anti* ratio was much poorer than in the previous examples (Table 4, entries 1 and 2); however, for catalyst **21**, this effect was less so (Table 4, entry 13 versus entry 10). The problem associated with increasing the relative amount of hydroxyacetone **16** might stem from the reagent acting as a protic solvent, and we next ran a series of experiments with catalysts **19a**, **19b** and **21** with **16** as the solvent (Table 4, entries 14–16). As expected, this led to a similar loss of *syn*:*anti* selectivity in all cases and much lower ees. This suggests that the protic nature of **16** may be an issue in these reactions. Finally, the proline-derived catalysts **23a** and **23b** were attempted (Table 4, entries 17, 18). These catalysts gave reasonable conversion but no appreciable *syn*:*anti* selectivity and mediocre ee, which was the opposite of that seen for the other catalysts. (similar reversals of selectivity have been reported [22,30] for proline-derived catalysts).

Table 4. Aldol reaction of **15** and **16** catalysed by **19a–f**, **21** and **23a,b** [(i)].

Entry	Cat.	T (d)	n	Conversion (%)	*syn*:*anti*	*Syn* ee	*Anti* ee
1	**19a**	2	0	58	62:38	50	72
2	**19b**	2	1	35	63:37	48	46
3	**19c**	2	2	32	66:34	34	36
4	**19d**	2	3	32	62:38	32	42
5	**19e**	2	4	32	68:32	30	38
6	**19f**	2	5	32	61:39	32	40
7	**21**	2	--	46	66:34	32	36
8	**19a**	4	0	63 [(ii)]	57:43	36	34
9	**19b**	4	1	63 [(ii)]	62:38	20	36
10	**21**	4	--	62 [(ii)]	63:37	24	32
11	**19a**	4	0	80 [(ii),(iii)]	51:49	52	60
12	**19b**	4	1	72 [(ii),(iii)]	57:43	38	60
13	**21**	4	--	86 [(ii),(iii)]	62:38	40	24
14	**19a**	4	0	90 [(iii),(iv)]	50:50	36	26
15	**19b**	4	1	88 [(iii),(iv)]	56:44	14	39
16	**21**	4	--	83 [(iii),(iv)]	55:45	16	14

Table 4. *Cont.*

Entry	Cat.	T (d)	n	Conversion (%)	*syn*:*anti*	*Syn* ee	*Anti* ee
17	**23a**	4	0	62	52:48	−30 (v)	−28 (v)
18	**23b**	4	1	48	52:48	−24 (v)	−24 (v)

(i) General conditions catalyst (0.2 equiv.), **15** (1.0 equiv.), **16** (10 equiv. unless stated), DMF (0.33 M relative to **15**), rt. (ii) Compound **15** used at 0.66 M; (iii) 20 equiv. of **16**; (iv) Reagent 16 used as solvent (0.33 M relative to **15**); (v) Opposite enantiomeric selectivity observed.

We next investigated the effect of varying solvent in the reaction (Table 5) and found that under the standard conditions, the best conversions were observed in THF (75%, Table 5, entry 1), ethanol (73%, Table 5, entry 2), acetonitrile (44%, Table 5, entry 3), and propan-2-ol (44%, Table 5, entry 4). It was observed, however, that the *syn*:*anti* selectivity of these systems was lower and slightly in favour of the anti-**17** product, but the ees of both the *syn*-**17** and *anti*-**17** were of the same magnitude as that observed in DMF (Table 5, entry 0; repeated for convenience). Other solvents gave considerably poorer conversion over 48 h particularly the protic solvents methanol, ethylene glycol, and water (Table 5, entries 6, 8, and 9); however, methanol did give good syn-anti selectivity over 18% conversion).

Table 5. Aldol reaction of **15** and **16** catalysed by **19a** in differing solvents (i).

Entry	Solvent	Conversion (%)	*syn*:*anti*	*syn* ee	*Anti* ee
0	DMF	58	62:38	50	72
1	THF	75	47:53	54	82
2	EtOH	73	47:53	54	60
3	^{i}PrOH	52	40:60	50	70
4	MeCN	44	48:52	50	72
5	DMSO	19	63:37	nd	nd
6	MeOH	18	80:20	nd	nd
7	CH_2Cl_2	12	33:67	nd	nd
8	$(CH_2OH)_2$	10	50:50	nd	nd
9	Water	0	--	--	--

(i) General conditions. Catalyst (0.2 equiv.), **15** (1.0 equiv.), **16** (10 equiv.), solvent (0.33 M relative to **15**), rt. nd = not determined.

Based on these experiments, we investigated the use of increased catalyst amount (0.2 equiv.) over a longer time period (96 h) in the best predicted solvents (Table 6). In all 4 reactions using 0.2 equivalents of catalyst, the conversion was considerably improved, with over 92–99% conversion for DMF, THF, and EtOH (Table 6, entries 1–3). The *syn*:*anti* selectivity was best in the case of DMF (Table 6, entry 1) and was poorer in the case of THF, EtOH, and MeOH (Table 6, entries 2–4). The ees for the anti-**17** product remained high at 75–86%, with the ees of the syn-**17** fairly consistent at 46–55% ee.

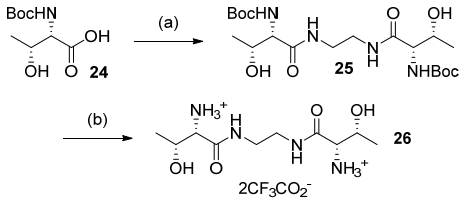
The diastereoselectivity of these reactions is low; however, in some cases, the ees are reasonable. In order to progress the work, we looked at the work of Jimeno, who reported [22] the use of the threonine acyl guanidine catalyst **14** (Scheme 4), which was reported to be a superior catalyst in this reaction in comparison to other amino acid acyl catalysts. It was suggested that a stabilizing hydrogen bonding network amongst the acylguanidinium moiety, the enamine nitrogen, and the aldehyde carbonyl oxygen was an important feature of this catalyst. We thus theorized that the incorporation of a threonine into our catalysts might improve selectivity. We attempted to prepare catalyst **25** via our standard coupling method using *N*-Boc-L-threonine **24**, activation using CDI in

dichloromethane, and coupling with ethylene diamine **8a** (n = 0). This method, however, led to the formation of a complex product, possibly polymeric in nature. We tried the alternate coupling method reported by Jimeno [22] using EDC.HCl and HOBt, which gave the protected intermediate **25** in 69% yield. This was smoothly deprotected to give **26** using TFA in chloroform (Scheme 6). We applied this catalyst to the aldol reaction and found that over the standard conditions (0.2 equivalents, 4 days), there was an increase in *syn*:*anti* selectivity (entry 1); however, the conversion was low, as was the ee of both *syn*-**17** and *anti*-**17**. We repeated the reaction at a lower temperature for 8 days (entry 2), and this gave a similar conversion and again poor ees. Reverting to room temperature and allowing the reaction to run for 10 days (Table 7, entry 3) gave a 71% conversion but only 22% ee for the *syn*-**17** product and 14% ee for *anti*-**17**.

Table 6. Aldol reaction of **15** and **16** catalysed by 0.2 equivalents of **19a** in differing solvents[(i)].

Entry	Solvent	Conversion (%)	*syn*:*anti*	*syn* ee	*Anti* ee
1	DMF	93	57:43	52	79
2	THF	99	45:55	55	76
3	EtOH	92	52:48	46	86
4	MeOH	71	52:48	48	75

(i) General conditions Catalyst (0.2 equiv.), **15** (1.0 equiv.), **16** (10 equiv.), solvent (0.33 M relative to **15**), rt.



Scheme 6. Preparation of **26** (a) (i) **24** (2.0 equiv.), EDC.HCl (2.30 equiv.), HOBt.H_2O (3.23 equiv.), DIPEA (2.25 equiv.), DMAP (0.20 equiv.), then (ii) **8a** (n = 0, 1.00 equiv.). (b) $CF_3CO_2H/CHCl_3$ (1:2, excess), 4 h.

Table 7. Aldol reaction of **15** and **16** catalysed by **26** [(i)].

Entry	Time	Conversion (%)	*syn*:*anti*	*syn* ee	*Anti* ee
1	4	36	64:36	32	6
2	8	40	63:37	22	14
3	10	71	61:39	22	14

(i) General conditions Catalyst **26** (0.2 equiv.), **15** (1.0 equiv.), **16** (10 equiv.), DMF (0.33 M relative to **15**), rt.

These results might indicate that any potential H-bonding interactions to the amino acid portion of catalyst **26** appear to be detrimental to the reaction. Indeed, the proximity of the two hydroxyl groups in catalyst **26** to any intermediates in the reaction might have a similar disruptive effect on conversion to that observed in the reactions performed in water, methanol, and ethylene glycol. The reaction, in agreement with the work of Jimeno [22], does show predominantly syn-selectivity (Table 7).

8. Conclusions on Aldol Reactions

From the aldol reactions investigated, we can conclude that catalyst **19a** appears to be the best of our catalysts for this process, leading to a slight bias for the *syn*-**17** product in acceptable ee. In most cases using **19a–f**, the L-phenylalanine-derived catalysts, the ees observed were always greater for the anti-**17** product. The use of L-proline-derived catalysts had a detrimental effect on selectivity and inverted the enantioselectivity, as observed by

others [22,30]. The use of an L-threonine-derived catalyst capable of H-bonding interactions had a detrimental effect on enantioselectivity. Jimeno [11] put forward a transition state **27** (from modelling studies) for his catalyst **14**, in which the aldehyde undergoes H-bonding interactions with the guanidinium portion of the enamine intermediate. This explains the *syn*-selectivity observed; however, no role for the hydroxyl group on the threonine residue was put forward. Barbas et al. [31] put forward a similar transition state **28** for the identical aldol reaction catalysed by L-threonine and tBuO-L-threonine. In these cases, the carboxylic acid of the amino acid is involved in H-bonding to the aldehyde, and there appears to be little difference in the *syn*-anti selectivity between the L-threonine and tBuO-L-threonine catalysts (Figure 4).

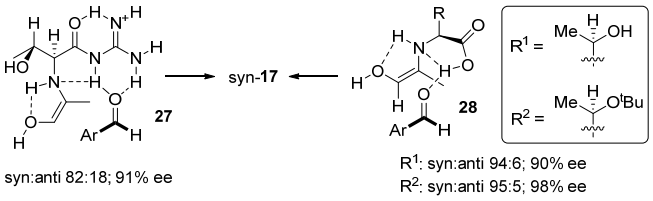


Figure 4. Aldol transition states proposed by Jimeno [11] and Barbas. [16].

Based on these observations and the poor selectivity observed with the L-threonine-derived catalyst **26**, we might speculate that a similar transition state is in operation. However, one complicating factor might be that the catalysts themselves might be present as dienamines in which both amine groups have reacted with the excess of hydroxyacetone. We hope to report further studies on similar catalysts in the future.

9. General Procedures

Unless otherwise noted, reactions were stirred and monitored by TLC. TLC plates were visualized using iodine, phosphomolybdic acid, or under UV light. All anhydrous reactions were conducted under a static argon atmosphere using oven-dried glassware that had previously been cooled under a constant stream of nitrogen. Reagents, dry solvents, and starting materials were purchased from commercial suppliers and used without further purification. Flash column chromatography was performed on Davisil® silica gel (35–70 microns) with the eluent specified in each case; TLC was conducted on precoated E. Merck silica gel 60 F_{254} glass plates. Unless specified, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (Bruker (UK) Ltd. Coventry, UK) with an internal deuterium lock at ambient temperature at 400/100 MHz with internal references of δ_H 7.26 and δ_C 77.16 ppm for $CDCl_3$, δ_H 3.31 and δ_C 49.00 ppm for CD_3OD, and δ_H 2.50 and δ_C 39.52 for d_6-DMSO. Infrared spectra were recorded on a Bruker Tensor 37 FT-IR. Mass spectra were determined on a Q Exactive Plus (Thermo Scientific) (Blue Scientific Limited, Cambridge, UK) instrument run with positive electrospray ionization (ESI). Melting points were determined on a Stuart SMP10 (Camlab Ltd. Cambridge UK) apparatus and are uncorrected. Optical rotations were measured in a 0.25 dm cell on an ADP440 polarimeter (Bellingham & Stanley Ltd., Weilheim, Germany). Control reactions between 2-hydroxy-1,4-napthoquinone **2** and **3** under standard conditions and between 4-nitrobenzaldehyde **15** and hydroxyacetone **16** under standard conditions, both in the absence of catalyst were determined to show no appreciable levels of conversion over standard reaction timescales.

10. Experimental

10.1. General Methods for the Preparation of Catalysts

Method A: preparation of 7a–e: CDI (2.3 equiv.) was added to a stirred suspension of *N*,*N*-dimethyl-L-phenylalanine (2.0 equiv.) in dry DMF (15 mL per mmol of *N*,*N*-dimethyl-L-phenylalanine), and the mixture was stirred with gentle warming until dissolved and stirring continued for 1 h. The mixture was then cooled (0 °C), and the diamine (1.0 equiv.) was added. After stirring for 24 h at room temperature, the reaction mixture was rotary

evaporated under reduced pressure then co-evaporated with heptane (3 times) to remove DMF. The products **7a–e** were purified by repeated column chromatography (0–20% MeOH/$CHCl_3$).

(2*S*,2′*S*)-*N*,*N*′-(ethane-1,2-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7a**.

Method A: Dimethyl-L-phenylalanine (500 mg, 2.60 mmol), 1,2-diaminoethane (78 mg, 1.30 mmol), CDI (484 mg, 2.3 mmol) gave **7a** (144 mg, 27%) as a white solid. **Rf** 0.32 (10% MeOH in $CHCl_3$); **Mp.** 117 °C; $[\alpha]_D^{20}$ 5.2 (c = 1.0, $CHCl_3$); δ_H 7.09–7.26 (10H, m, 2 × Ph), 6.18 (2H, br s, 2 × NH), 3.12–3.22 (4H, m, 2 × CH_2), 3.03 (2H, dd, *J* 8.4, 12.9, 2 × CH), 2.85–2.96 (2H, m, 2 × CH), 2.79 (2H, dd, *J* 4.7, 13 Hz, 2 × CH), 2.25 (12H, s, 4 × Me); δ_C 172.2, 139.6, 129.6, 128.5, 126.3, 71.1, 42.4, 39.0, 33.9; ν_{max} 3303, 2926, 2859, 2828, 2782, 1648, 1536, 1454, 1238. **MS** (ESI) *m*/*z* 206.1 (100%, $[M+2H]^{2+}$), 411.3, (15%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 411.2752, $C_{24}H_{35}N_4O_2^+$ ($[M+H]^+$) requires 411.2755.

(2*S*,2′*S*)-*N*,*N*′-(propane-1,3-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7b**.

Method A: Dimethyl-L-phenylalanine (750 mg, 3.89 mmol), 1,3-diaminopropane (144 mg, 1.94 mmol), CDI (882 mg, 5.44 mmol) gave **7b** (192 mg, 23%) as a white solid. **Rf** 0.23 (10% MeOH in $CHCl_3$); **Mp**. 106 °C; $[\alpha]_D^{20}$ +22.4 (c = 1.1, $CHCl_3$); δ_H 7.24–7.25 (8H, m, 8 × CH), 7.13–7.19 (2H, m, 2 × CH), 6.97 (2H, br t, *J* 6.2 Hz, 2 × NH) 3.22 (2H, dd, *J* 5.4, 7.6 Hz, 2 × CH), 3.16 (2H, dd, *J* 13.3, 7.6 Hz, 2 × CH), 2.92–3.10 (4H, m, 2 × CH_2), 2.89 (2H, dd, *J* 13.3, 5.4 Hz, 2 × CH) 2.32 (12H, s 4 × Me), 1.43 (2H, pentet, *J* 6.4 Hz, CH_2); δ_C 172.3, 139.7, 129.4, 128.4, 126.2, 71.2, 42.4, 35.8, 33.6, 29.8; ν_{max} 3310, 2973, 2933, 2775, 1639, 1533, 1494, 1266; **MS** (ESI) *m*/*z* 213.1 (100%, $[M+2H]^{2+}$), (425.3, (98%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 425.2910, $C_{24}H_{37}N_4O_2^+$ ($[M+H]^+$) requires 425.2911.

(2*S*,2′*S*)-*N*,*N*′-(butane-1,4-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7c**.

Method A: Dimethyl-L-phenylalanine (500 mg, 2.59 mmol), 1,4-diaminobutane (114 mg, 1.29 mmol), CDI (503 mg, 3.10 mmol) gave **7c** (189 mg, 33%) as a white solid. **Rf** 0.26 (10% MeOH in $CHCl_3$); **Mp**. 123 °C; $[\alpha]_D^{20}$ +10.0 (c = 1.0, $CHCl_3$); δ_H 7.18–7.20 (8H, m, 8 × CH), 7.07–7.13 (2H, m, 2 × CH), 6.80 (2H, br t, *J* 6.0 Hz, 2 × NH), 3.18 (2H, dd, *J* 5.4, 7.5 Hz, 2 × CH), 3.02–3.13 (6H, m, 2 × CH, 2 × CH_2), 2.81 (2H, dd, *J* 5.4, 13.5 Hz, 2 × CH), 2.25 (12H, s, 4 × Me), 1.23–1.30 (4H, m, 2 × CH_2); δ_C 172.1, 139.9, 129.4, 128.4, 126.2, 71.0, 42.3, 38.8, 33.0, 27.0; ν_{max} 3310, 2933, 2865, 2827, 2775, 1642, 1535, 1494, 1248; **MS** (ESI) *m*/*z* 220.1 (4%, $[M+2H]^{2+}$), 439.3, (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 439.3065, $C_{24}H_{39}N_4O_2^+$ ($[M+H]^+$) requires 439.3068.

(2*S*,2′*S*)-*N*,*N*′-(pentane-1,5-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7d**.

Method A: Dimethyl-L-phenylalanine (500 mg, 2.58 mmol), 1,5-diaminopentane (132 mg, 1.29 mmol), CDI (502 mg, 3.10 mmol) gave **7d** (191 mg, 33%) as a white solid. **Rf** 0.23 (10% MeOH in $CHCl_3$); **Mp.** 76 °C; $[\alpha]_D^{20}$ +16.0 (c = 0.96, $CHCl_3$,); δ_H 7.16–7.19 (8H, m, 8 × CH), 7.08–7.13 (2H, m, 2 × CH), 6.75 (2H, br t, *J* 6.1 Hz, 2 × NH), 3.05–3.19 (8H, m 4 × CH, 2 × CH_2), 2.81 (2H, dd, *J* 13.4, 5.3 Hz, 2H, 2 × CH); 2.24 (12H, s, 4 × Me), 1.28–1.36 (4H, m, 2 × CH_2), 1.07–1.14 (2H, m, CH_2); δ_C 172.0, 139.9, 129.3, 128.4, 126.2, 71.0, 42.3, 38.9, 33.0, 29.3, 24.2; ν_{max} 3310, 2940, 1640, 1536, 1454, 1254; **MS** (ESI) *m*/*z* 227.1 (4%, $[M+2H]^{2+}$), 445.3, (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 453.3221, $C_{27}H_{41}N_4O_2^+$ ($[M+H]^+$) requires 453.3224.

(2*S*,2′*S*)-*N*,*N*′-(hexane-1,6-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7e**.

Method A: Dimethyl-L-phenylalanine (496 mg, 1.29 mmol), 1,6-diaminopropane (150 mg, 1.94 mmol), CDI (502 mg, 3.10 mmol) gave **7b** (193 mg, 31%) as a white solid. **Rf** 0.25 (10% MeOH in $CHCl_3$); **Mp**. 98 °C; $[\alpha]_D^{20}$ +12 (c = 1.1, $CHCl_3$); δ_H 7.15–7.23 (8H, m, 8 × CH), 7.06–7.13 (2H, m, 2 × CH), 6.74 (2H, br t, *J* 5.2 Hz, 2 × NH), 3.02–3.18 (8H, m, 4 × CH_2), 2.81 (2H, dd, *J* 13.1, 5.0 Hz, 2 × CH), 2.24 (12H, s, 4 × Me), 1.25–1.35 (4H, m, 2 × CH_2), 1.07–1.21 (4H, m. 2 × CH_2); δ_C 172.1, 140.1, 129.4, 128.4, 126.2, 71.1, 42.4, 39.0, 33.0, 29.5, 26.4; ν_{max} 3306, 2932, 2774, 1643, 1536, 1454, 1249. **MS** (ESI) 467.3, (100%, $[M+H]^+$). **HRMS** (ESI) *m*/*z* found 467.3378, $C_{28}H_{42}N_4O_2^+$ ($[M+H]^+$) requires 467.3381.

Method B, preparation of **7a**, **7b**, **7f**, and **10**.

General method: (i) CDI (2.2 equiv.) was added in portions over 5 min to a stirred solution of Z-Phe-OH (2.0 equiv.) dissolved in CH_2Cl_2 (150 mL). After 10 min, the required

amine (1.0 equiv.) was added dropwise as a liquid or dissolved in a small volume of CH_2Cl_2. After 24 h, diethyl ether (100 mL) was added to the solidified mass, which was then filtered through a sinter and the solid washed with 1:1 dichloromethane:diethyl ether until the product was free of imidazole. Drying the product under vacuum gave the required intermediates in 94%, 89%, and 72% yields, respectively. In the case of the intermediate for **10**, the product did not precipitate, and thus the reaction was washed with citric acid solution (aq. 10%, 4 × 50 mL), sodium bicarbonate (aq. sat., 2 × 50 mL), and brine (3 × 50 mL), dried ($MgSO_4$) to give the required product in 96% yield. Data for the first two bis-Cbz-protected intermediates was in full agreement with the literature [32]. **(ii)** The bis-Cbz-protected intermediate (1 equiv.) was suspended in methanol (100 mL per gram), and formaldehyde solution (aq. 37%, 13 equiv.) and Pd/C (10% *w*/*w*, 0.50 g per g of starting material) were added. The mixture was vigorously stirred under a hydrogen atmosphere for 5–14 days. The reaction mixture was filtered through celite, which was washed with methanol and evaporated. The mass obtained was co-evaporated with water (3 × 25 mL) to remove excess formaldehyde, then co-evaporated with toluene (2 × 25 mL) to remove water. The residue was dissolved in chloroform, dried ($MgSO_4$), filtered, and evaporated to give the crude products. The products **7a**, **7b**, **7f**, and **10** were purified by column chromatography (0–20% MeOH/$CHCl_3$) and were obtained as solids in 30%, 13%, and 76% yield, respectively. Data for **7a** and **7b** were identical to that reported above.

(2*S*,2′*S*)-*N*,*N*′-(heptane-1,7-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **7f**.

Method B: **(i)** Cbz-L-phenylalanine (2.50 g, 8.35 mmol), 1,7-diaminopropane (530 mg, 4.07 mmol), and CDI (1.50 g, 9.25 mmol) gave dibenzyl ((2*S*,2′*S*)-(heptane-1,7-diylbis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate (intermediate) (2.05 g, 2.90 mmol, 72%) as a white solid. **Mp**. 195–8 °C; $[\alpha]_D^{20}$ +17.1 (c 4.1, DMSO); δ_H (d_6-DMSO) 7.95 (2H, br t, *J* 5.8 Hz, 2 × NH), 7.48 (2H, br d, *J* 8.7 Hz, 2 × NH), 7.05–7.35 (20H, m, 4 × Ph), 4.89–4.97 (4H, m, 2 × CH_2), 4.16–4.22 (2H, m, 2 × CH), 2.97–3.11 (4H, m, 2 × CH_2), 2.93 (2H, dd, *J* 13.7, 4.9 Hz, 2 × CH), 2.75 (2H, dd, *J* 13.7, 10.0 Hz, 2 × CH), 1.16–1.50 (10H, m. 5 × CH_2); δ_C (d_6-DMSO) 171.1, 155.8, 138.1, 137.1, 129.2, 128.3, 128.0, 127.7, 127.5, 126.2, 65.2, 56.3, 38.5, 37.8, 29.0, 28.5, 26.3; ν_{max} 3299, 3062, 3031, 2936, 2854, 1692, 1648, 1532, 1286, 1258, 1239; **MS** (ESI) *m*/*z* (693.4 (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 693.3660, $C_{41}H_{49}N_4O_6^+$ ($[M+H]^+$) requires 693.3647. **(ii)** The above Cbz-protected intermediate (1.00 g, 1.44 mmol) and formaldehyde (aq. 37%, 1.51 mL, 18.7 mmol) on hydrogenation (Pd/C 10% *w*/*w*, 0.50 g) for 5 days gave **7f** (0.53 g, 1.10 mmol) in 76% yield as a white solid. **Rf** 0.25 (10% MeOH in $CHCl_3$); **Mp**. 93–5 °C; $[\alpha]_D^{20}$ +7.2 (c = 1.0, $CHCl_3$); δ_H 7.17–7.41 (10H, m, 2 × Ph), 6.91 (2H, br s, 2 × NH), 3.35–3.44 (2H, m, 2 × CH), 3.14–3.26 (6H, m, 2 × CH, 2 × CH_2), 2.95 (2H, dd, *J* 13.7, 4.7 Hz, 2 × CH), 2.40 (12H, s, 4 × Me), 1.37–1.44 (4H, m, 2 × CH_2), 1.18–1.31 (6H, m. 3 × CH_2); δ_C 171.5, 139.6, 129.4, 128.5, 126.3, 70.8, 42.2, 39.2, 33.1, 29.5, 28.8, 26.8; ν_{max} 3268, 3086, 3028, 2928, 2858, 2826, 2772, 1641, 1557, 1250; **MS** (ESI) 241.2 (100%, $[M+2H]^{2+}$), 481.4, (4%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 241.1808, $C_{28}H_{46}N_4O_2^{2+}$ ($[M+2H]^{2+}$) requires 241.1805, *m*/*z* found 481.3540, $C_{28}H_{45}N_4O_2^+$ ($[M+H]^+$) requires 481.3537.

(2*S*,2′*S*)-*N*,*N*′-(2,2-dimethylpropane-1,3-diyl)bis(2-(dimethylamino)-3-phenylpropanamide) **10**.

Method B (i) Cbz-L-phenylalanine (3.69 g, 12.33 mmol), 1,3-diamino-2,2-dimethylpropane **9** (0.60 g, 5.87 mmol), CDI (2.19 g, 13.51 mmol) gave dibenzyl ((2*S*,2′*S*)-((2,2-dimethylpropane-1,3-diyl)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate (3.76 g, 5.66 mmol) in 96% yield as a white solid. **Mp.** 91–94 °C; $[\alpha]_D^{20}$ -7.3 (c = 4.0, $CHCl_3$); δ_H 7.04–7.26 (20H, m, 4 × Ph), 7.00 (2H, br s, 2 × NH), 5.51 (2H, br d, *J* 8.0 Hz, 2 × NH), 4.90–5.02 (4H, m, 2 × CH_2), 4.30–4.47 (2H, m, 2 × CH), 2.79–3.13 (4H, m, 2 × CH_2), 2.54–2.93 (2H, m, 2 × CH_2) 0.55 (6H, s, 2 × CH_3); δ_C 172.0, 156.1, 136.5, 136.2, 129.4, 128.8, 128.6, 128.3, 128.1, 127.1, 67.1, 56.5, 46.1, 34.8, 36.3, 23.5; ν_{max} 3308, 3063, 3031, 2958, 1701, 1654, 1526, 1497, 1234, 1027, 738, 695; **MS** (ESI) *m*/*z* (665.3 (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 665.3336, $C_{39}H_{45}N_4O_6^+$ ($[M+H]^+$) requires 665.3334. **(ii)** The above Cbz-protected intermediate (1.59 g, 2.39 mmol) and formaldehyde solution (aq. 37%, 2.6 mL, 35.0 mmol) on hydrogenation (Pd/C 10% *w*/*w*, 0.50 g) for 5 days gave **10** (0.688 g, 1.48 mmol) in 63%

yield as a white solid. **Mp.** 81–84 °C; $[\alpha]_D^{20}$ +22.5 (c = 4.2, $CHCl_3$); δ_H 7.07–7.23 (12H, m, 2 × Ph, 2 × NH), 3.22 (2H, dd, *J* 8.1, 5.5 Hz 2 × CH), 3.08 (2H, dd, *J* 13.7, 8.1 Hz 2 × CH), 2.86 (2H, dd, *J* 13.7, 5.5 Hz 2 × CH), 2.62–2.72 (4H, m, 2 × CH_2), 2.30 (12H, s, 4 × Me), 0.58 (6H, m. 2 × Me); δ_C 172.0, 139.2, 129.3, 128.4, 126.2, 71.0, 45.6, 42.3, 36.0, 34.1, 23.6; υ_{max} 3304, 3063, 3030, 2959, 1700, 1653, 1526, 1235, 739, 695; **MS** (ESI) 227.2 (100%, $[M+2H]^{2+}$); **HRMS** (ESI) *m*/*z* found 227.1648, $C_{27}H_{42}N_4O_2^{2+}$ ($[M+H]^{2+}$) requires 227.1648.

Method C: preparation of 7b. (i) Dibenzyl ((2*S*,2′*S*)-(propane-1,3-diylbis(azanediyl))-bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate [32] (8.12 g, 12.75 mmol, prepared as in Method B, part (i)) was added in portions to HBr in AcOH (35% 100 mL, excess) and the mixture stirred for 4 h. Diethyl ether (100 mL) was added and the supernatant liquid decanted from the precipitated solid. This solid was dissolved in water (100 mL) which was extracted with diethyl ether (3 × 50 mL) then basified (NaOH to pH 12) and then further extracted with chloroform (3 × 100 mL). The combined chloroform extracts were dried ($MgSO_4$), filtered and evaporated to give (2*S*,2′*S*)-N,N′-(propane-1,3-diyl)bis(2-amino-3-phenylpropanamide) [32] as a white solid (4.14 g, 11.24 mmol). **(ii)** This product was dissolved in methanol (50 mL), formaldehyde solution (aq. 37%, 12.1 mL, 0.15 mol) and Pd/C (10% *w*/*w*, 1.0 g) were added, and the mixture stirred under a hydrogen atmosphere for 5 days. The mixture was filtered through a celite© pad which was washed with MeOH, and the filtrate evaporated under reduced pressure. After co-evaporation with water (3 × 50 mL) and toluene (2 × 50 mL) the solid residue was dissolved in chloroform, dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in chloroform (100 mL) and extracted with hydrochloric acid (aq. 2N, 40 mL) and the aqueous phase separated and extracted with chloroform (2 × 50 mL) then basified with NaOH (aq. 2M to pH 14) and extracted with chloroform (3 × 50 mL). These extracts were dried and evaporated to give **7b** (4.34 g, 10.22 mmol) in 80% yield as a white solid which gave identical data to that reported above.

Method D: Preparation of 10. (i) CDI (2.55 g, 15.8 mmol) was added to a stirred solution of Boc-L-phenylalanine (3.82 g, 14.39 mmol) in CH_2Cl_2 (50 mL). After 10 min, 1,3-diamino-2,2-dimethylpropane **9** (0.70 g, 6.85 mmol) was added and the mixture stirred for 48 h. The reaction was filtered, and the filtrate washed with citric acid solution (aq. 10%, 4 × 50 mL), sodium bicarbonate (aq. sat., 2 × 50 mL) and brine (3 × 50 mL), dried ($MgSO_4$), filtered and evaporated to give **20** (2.98 g, 4.99 mmol) in 72% yield as a white solid. **Mp.** 78–82 °C; $[\alpha]_D^{20}$ -9.6 (c = 4.0, $CHCl_3$); δ_H 7.09–7.24 (10H, m, 4 × Ph), 6.75–6.93 (2H, m, 2 × NH), 5.08 (2H, br d, *J* 7.7 Hz, 2 × NH), 4.26–4.31 (2H, m, 2 × CH), 2.93–3.03 (4H, m, 2 × CH_2), 2.60–2.77 (4H, m, 2 × CH_2) 1.34 (18H, s, 6 × CH_3), 0.62 (6H, s, 2 × CH_3); δ_C 172.2, 155.6, 136.8, 129.4, 128.7, 127.0, 80.2, 56.2, 46.0, 38.4, 36.4, 36.4, 28.4, 23.6; υ_{max} 3305, 3062, 2974, 2930, 1654, 1524, 1496, 1247, 1164, 698; **MS** (ESI) *m*/*z* (579.4 (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 597.3648, $C_{33}H_{49}N_4O_6^+$ ($[M+H]^+$) requires 597.3647. **(ii)** Compound **20** (1.00 g, 1.67 mmol) was dissolved in dichloromethane (10 mL), cooled (0 °C) and trifluoroacetic acid (5 mL) was added. After stirring overnight, the mixture was evaporated and dissolved in water (15 mL) following which excess NaOH (aq. 2M) was added, and the mixture extracted with chloroform (3 × 50 mL). The combined organic extract were dried ($MgSO_4$), filtered and evaporated to give the diamine which was used in the next step without further purification. **(iii)** The diamine was dissolved in methanol (5 mL per gram) and formaldehyde solution (aq. 37%, 2.50 mL, 33.6 mmol, 13.0 equiv.) and RaneyNi (10% *w*/*w*, 0.25 g) were added. The mixture was vigorously stirred under a hydrogen atmosphere for 5 days and the reaction mixture was filtered through celite under a blanket of nitrogen (**CAUTION** RaneyNi is prone to ignition in oxygen) which was washed with further methanol. The filtrate was evaporated, and the residue obtained was co-evaporated with water (3 × 25 mL) to remove excess formaldehyde then co-evaporated with toluene (2 × 25 mL) to remove water. The residue was redissolved in chloroform, dried ($MgSO_4$), filtered and evaporated to give **10** (0.55 g, 1.22 mmol) in 73% yield as a gum. Data for **10** was identical to that reported above.

(2*S*,2′*S*)-N,N′-(ethane-1,2-diyl)bis(1-methylpyrrolidine-2-carboxamide) **11a**.

(2*S*,2′*S*)-*N*,*N*′-(Ethane-1,2-diyl)bis(pyrrolidine-2-carboxamide) [29] (0.87 g, 3.42 mmol (Prepared by coupling Cbz-L-Pro-OH and ethylene diamine (Method C i), 88%) then HBr/AcOH deprotection (Method D **(i)**, 65%)), formaldehyde solution (aq. 37%, 3.28 mL, 44.0 mmol, 13.0 equiv.) and RaneyNi (10% *w*/*w*, 0.25 g) in methanol (5 mL) using **Method D (iii)** over 7 days (as reported above for **10**) gave **11a** (0.63 g, 2.23 mmol) in 65% yield as a white solid. **Mp.** 154–155 °C; **Rf** 0.23 (10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ −120.4 (c = 4, $CHCl_3$); δ_H 7.60 (2H, br s, 2 × NH), 3.29–3.46 (4H, m, 2 × CH_2), 3.04–3.12 (2H, m, 2 × CH), 2.88 (2H, dd, *J* 5.2, 10.2 Hz, 2 × CH), 2.33 (6H, s, 2 × Me), 2.30–2.37 (2H, m, 2 × CH), 2.12–2.24 (2H, m, 2 × CH), 1.63–1.84 (6H, m, 2 × CH, 2 × CH_2); δ_C 175.2, 68.9, 56.7, 41.8, 38.8, 31.1, 24.3; ν_{max} 3275, 2964, 2938, 2872, 3840, 2782, 2763, 1658, 1510, 1457, 1427, 1226, 1048, 745; **MS** (ESI) 283.2, (10%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 283.2126, $C_{14}H_{27}N_4O_2^+$ ($[M+H]^+$) requires 283.2129.

(2*S*,2′*S*)-*N*,*N*′-(propane-1,2-diyl)bis(1-methylpyrrolidine-2-carboxamide) **11b**.

(2*S*,2′*S*)-*N*,*N*′-(propane-1,3-diyl)bis(pyrrolidine-2-carboxamide) [28] (Prepared by coupling Cbz-Pro-OH and propane-1,3-diamine (Method C (i), 77%) then HBr/AcOH deprotection (Method D (i), 83%). data for dibenzyl 2,2′-((propane-1,3-diylbis- (azanediyl))bis(carbonyl))(2S,2′S)-bis(pyrrolidine-1-carboxylate; gum, $[\alpha]_D^{20}$ −24 (c = 4.0 $CHCl_3$); δ_H (d_6-DMSO) 7.83–8.02 (2H, m, 2 × NH), 7.19–7.42 (10H, m, 2 × Ph), 4.94–5.13 (4H, m, 2 × CH_2), 4.06–4.21 (2H, m, 2 × CH), 3.28–3.55 (4H, m, 2 × CH_2), 2.88–3.12 (4H, m, 2 × CH_2), 1.91–1.99 (2H, m, 2 × CH), 1.68–1.91 (6H, m, 2 × CH, 2 × CH_2), 1.37–1.56 (2H, m. CH_2); δ_C (d_6-DMSO) 172.1/172.0/171.8/171.8, 145.1/153.9, 137.0, 128.4/128.3/128.2, 127.8/127.6/127.6/127.5, 127.1/127.0, 65.9/65.8/65.2, 60.3/59.7, 47.1/46.5, 36.1/36.0/36.0/35.8, 31.3/30.2, 29.2, 23.9/23.1; ν_{max} 3292, 3065, 2952, 2879, 1692, 1655, 1532, 1411, 1354, 1239, 1209, 1175, 1118, 1090, 917, 728, 696; **MS** (ESI) *m*/*z* 537.3 (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 537.2708, $C_{29}H_{37}N_4O_6^+$ ($[M+H]^+$) requires 537.2708.), 0.63 g, 2.35 mmol), formaldehyde solution (aq. 37%, 2.45 mL, 32.6 mmol, 13.9 equiv.) and RaneyNi (10% *w*/*w*, 0.25 g) in methanol (4 mL) using Method D **(iii)** gave **11b** (0.41 g, 1.38 mmol) in 59% yield as a white solid. **Mp.** 99–102 °C; **Rf** 0.29 (10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ −132.0 (c = 4, $CHCl_3$); δ_H 7.57 (2H, br s, 2 × NH), 3.17–3.31 (4H, m, 2 × CH_2), 3.03–3.15 (2H, m, 2 × CH), 2.88 (2H, dd, *J* 4.8, 9.9 Hz, 2 × CH), 2.35 (6H, s, 2 × Me), 2.28–2.41 (2H, m, 2 × CH), 2.13–2.25 (2H, m, 2 × CH), 1.61–1.86 (8H, m, 2 × CH, 3 × CH_2); δ_C 174.8, 69.0, 56.7, 41.8, 35.7, 31.1, 30.1, 24.2; ν_{max} 3290, 2956, 2940, 2926, 2878, 2744, 1651, 1523, 1457, 1152, 774: **MS** (ESI) 227.2, (10%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 297.2283, $C_{15}H_{29}N_4O_2^+$ ($[M+H]^+$) requires 297.2285.

(2*S*,2′*S*)-*N*,*N*′-(2,2-dimethylpropane-1,3-diyl)bis(1-methylpyrrolidine-2-carboxamide) **12**.

(i) Cbz-L-proline (2.28 g, 9.15 mmol, 2.10 equiv.), diamine **9** (0.44 g, 4.31 mmol, 1.0 equiv.) and CDI (1.92 g, 11.84 mmol, 2.6 equiv.) gave dibenzyl 2,2′-(((2,2-dimethylpropane-1,3-diyl)bis(azanediyl)) bis(carbonyl))(2S,2′S)-bis(pyrrolidine-1-carboxylate) (2.44 g, 4.32 mmol) in 95% yield as a gum using Method B, part **(i)**. $[\alpha]_D^{20}$ -51 (c = 3.0, $CHCl_3$); δ_H (mixture of rotamers) 8.08/8.13/8.24/8.39/8.52 (2H, br s, NH), 7.04–7.58 (11H, m, 2 × Ph, NH), 4.90–5.19 (4H, m, 2 × CH_2), 4.29–4.38 (2H, m, 2 × CH), 3.39–3.76 (4H, m, 2 × CH_2), 2.61–3.10 (4H, m, 2 × CH_2) 1.86–2.25 (8H, m, 4 × CH_2), 0.61/0.69/0.80/0.88 (6H, br s, 2 × Me); δ_C 172.6/173.0, 154.9/155.6, 149.3, 148.5, 136.3/136.5, 136.2/137.1, 133.7/133.9, 127.7/127.8/128.0/128.4/128.5/128.7/128.8/129.2/130.0/130.5, 119.7, 117.2, 116.0, 69.9, 67.1, 60.8/61.0, 45.2/45.9/46.6/46.9/47.4, 36.6, 31.4, 29.1/29.4, 24.5/24.7, 23.4/23.6. ν_{max} 3292, 3056, 2952, 2880, 1692, 1655, 1411, 1354, 1090, 728, 696; **MS** (ESI) 565.3, (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 565.3020, $C_{31}H_{41}N_4O_6^+$ ($[M+H]^+$) requires 565.3021. **(ii)** The above compound (2.33 g, 4.13 mmol) was deprotected with HBr/AcOH as in method C part **(ii)** to give (2*S*,2′*S*)-*N*,*N*′-(2,2-dimethylpropane-1,3-diyl)bis(pyrrolidine-2-carboxamide) (1.00 g, 3.38 mmol) in 82% yield as a gum which was used in the next step without further purification. $[\alpha]_D^{20}$ -73.8 (c 2.75, $CHCl_3$); δ_H (d_6-DMSO) 8.13 (2H, t, *J* 6.8 Hz, 2 × NH), 3.52 (2H, dd, *J* 5.3, 8.6 2 × CH), 3.33 (2H, br s, 2 × NH obscured), 2.65–2.95 (8H, m, 4 × CH_2), 1.83–2.04 (2H, m, 2 × CH) 1.55–1.74 (6H, m, 2 × CH, 2 × CH_2), 0.74 (6H, s, 2 × Me); δ_C 174.8, 60.3, 46.7, 45.0, 36.5, 30.7, 25.8, 23.2; ν_{max} 3359, 3281, 2959, 2870, 1639, 1523; **MS** (ESI) 149.1, (100%, $[M+H]^{2+}$); 297.2, (5%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 297.2282, $C_{15}H_{29}N_4O_2^+$

([M+H]$^+$) requires 297.2285. **(ii)** The above compound (0.88 g, 2.97 mmol), formaldehyde solution (aq. 37%, 4.7 mL, 63.0 mmol, 21.0 equiv.) and RaneyNi (10% *w*/*w*, 0.25 g) in methanol (5 mL) using Method D **(iii)** (as reported above for **10**) gave crude material which was purified by column chromatography (0–2% MeOH in chloroform) gave **12** (0.38 g, 1.14 mmol) in 38% yield as a gum. **Rf** 0.38 (10% MeOH in $CHCl_3$); $[\alpha]_D^{20}$ -24 (c = 4, $CHCl_3$); δ_H 7.78 (2H, t, *J* 7.1 Hz, 2 × NH), 3.10–3.15 (2H, m, 2 × CH), 3.00 (2H, dd, *J* 6.9, 13.7 Hz, 2 × CH), 2.96 (2H, dd, *J* 6.9, 13.7 Hz, 2 × CH), 2.88 (2H, dd, *J* 5.2, 10.2 Hz, 2 × CH), 2.37 (6H, s, 2 × Me), 2.29–2.35 (2H, m, 2 × CH), 2.13–2.24 (2H, m, 2 × CH), 1.71–1.83 (6H, m, 2 × CH, 2 × CH_2) 0.85 (6H, s, 2 × CH_3); δ_C 175.1, 69.1, 56.7, 45.4, 41.8, 36.8, 31.3, 24.3, 23.6; υ_{max} 3360, 3283, 2959, 2870, 2845, 2785, 1648, 1518, 1451, 1198, 1179, 979; **MS** (ESI) 163.1 (100%, $[M+2H]^{2+}$); 325.3, (15%, $[M+H]^+$); **HRMS** *m*/*z* found 163.1334, $C_{17}H_{32}N_4O_2^{2+}$ ($[M+2H]^{2+}$) requires 163.1335; (ESI) *m*/*z* found 325.2596, $C_{17}H_{32}N_4O_2^+$ ($[M+H]^+$) requires 325.2598.

10.2. Preparation of **19a–f** *and* **17a,b**

Compounds **18a–f**, **20**, **22a,b** and **24** were prepared using Method D (i). In the case of **18a–f** the compounds were isolated by filtration and trituration with diethyl ether. Compounds **18a–e** [27–29] and **22a,b** [28,29] gave data in accordance with the literature.

Di-*tert*-butyl ((2*S*,2′*S*)-(heptane-1,7-diylbis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate **18f**.

Mp. 132–135 °C; $[\alpha]_D^{20}$ +15 (c = 4.0, $CHCl_3$); δ_H (d_6-DMSO, mixture of rotamers) 7.82/7.81–7.90 (2H, br m,/t, *J* 5.2 Hz, 2 × NH), 7.15–7.27 (10H, m, 2 × Ph) 6.43/6.85 (2H, d/d, *J* 7.5/8.7 Hz, 2 × NH), 3.95–4.05/4.08–4.13 (2H, m/m 2 × CH), 2.95–3.10 (4H, m, 2 × CH_2), 2.89 (2H, dd, *J* 4.6, 13.0 Hz, 2 × CH) 2.72/2.61–2.77 (2H, dd/m, *J* 10.2, 13.0 Hz, 2 × CH), 1.30 (18H, s, 2 × *t*Bu), 1.10–1.42 (10 H, m, 5 × CH_2); δ_C 171.3, 155.2, 138.2, 129.2, 128.0, 126.2, 77.9/78.1, 55.8/57.3, 38.3/38.5, 37.8, 29.0, 28.5, 28.2/27.9, 26.3; υ_{max} 3342, 3319, 2964, 2924, 2852, 1683, 1654, 1252, 1171; **MS** (ESI) 623.4, (100%, $[M+H]^+$); **HRMS** (ESI) *m*/*z* found 625.3960, $C_{35}H_{53}N_4O_6^+$ ($[M+H]^+$) requires 625.3960.

10.3. Preparation of **19a–f**, **21**, **23a,b** *and* **25**

Compounds **19a–f, 21** and **23a,b** were prepared by dissolving the corresponding Boc-protected precursor **18a–f**, [25–27] **20** or **22a,b** [28,29] (0.17 mmol) in chloroform (3 mL) which was cooled (0°C) and trifluoroacetic acid (1–1.5 mL) was added. After stirring at rt for 3 h the reaction was evaporated to dryness and the product dried under vacuum for 24 h. Compound **25** was prepared from diamine **24** (50 mg, 0.17 mmol) by dissolving in chloroform (3 mL) which was cooled (0°C) and trifluoroacetic acid (1 mL) added, then evaporated to dryness under vacuum for 24 h. The catalysts were used directly in the aldol reaction without further purification.

(2*S*,2′*S*)-1,1′-(ethane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **19a**.

White solid, **Mp.** 155–159 °C; $[\alpha]_D^{20}$ +36.1 (c 6.1, MeOH); δ_H (d_6-DMSO) 8.61 (2H, br s 2 × NH), 8.31 (6H, br s, 6 × NH), 7.03–7.51 (10H, m, 2 × Ph), 3.86–4.01 (2H, m, 2 × CH), 2.84–3.11 (8H, m, 4 × CH_2); δ_C 168.1, 158.7 (C, q, $^2J_{CF}$ 33.6 Hz) 135.1, 129.5, 128.6, 127.2, 116.6 (C, q, J_{CF} 296.5 Hz), 53.8, 38.0, 37.0; υ_{max} 3321, 3112, 2981, 2867, 2823, 1743, 1671, 1552, 1496, 1058, 655; **MS** (ESI) 178.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 178.1100, $C_{20}H_{28}N_4O_2^{2+}$ ($[M]^{2+}$) requires 178.1101.

(2*S*,2′*S*)-1,1′-(propane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **19b**.

Gum; $[\alpha]_D^{20}$ +19.3 (c 10.3, MeOH); δ_H (d_6-DMSO, mixture of rotamers) 8.40 (2H, t, *J* 5.7 Hz, 2 × NH), 8.03/8.31 (6H, br s, 6 × NH), 7.19–7.32 (10H, m, 2 × Ph), 3.86–4.03 (2H, m, 2 × CH), 2.73–3.07 (8H, m, 4 × CH_2), 1.35/1.86 (2H, 2 × pentet, *J* 7.6/6.7 Hz CH_2); δ_C 167.8, 158.7 (C, q, $^2J_{CF}$ 33.6 Hz) 135.1, 129.5, 128.6, 127.2, 116.5 (C, q, J_{CF} 296.6 Hz), 53.7, 37.2, 36.3/36.4, 25.3/28.3; υ_{max} 3095, 2980, 2873, 1764, 1664, 1499, 1140, 629; **MS** (ESI) 185.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 185.1179, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 185.1179.

(2*S*,2′*S*)-1,1′-(butane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **19c**.

Gum; $[\alpha]_D^{20}$ +46.5 (c 4.0, MeOH); δ_H (d_6-DMSO) 8.40 (2H, t, *J* 5.7 Hz, 2 × NH), 8.31 (6H, br s, 6 × NH), 7.19–7.35 (10H, m, 2 × Ph), 3.89–4.03 (2H, m, 2 × CH), 2.81–3.14 (8H, m, 4 × CH_2), 1.05–1.26 (4H, m, 2 × CH_2); δ_C 167.8, 158.7 (C, q, $^2J_{CF}$ 34.7 Hz) 135.2, 129.6, 128.6, 127.2, 116.4 (C, q, J_{CF} 294.0 Hz), 53.7, 38.3, 37.3, 26.0; ν_{max} 2941, 1776, 1663, 1137, 700; **MS** (ESI) 192.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 192.1256, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 192.1257.

(2*S*,2′*S*)-1,1′-(pentane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) - bistrifluoroacetate salt **19d**.

Gum; $[\alpha]_D^{20}$ +54.2 (c 4.0, MeOH); δ_H (d_6-DMSO) 8.40 (2H, t, *J* 5.5 Hz, 2 × NH), 8.27 (6H, br s, 6 × NH), 7.19–7.34 (10H, m, 2 × Ph), 3.86–3.98 (2H, m, 2 × CH), 2.93–3.12 (4H, m, 2 × CH, 2 × CH_2), 2.81–2.92 (2H, m, 2 × CH), 1.12–1.26 (4H, m, 2 × CH_2), 0.90–1.01 (2H, m, CH_2); δ_C 167.5, 158.5 (C, q, $^2J_{CF}$ 35.1 Hz) 135.0, 129.5, 128.5, 127.2, 116.2 (C, q, J_{CF} 293.4 Hz), 53.6, 38.5, 37.2, 28.4, 23.5; ν_{max} 2945, 1763, 1664, 1147, 700; **MS** (ESI) 199.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 199.1335, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 199.1335.

(2*S*,2′*S*)-1,1′-(hexane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **19e**.

Gum; $[\alpha]_D^{20}$ +39.0 (c 4.0, MeOH); δ_H (d_6-DMSO) 8.34 (2H, t, *J* 5.5 Hz, 2 × NH), 8.28 (6H, br s, 6 × NH), 7.20–7.33 (10H, m, 2 × Ph), 3.87–4.00 (2H, m, 2 × CH), 3.04–3.14 (2H, m, 2 × CH), 2.99 (4H, d, *J* 6.3 Hz, 2 × CH_2), 2.86–2.96 (2H, m, 2 × CH), 1.12–1.32 (4H, m, 2 × CH_2), 0.96–1.12 (4H, m, 2 × CH_2); δ_C 167.9, 158.8 (C, q, $^2J_{CF}$ 35.0 Hz) 139.8, 129.9, 128.9, 127.6, 117.1 (C, q, J_{CF} 296.8 Hz), 54.0, 39.1, 37.6, 29.1, 26.4; ν_{max} 2940, 1763, 1663, 1146, 699; **MS** (ESI) 206.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 206.1415, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 206.1414.

(2*S*,2′*S*)-1,1′-(heptane-1,2-diylbis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **19f**.

Gum; $[\alpha]_D^{20}$ +42.9 (c 4.0, MeOH); δ_H (d_6-DMSO) 8.34 (2H, t, *J* 5.6 Hz, 2 × NH), 8.29 (6H, br s, 6 × NH), 7.20–7.33 (10H, m, 2 × Ph), 3.88–4.00 (2H, m, 2 × CH), 3.06–3.15 (2H, m, 2 × CH), 3.00 (4H, d, *J* 6.9 Hz, 2 × CH_2), 2.86–2.96 (2H, m, 2 × CH), 1.18–1.35 (4H, m, 2 × CH_2), 1.02–1.17 (6H, m, 3 × CH_2); δ_C 167.6, 158.6 (C, q, $^2J_{CF}$ 35.8 Hz) 135.1, 129.5, 128.5, 127.2, 116.1 (C, q, J_{CF} 296.0 Hz), 53.6, 38.7, 37.2, 37.6, 28.7, 28.5, 26.3; ν_{max} 2938, 2863, 1776, 1662, 1141, 700; **MS** (ESI) 213.2, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 213.1492, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 213.1492.

(2*S*,2′*S*)-1,1′-((2,2-Dimethylpropane-1,3-diyl)bis(azanediyl))bis(1-oxo-3-phenylpropan-2-aminium) bistrifluoroacetate salt **21**.

Gum; $[\alpha]_D^{20}$ +45.8 (c 4.0, MeOH); δ_H (d_6-DMSO) 8.21 (6H, s 6 × NH), 8.22 (2H, t, *J* 5.4 Hz, 2 × NH), 7.20–7.42 (10H, m, 2 × Ph), 3.99–4.15 (2H, m, 2 × CH), 3.01 (4H, d, *J* 7.3 Hz, 2 × CH_2), 2.85 (2H, dd, *J* 6.7, 13.5 Hz, 2 × CH), 2.85 (2H, dd, *J* 5.7, 13.5 Hz, 2 × CH), 0.56 (6H, s, 2 × Me); δ_C 168.5, 158.8 (C, q, $^2J_{CF}$ 35.7 Hz), 135.1, 129.6, 128.8, 127.4, 116.1 (C, d, J_{CF} 269.6 Hz), 53.8, 46.7, 37.4, 36.2, 25.9; ν_{max} 2968, 1764, 1666, 1145, 699; **MS** (ESI) 199.1, (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 199.1334, $C_{23}H_{36}N_4O_2^{2+}$ ($[M]^{2+}$) requires 199.1335.

(2*S*,2′*S*)-2,2′-((ethane-1,2-diylbis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) bistrifluoroacetate salt **23a**.

Gum; $[\alpha]_D^{20}$ −22.8 (c 4.0, MeOH); δ_H (d_6-DMSO) 9.81 (2H, br s, 2 × NH), 8.68–8.78 (2H, m, 2 × NH), 8.53 (2H, br s, 2 × NH), 4.09–4.19 (2H, m, 2 × CH), 3.12–3.30 (8H, m, 2 × CH_2), 2.18–2.30 (2H, m, 2 × CH), 1.80–1.92 (6H, m, 2 × CH, 2 × CH_2); δ_C 168.4, 158.8 (C, q, $^2J_{CF}$ 34.7 Hz), 116.8 (C, d, J_{CF} 295.1 Hz), 59.1, 45.7, 38.5, 29.5, 23.6; ν_{max} 3290, 3085, 2992, 2958, 1665, 1572, 1169, 1131, 835, 796, 720, 678; **MS** (ESI) 128.1 (100%, $[M]^{2+}$); **HRMS** (ESI) *m*/*z* found 128.0942, $C_{12}H_{24}N_4O_2^{2+}$ ($[M]^{2+}$) requires 128.0944.

(2*S*,2′*S*)-2,2′-((ethane-1,2-diylbis(azanediyl))bis(carbonyl))bis(pyrrolidin-1-ium) bistrifluoroacetate salt **23b**.

Gum; $[\alpha]_D^{20}$ −36.7 (c 4.0, MeOH); δ_H (d_6-DMSO) 9.63–9.96 (2H, br m, 2 × NH), 8.63 (2H, t, *J* 5.6 Hz, 2 × NH), 8.44–8.59 (2H, br m, 2 × NH), 4.08–4.27 (2H, m, 2 × CH), 3.06–3.33

(8H, m, 4 × CH_2), 2.18–2.39 (2H, m, 2 × CH), 1.75–1.97 (6H, m, 2 × CH, 2 × CH_2), 1.53–1.70 (2H, m, CH_2); δ_C 168.2, 159.0 (C, q, $^2J_{CF}$ 35.4 Hz), 116.5 (C, q, J_{CF} 292.8 Hz), 59.2, 45.7, 36.7, 29.8, 28.7, 23.7; ν_{max} 3290, 3092, 2967, 1779, 1665, 1567, 1168, 1132, 835, 797, 721, 704; **MS** (ESI) 135.1 (100%, $[M]^{2+}$); **HRMS** (ESI) m/z found 135.1021, $C_{13}H_{26}N_4O_2^{2+}$ ($[M]^{2+}$) requires 135.1022.

Di-tert-butyl ((2*S*, 2′*S*, 3*R*, 3′*R*)-(ethane-1,2-diylbis(azanediyl))bis(3-hydroxy-1-oxobutane-1,2-diyl))dicarbamate **25**.

EDC.HCl (887 mg, 4.63 mmol, 2.30 equiv.), HOBt.H_2O (840 mg, 6.50 mmol, 3.23 equiv.), DIPEA (0.79 mL, 585 mg, 4.52 mmol, 2.25 equiv.) and DMAP (50 mg, 0.41 mmol, 0.20 equiv.) were added sequentially to a cooled (0 °C) solution of L-Boc-Thr **24** (908 mg, 4.14 mmol, 2.06 equiv.) in dry DMF (40 mL) After 1 h, ethylene diamine **8a** (n = 0, 121 mg, 0.134 mL, 2.01 mmol, 1.00 equiv.) was added and the resulting mixture was stirred to rt for 48 h. The mixture was diluted with EtOAc (150 mL), washed with $NaHCO_3$ solution (aq., sat. 2 × 50 mL) and brine (2 × 100 mL), then dried ($MgSO_4$) and evaporated under reduced pressure. Column chromatography of the crude product (0–2% MeOH in CH_2Cl_2) gave **25** (645 mg, 1.39 mmol) in 69% yield as a white solid. $[\alpha]_D^{20}$ +14.5 (c 4.0, $CHCl_3$); **Mp.** 82–85 °C; δ_H 7.19–7.36 (2H, br m, 2 × NH), 5.72–5.94 (2H, br m, 2 × NH), 4.28–5.39 (2H, br m, 2 × CH), 4.18 (2H, br s, 2 × OH) 4.04 (2H, br d, *J* 6.0 Hz, 2 × CH), 3.44–3.61 (2H, br m, 2 × CH), 3.19–3.26 (2H, br m, 2 × CH), 1.43 (18H, s, 6 × Me), 1.17 (6H, d, *J* 6.0 Hz, 2 × Me); δ_C 172.9, 156.5, 80.5, 67.2, 59.8, 39.8, 28.4, 19.3; ν_{max} 3326, 2978, 2935, 1688, 1649, 1497, 1366, 1248, 1161, 910, 729; **MS** (ESI) 463.3 (100%, $[M+H]^+$); **HRMS** (ESI) m/z found 463.2753, $C_{20}H_{38}N_4O_8^+$ ($[M+H]^+$) 463.2762.

(2*S*, 2′*S*, 3*R*, 3′*R*)-1,1′-(ethane-1,2-diylbis(azanediyl))bis(3-hydroxy-1-oxobutan-2-aminium) bistrifluoroacetate **26**.

Compound **25** (105 mg, 0.228 mmol) was dissolved in chloroform (4 mL), cooled (0 °C) and trifluoroacetic acid (2 mL) was added. After stirring to rt over 24 h the reaction was evaporated to dryness and the product dried under vacuum for 24 h to give **26** (109 mg) as a gum. This was used directly in the aldol reaction without further purification. $[\alpha]_D^{20}$ +3.6 (c 2.7, MeOH); δ_H 8.63–8.70 (2H, br m, 2 × NH), 8.01–8.22 (4H, br m, 2 × NH_2), 6.73–8.34 (2H, br s, 2 × OH), 3.85–3.93 (2H, m, 2 × CH), 3.42–3.54 (2H, m, 2 × CH), 3.08–3.31 (4H, m, 2 × CH_2), 1.12 (6H, d, *J* 6.3 Hz); δ_C 167.2, 158.6 (C, q, $^2J_{CF}$ 35.8 Hz), 116.3 (C, q, J_{CF} 296.0 Hz), 65.7, 58.5, 38.2, 20.0; ν_{max} 3254, 3087, 2983, 1662, 1534, 1169, 1181, 1130, 839, 799, 722; **MS** (ESI) 132.1 (100%, $[M]^{2+}$), 263.2 (25%, $[M-H]^+$); **HRMS** (ESI) m/z found 103.0892, $C_{21}H_{30}N_4O_2^{2+}$ ($[M]^{2+}$) requires 103.0893; m/z found 263.1712, $C_{21}H_{30}N_4O_2^{2+}$ ($[M-H]^+$) requires 263.1714.

10.4. General Method for the Reaction of 2-Hydroxy-1,4-napthoquinone **1** *with β-Nitrostyrene* **2**

2-Hydroxy-1,4-napthoquinone **1** (100 mg, 0.574 mmol) and the required catalyst (0.1 equiv.) were dissolved in the requisite solvent (10 mL) and cooled (−20 °C). *β*-Nitrostyrene **2** (128.5 mg, 0.861 mmol, 1.5 equiv.) was then added and the mixture stirred for the required time and temperature. On completion the solvent was evaporated to give a deep red residue which was purified by column chromatography (2–4% EtOAc in petroleum ether to remove excess **2** then CH_2Cl_2) to give **3** as a yellow solid. Enantiomeric excesses were determined on a CHIRALPAK IA column (250 × 4.6 mm) with 90% hexane with 0.1% TFA, 8% ethanol and 2% dichloromethane as the mobile phase detecting at 254 nm. For a 44% ee sample, S enantiomer 18.1 min, R enantiomer 24.2 min, $[\alpha]_D^{22}$ −12.1 (acetone, c 1.52; lit. $[\alpha]_D^{17}$ −44.8 (acetone, c 1.0) [33], lit. $[\alpha]_D^{25}$ −34 (acetone, c 1.0) [34].

10.5. General Method for the Aldol Reaction between 4-Nitrobenzaldehyde **15** *and Hydroxyacetone* **16**

The catalyst (0.2 equiv) was dissolved in the required solvent, *p*-nitrobenzaldehyde **15** (1 equiv.) was added and once dissolved hydroxyacetone **16** (10–20 equiv.). The solution was stirred for the required time, diluted with water (250 mL) and the mixture extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried with magnesium sulphide, filtered and evaporated. Analysis by ^{1}H NMR gave the conversion and

syn:anti ratio (see SI). Purification by column chromatography (eluting with 10% EtOAc in petroleum ether to remove unreacted **15** was followed by 40–60% EtOAc in petroleum ether) combination of the fractions containing **17** was followed by HPLC analysis to determine ee (see SI). Selected data for the syn-**17** diol δ_H = 5.20 (1H, d, *J* 2.7 Hz) and 5.20 (1H, d, *J* 2.7 Hz) ppm and the anti-**17** diol, δ_H = 5.03 (1H, d, *J* 4.6 Hz) and 4.41 (1H, d, *J* 4.6 Hz) ppm. HPLC data:[20] Diacel chiralpak AD (250 × 4.6 mm), hexane/i-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm: t_R = 18.4 min (Major anti enantiomer, (3S,4S)), t_R = 21.3 min (Minor anti enantiomer, (3R,4R)), t_R = 26.7 min (Minor syn enantiomer (3S,4R)) and t_R = 37.8 min (Major syn enantiomer, (3R,4S)). Phonemenex Lux® 3 µm Amylose-1 column (150 × 4.6 mm), hexane/i-PrOH = 90:10, flow rate 1 mL/min, λ = 209 nm: t_R = 14.7 min (Major anti enantiomer, (3S,4S)), t_R = 16.0 min (Minor anti enantiomer, (3R,4R)), t_R = 19.4 min (Minor syn enantiomer (3S,4R)) and t_R = 22.9 min (Major syn enantiomer, (3R,4S)).

11. Crystallography

A single colourless needle-shaped crystal of **11a** with dimensions 0.340 × 0.025 × 0.020 mm^3 was mounted on a Rigaku 007HF diffractometer with HF Varimax confocal mirrors, a UG2 goniometer and HyPix 6000HE detector. The crystal was kept at a steady *T* = 100(2) K during data collection. Table 3 contains the basic crystallographic data. CCDC2211459 contains supplementary X-ray crystallographic data for **11a**. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/structures/ (accessed on 15 August 2024), or from the Cambridge Crystallographic Data Centre, Union Road, Cambridge, CB2 1EZ; fax (+44) 1223-336-033 or email: deposit@ccdc.cam.ac.uk.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/reactions5030027/s1. HPLC data for Michael adduct **3**, HPLC data for Aldols **17**, Catalysed reactions of acetylacetone or 1,3-diphenyl-1,3-propanedione with *β*-Nitrostyrene **2** and NMR spectra for all new compounds.

Author Contributions: Conceptualization, P.J.M.; methodology, Z.S.A.-T., D.F., L.G., P.K., P.J.M., N.B.W., O.T.W.; formal analysis, Z.S.A.-T., S.J.C., A.C., P.N.H., L.F.J., R.K., P.J.M., G.J.T., O.T.W.; investigation, Z.S.A.-T., D.F., L.G., P.K., P.J.M., N.B.W., O.T.W., resources, S.J.C., A.C., P.N.H., R.K., P.J.M., G.J.T.; writing—original draft preparation, P.J.M.; writing—review and editing, Z.S.A.-T., S.J.C., D.F., L.G., P.N.H., L.F.J., P.K., P.J.M., N.B.W., O.T.W.; supervision, P.J.M.; project administration, P.J.M.; funding acquisition, P.J.M. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded in part by the Iraqi government (Z.S.A.-T.) and supported by the Centre for Environmental Biotechnology Project part-funded by the European Regional Development Fund (ERDF; RK) through the Welsh Government. Support was given by the EPSRC via the EPSRC National Crystallography Service.

Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Acknowledgments: The authors would like to thank the Iraqi government (Z.S.A.-T.) and acknowledge the support of the Centre for Environmental Biotechnology Project part-funded by the European Regional Development Fund (ERDF; RK) through the Welsh Government. We also thank the EPSRC National Crystallography Service at the University of Southampton.

Conflicts of Interest: The authors declare no conflict of interest.

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