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N-carbamate protected amino acid derived guanidine organocatalysts

Zahraa S. Al-Taie [a, b], Joseph M. Anderson [b], Laura Bischoff [b], Jeppe Christensen [c, d], Simon J. Coles [d], Richard Froom [b], Mari E. Gibbard [b], Leigh F. Jones [e], Frank F.J. de Kleijne [b], Patrick J. Murphy [b, *], Emma C. Thompson [b]

[a] Department of Chemistry, College of Science, Al-Nahrain University, Baghdad, Iraq
[b] School of Natural Sciences (Chemistry), Bangor University, Gwynedd, LL57 2UW, UK
[c] Diamond Light Source, Didcot, OX12 0DE, UK
[d] EPSRC National Crystallography Service, School of Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK
[e] School of Biological, Physical and Forensic Sciences, University of Wolverhampton, Wolverhampton, WV1 1LY, UK

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ABSTRACT

We report the preparation of a range of *N*-protected amino acid derived guanidine organocatalysts and their application to the Michael addition of 2-hydroxy-1,4-napthoquinone to β-nitrostyrene, achieving a maximum ee of 26%. Whilst these catalysts gave poor ees, the structural variation together with the X-ray crystallographic study of the intra- and intermolecular hydrogen bonding reported suggest that the C_2-symmetric catalysts are lead compounds for the further development of this methodology.

1. Introduction

We recently reported [1] the preparation of a range of amino acid derived guanidines which were shown to have some potential as asymmetric organocatalysts however several problems were apparent from the work. This 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. The best of these catalysts **1** was found to catalyse the formation of the Michael adduct **4** in 56% ee and 49% yield from the addition of 2-hydroxy-1,4-napthoquinone **2** to β-nitrostyrene **3** (Scheme 1).

A major problem observed with this reaction were related to the integrity of the catalyst **1** which was formed from the CDI mediated coupling of *N*–Me-L-proline with *N*-Cbz-guanidine in DMF. It was found that during the coupling the intermediate imidazole amide was prone to racemisation in the presence of even weakly basic guanidine reactants or the internal *N*-methyl functionality. In order to alleviate this problem and to investigate the role of the guanidine in the catalytic process we considered removing the internal amine base. We visualized a group of potential catalyst structures **5a,b** and **6a,b** derived from L-proline and **7a-h** and **8a-d** derived from L-alanine or L-phenylalanine. In these catalysts the nitrogen is protected by a Boc or Cbz-protecting group as this will suppress racemisation [2]. One problem that might arise is a lowering of the basicity of the catalyst system which will lead to slower rates of conversion of the base catalysed reaction (Fig. 1).

2. Preparation of catalysts

The required *N*-protected amino acids and guanidines were available commercially or were prepared by literature methods [3,4]. Catalysts **5a,b** were prepared (Scheme 2) by activating the required *N*-Cbz- **9a** or *N*-Boc-L-proline **9b** with CDI in dry DMF at 0 °C, followed by the addition of either *N*-Cbz-guanidine **10a** or *N*-Boc-guanidine **10b** stirring for 24 h (Table 1, entries 1 and 2). Work up and chromatography gave the desired compounds, **5a** and **5b,** in 40 and 67% yield respectively. The C_2-symmetric catalyst **6b** was prepared by similarly activating 2.0 equiv. of **9b** and adding this solution via cannula to a DMF solution of guanidine, generated from guanidinium chloride and sodium hydride (Table 1 entry 4). Work

* Corresponding author. School of Natural Sciences (Chemistry), Bangor University, Bangor, Gwynedd, LL57 2UW, UK.
E-mail address: chs027@bangor.ac.uk (P.J. Murphy).

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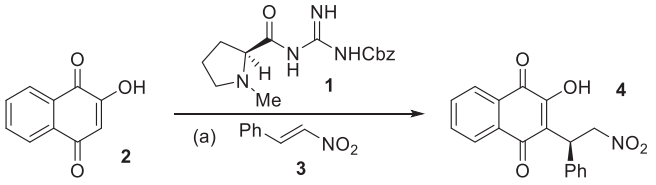


Scheme 1. Catalytic Michael addition leading to 4: Catalyst (0.1 equiv.), −78 °C, 5 h then −20 °C 48h. 49%, 56% ee.

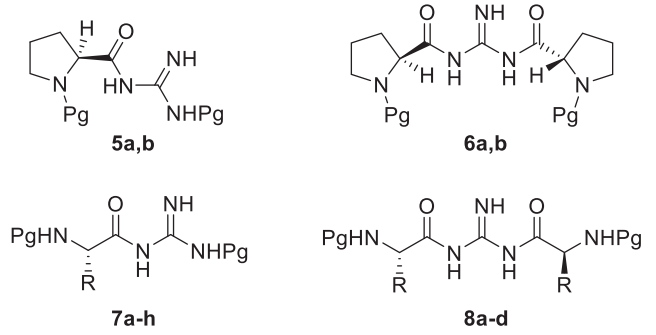
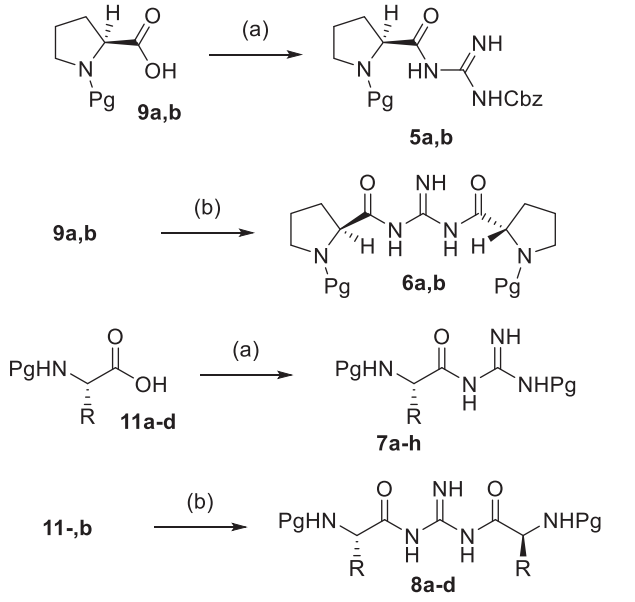


Fig. 1. Proposed catalysts; PG = Boc, Cbz; R = Me, Bn.



Scheme 2. Preparation of catlysts **5**–**8** (a) Method: i) **9a** (Pg = Cbz), **9b** (Pg = Boc), **11a** (Pg = Boc, R = Me), **11b** (Pg = Cbz, R = Me), **11c** (Pg = Boc, R = Bn) or **11d** (Pg = Cbz, R = Bn), CDI, DMF. ii) *N*-Cbz-guanidine **10a**, or *N*-Boc-guanidine **10b** (1.0 equiv.), rt, 24–72 h. (b) Method B: i) **9a** (Pg = Cbz) or **9b** (Pg = Boc), CDI, DMF; ii) Guanidine·HCl (0.5 equiv., NaH, DMF; iii) Combine and stir, 24–72 h, rt.

up and chromatography gave the **6b** in 97% yield. We attempted the preparation of the corresponding Cbz-catalst **6a** from **9a** using this method unfortunately despite numerous attempts we were unable to prepare this as the catalyst was inseparable from reaction by-products due to its high polarity (Table 1, entry 3). Catalysts **7a-d** (R = Me) and **7e-h** (R = Bn) were prepared from either *N*-Boc-L-alanine **11a**, *N*-Cbz-L-alanine **11b**, *N*-Boc-L-phenylalanine **11c** or *N*-Cbz-L-phenylalanine **11c** in 19–84% yield, however heating to 40 °C

Table 1
Preparation of catalysts **5**–**8**.

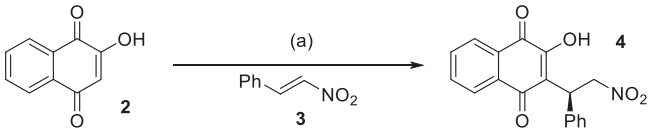
Entry	Catalyst	Yield	Method - SM	R	N-Pg	G-Pg
1	**5a**	67	A - **9a**	–	Cbz	Cbz
2	**5b**	40	A - **9b**	–	Boc	Cbz
3	**6a**	0	B - **9a**	–	Cbz	–
4	**6b**	97	B - **9b**	–	Boc	–
5	**7a**	63	A - **11a**	Me	Boc	Boc
6	**7b**	71	A - **11a**	Me	Boc	Cbz
7	**7c**	49	A - **11b**	Me	Cbz	Boc
8	**7d**	75	A - **11b**	Me	Cbz	Cbz
9	**7e**	44	A - **11c**	Bn	Boc	Boc
10	**7f**	72	A - **11c**	Bn	Boc	Cbz
11	**7g**	84	A - **11d**	Bn	Cbz	Boc
12	**7h**	19	A - **11d**	Bn	Cbz	Cbz
13	**8a**	65	A - **11a**	Me	Boc	–
14	**8b**	55	A - **11b**	Me	Cbz	–
15	**8c**	80	A - **11c**	Bn	Boc	–
16	**8d**	49	A - **11d**	Bn	Cbz	–

(i) See Scheme 1. (ii) N-Pg = amino acid protection G-Pg = guanidine protection.

for 48 h was required to effect reaction in the case of **7a** and **7h**. (Table 1, entry 5–12). The catalysts **8a,b** (R = Me) and **8c,d** (R = Bn) were similarly prepared in 49–80% yield after work-up and purification (Table 1, entries 13–16).

3. Catalytic studies

Initially the *N*-proline derived catalysts **5a**, **5b** and **6** catalysts were applied to the Michael reaction to give adduct **4**. (Scheme 3, Table 2, entries 1–3). The first unsurprising observation is that the yields for these catalytic reactions were all low and the reaction times relatively long which must arise from the low basicity of these catalysts. The *N*-Boc-proline catalyst **5b** gave very poor ee's (1–5%) over the range of four solvents studied, whilst the *N*-Cbz-proline catalyst **5a** gave generally better ees (8–18%) but slower reactions. The C_2-symmetric catalyst **6b** gave better ees (12–22%) and benzene and toluene appeared to be the best solvents (both gave 22% ee). The L-alanine and L-phenylalanine derived catalysts **7a-h** were then investigated and again the reactions using these catalysts (entries 4–11) were slow, requiring several days to reach a reasonable yield. Where the reactions were relatively quick and higher yielding (2–8 days; entries 4, 10 and 11) the ee's were very poor. The best ees were observed with **7b** (entry 5) and **7c** (entry 6), which gave 16% and 14% ee in toluene respectively, but the reactions were very slow and yields poor. The C_2-symmetric catalysts **8a-d**, were next utilised in the Michael reaction to form **4** (entries 12–17). The *N*-Boc-L-alanine catalyst **8a** effected the reaction in a high yield over 9 days (entry 12) however the ee observed for either solvents was poor. The corresponding *N*-Boc-L-phenylalanine catalyst **8c** was however completely inactive in this reaction (entry 15) which we initially thought might be a consequence of high steric hindrance. Repeating the reaction using benzoic acid as a co-catalyst (entry 16) led to slow conversion to the product but the ees in both solvents were low. Surprisingly the assumed less sterically hindered *N*-Cbz-L-alanine catalyst **8b** was also completely inactive in this reaction (entry 13). This might suggest that steric factors are not the primary consideration in these reactions and that intramolecular H-bonding plays a significant role. Similarly repeating the reaction using benzoic acid as a co-catalyst (entry 14) led to slow conversion to the product but the ees in both solvents were again low. Finaly the *N*-Cbz-L-phenylalanine catalyst **8d** was



Scheme 3. Catalytic studies: Conditions: See Table 2, Catalyst (0.1 equiv.), 0 °C 7–8 h then rt.

Table 2
Catalytic studies.[a]

Entry	Cat.	CH_2Cl_2	PhMe	Xylene	PhH
1	**5a**	18 (5/55)	13 (5/31)	8 (5/32)	8 (2/30)
2	**5b**	5 (1/38)	4 (1/22)	1 (3/30)	4 (1/25)
3	**6b**	**18** (1/38)	**22** (48/30)	12 (23/41)	**22** (48/25)
4	**7a**	2 (6/49)	2 (7/81)		
5	**7b**	6 (18/47)	**14** (12/11)		
6	**7c**	12 (10/37)	**16** (11/37)		
7	**7d**	6 (10/51)	**10** (10/24)		
8	**7e**	5 (9/67)	0 (9/84)		
9	**7f**	6 (17/68)	**12** (11/18)		
10	**7g**	3 (8/74)	2 (8/73)		
11	**7h**	5 (3/84)	0 (2/56)		
12	**8a**	3 (9/85)	3 (9/70)		
13	**8b**	NR	NR		
14	**8b**[b]	10 (24/95)	6 (11/70)		
15	**8c**	NR	NR		
16	**8c**[b]	5 (24/48)	8 (9/32)		
17	**8d**	**26** (22/22)	**15** (12/46)		

[a] Results are given as ee (time (d)/yield (%)).
[b] Benzoic acid (0.1 equiv.) was added.

studied (entry 17) and this was found to be the best of these catalysts leading to a slow conversion to the product in poor yield but with better ees in dichloromethane (26%) and toluene (15%).

3.1. X-ray and NMR

Analysis of the NMR data for the catalysts in all cases gave evidence of the presence of a rotamers in solution. In particular the catalysts with a Boc-carbamate protecting group gave evidence of multiple species in solution with multiple signals present. We attempted to crystallisation all of the catalysts from a variety of solvents and in the majority of cases only amorphous solids were obtained. Only compound **7b** and **7f** gave crystals suitable for X-ray analysis. Pleasingly neither of these appeared to be racemised in the crystal form which supports our premise of using *N*-protected amino acids. Catalyst **7b**, crystallises in the $P2_1$ space group and comprises two complete molecules within the asymmetric unit. Each dimer is bound through a strong and highly directional intermolecular H-bond between an amide proton and a nearby carbonyl O-donor atom (N4(HN4)···O9 = 1.95 Å), as well as a number of aliphatic C–H···O interactions (e.g. C34(H34A)···O2 = 2.88 Å, C16(H16A)···O6 = 2.87 Å and C12(H12A)···O8 = 2.69 Å) (Fig. S1 in appendix 1). Catalyst **7b** is derived from L-alanine, which has a *E*-amide arrangement with the carbonyl of the amide having a *E*-bc type H-bonding type [1] (bond b; N2(HN2B)···O3 = 1.98 Å and bond c; N3(HN3)···O2 = 1.97 Å). Additionally an H-bond was observed between the guanidine NH and the Boc-protecting group (bond f; N3(HN3)···O4 = 3.04 Å) and possibly a weaker H-bond between the Boc-protecting group NH and the Cbz-protecting group carbonyl (bond g; N4(HN4)···O2 = 3.40 Å). This is an *E*-amide-bcf(g) pattern (Fig. 2).

Organocatalyst **7f** crystallises in the P1 space group and akin to **7b**, its asymmetric unit comprises two complete organocatalyst moieties (Fig. S3). In both molecules, extensive intramolecular H-bonds (e.g. N2(HN2A)···O2 = 1.97 Å, N4(HN4)···O5 = 2.27 Å and N6(HN6B)···O8 = 2.13 Å) and C–H···π interactions (e.g. $[C18–C23]_{centroid}$···(H16C)C16 = 4.10 Å and $[C41–C46]_{centroid}$···(H38B)C36 = 4.20 Å) are observed (Fig. 4). On close examination of the structure of compound **7f**, it again possessed an *E*-amide arrangement but with the amide N–H not involved in any intramolecular H-bonds to the carbamate protecting group of the guanidine. Instead there was a long distance interaction between the Boc-carbonyl and the amide N–H (bond f; N3(HN3)···O4 = 3.49 Å) was observed. The guanidine NH_2 had two

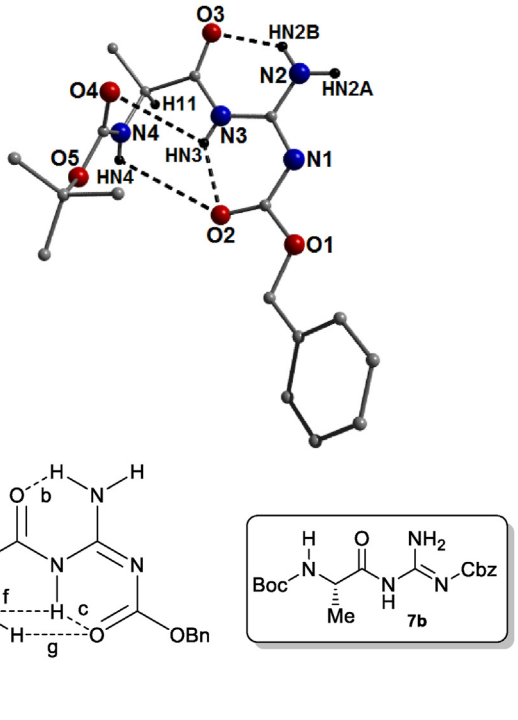


Fig. 2. The X-ray crystal structure and corresponding ChemDraw representations of **7b**. The dashed lines represent intramolecular H-bonding at distances: (b) N2(HN2B)···O3 = 1.98 Å; (c)N3(HN3)···O2 = 1.97 Å along with the long-contacts (f) N3(HN3)···O4 = 3.04 Å and (g) N4(HN4)···O2 = 3.40 Å. The stereogenic proton has been labelled (H11).

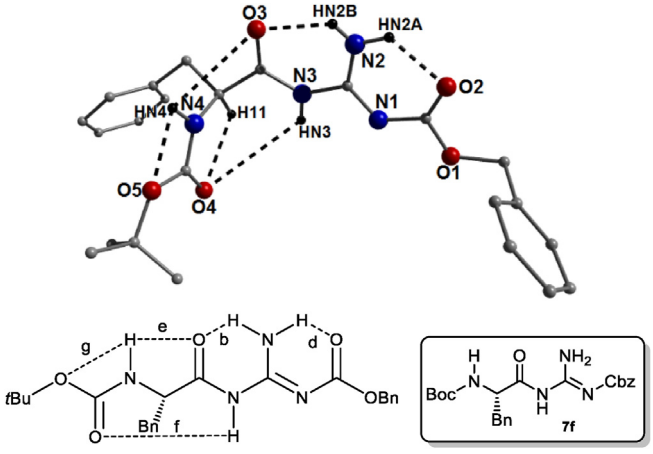


Fig. 3. The X-ray crystal structure and ChemDraw representations of **7f**. The dashes lines represent the H-bonds: (d) N2(HN2A)··· O2 = 1.97 Å; (b) N2(HN2B)···O3 = 2.17 Å; (e) N4(HN4)···O3 = 3.12 Å; (f) N3(HN3)···O4 = 3.49 Å (long contact); (g) N4(HN4)···O5 = 2.27 Å and C11(H11)···O4 = 2.42 Å. The chiral proton has been labelled (H11).

H-bonds of the *E*-bd type (bond b; N2(HN2B)···O3 = 2.17 Å and bond d; N2(HN2A)···O2 = 1.97 Å) and a H-bond between the NH of the Boc protecting group and the amide oxygen was also observed (bond e; N4(HN4)···O3 = 3.12 Å). Overall this is an *E*-amide-bde(f) pattern (Fig. 3).

As highlighted in Fig. 4, the crystallographically equivalent organocatalyst units in **7f** are connected via a number of intermolecular H-bonding interactions, resulting in planar sheets that propagate along the *a* unit cell direction (Scheme 4). In order to obtain packing efficiency, these individual H-bonded 2D sheets arrange in a parallel and interdigitated motif along the *b* unit cell direction and are held together by intermolecular C—H···π and C—H···O interactions at distance of 3.80 Å ($[C41—C46]_{centroid}$···H7B) C7) and 2.54 Å (C23(H23)···O7), respectively. This packing efficiency is best shown in Scheme 4, whereby each H-bonded sheet is represented in space-fill mode and using a different colour.

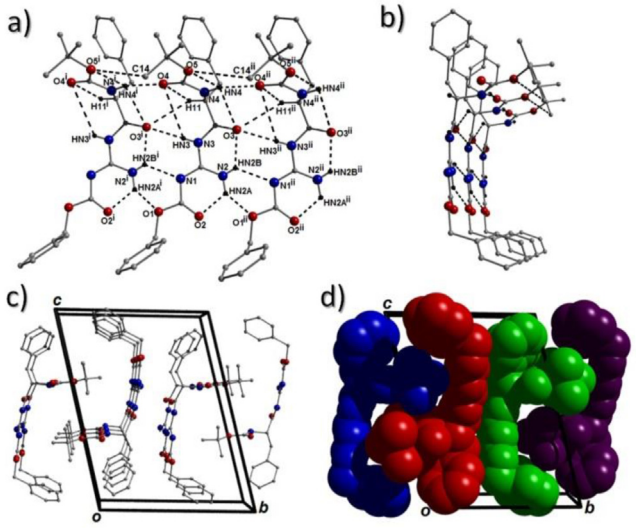
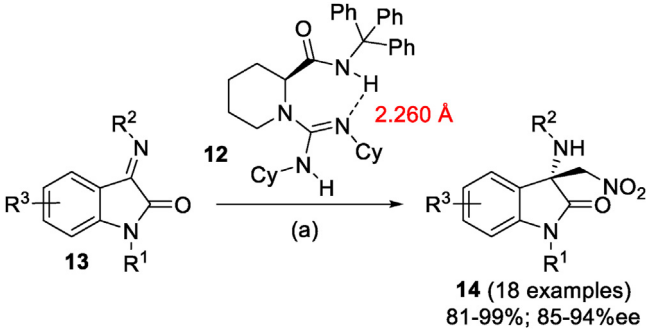


Fig. 4. A planar 2-D sheet comprising on individual **7f** units connected through numerous intermolecular hydrogen bonds (dashed lines) as viewed perpendicular (a) and parallel to the plane. Intermolecular H-bond distances: N2(HN2A)^{i}···O1 = 2.09 Å; N2(HN2B)^{ii}···N1 = 2.35 Å; N3(HN3)^{ii}···O3 = 2.37 Å; C11(H11)^{ii}···O3 = 2.93 Å; N4(HN4)^{ii}···O4 = 2.14 Å and C14(H14B)^{ii}···O5 = 3.02 Å. Symmetry code (i) = (−1+*x*, *y*, *z*); (ii) = (1+*x*, *y*, *z*). (c) Packing arrangement observed in **7f** as viewed along the *a* unit cell direction along with its space-fill represented version (d). Each colour represents an individual 2D hydrogen bonded sheet in **7f** (as shown in a).

Whilst X-ray conformations are not a measure of conformation in solution it was interesting to note that the two structures are structurally similar in that the carbamates are identical and the only differences are the amino acid R-group (Me versus Bn). The ^{1}H spectra of **7b** and **7f** in $CDCl_3$ displays a mixture of rotamers in both cases and the guanidine NH-protons are broadened. The corresponding ^{1}H spectra in DMSO-d_6 however gave separate and relatively sharp signals for each NH of the guanidines of **7b** (δ_H = 11.30/8.90/8.86 (3 × 1H, 3 x br s)) and **7f** (δ_H = 11.36/8.94/8.85 (3 × 1H, 3 x br s)). This might suggest the two catalysts which give reasonable ees in the catalytic reaction possess similar structures in solution.

4. Conclusions

The overall conclusion from the reactions of the *N*-protected amino acids is that these processes are typically slower than the corresponding *N*-alkyl catalysts and that there is no appreciable increase in ee's. There is strong apparent correlation between the different general types of the catalysts however, two of the better catalysts of this class were the C_2-symmetric examples **6** (18—22% ee over three solvents) and **8d** (15—26% ee over two solvents), which gave encouraging results. Unfortunately, we could not obtain suitable crystals of either of these catalysts to investigate H-bonding patterns present and no real rationale for the higher ee's observed with these catalysts can be offered. However steric factors do not seem to be paramount and this possibly points to intramolecular hydrogen bonding being a key to developing an effective system. In addition, the level of disorder of these compounds in solution is apparent from NMR studies and it has been reported that the presence of multiple catalytic structures in solution leads to lower ees in reactions of related guanidines [5]. Our overall goals in this research was to develop a catalyst which takes part in strong associative interactions with the reactants in this process and this study has focused on one reaction. The modifications made to the catalyst structures from our previous work [1] have not lead to any improvement in ee and it is apparent that the H-bonding patterns observed are not predictable. This might suggest that the ability of the guanidine to form multiple strong H-bonds is not a favorable one and our original goal [1] to employ a simplified range of base catalysts might be more advantageous [6]. Interestingly, Liu et al. reported [7] the use of chiral bi-functional guanidines **12** to catalyse the aza-Henry reactions of isatin derived ketimines **13** with nitromethane. The authors put forward a model where the strong intramolecular N—H bond (2.260 Å; Scheme 4) is broken by the deprotonation of nitromethane. When this intramolecular hydrogen bonding is removed by this chelation, the amide group is thought to act as a Brønsted acid to activate ketimine **13** eventually leading to the formation of the product **14** (Scheme 4). Obviously this report infers that changes in the H-bonding pattern are a consideration and targeting systems with weaker H-bonding interaction in the solid state might be a factor in the success of these reactions. We will report further findings in this area in due course.[†]



Scheme 4. (a) i) **12** (10 mol %), **13**, $MeNO_2$, PhMe, −30 °C, 72 h.R ^{1} = Me, Bn; R^2 = Boc, EtO_2C; R^3 = H, F, Cl, Br, I, Me, F_3CO, CF_3.

[†] Note added in proof. A publication [10] detailing the use of amino acylguanidines as bioinspired catalysts for the asymmetric aldol reaction, reports on a threonine derived amino acylguanidine organocatalyst. Catalysis of the asymmetric aldol addition of hydroxyacetone with this catalyst, afforded predominantly syn-diastereselectivity and high ee. MMFF modelling suggested the presence of extensive hydrogen bonding network between the acylguanidinium group and the reaction intermediates.

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 (*N*-Boc-L-proline **9a**, *N*-Boc-L-alanine **11a**, *N*-Cbz-L-alanine **11b**, *N*-Boc-L-phenylalanine **11c** and *N*-Cbz-L-phenylalanine **11d**) were purchased from commercial suppliers and used without further purification. Other starting materials (*N*-Cbz-L-proline **11b** [3], *N*-Cbz-guanidine **10a** [4] and *N*-Boc-guanidine **10b** [4]) were prepared according to literature procedures. Flash column chromatography was performed on Davisil® silica gel (35–70 μm) with the eluent specified in each case, TLC was conducted on precoated E. Merck silica gel 60 F_{254} glass plates. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer with an internal deuterium lock at ambient temperature at 400/100 MHz with internal references of δ_H 7.26 and δ_C 77.016 ppm for $CDCl_3$. Infrared spectra were recorded on a Bruker Tensor 37 FT-IR. Mass spectra were determined on a Q Exactive Plus (Thermo Scientific) instrument run with positive electrospray ionization (ESI). Melting points were determined on a Stuart SMP10 apparatus and are uncorrected. Optical rotations were measured in a 0.25 dm cell on an ADP440 polarimeter (Bellinghan & Stanley Ltd.).

Experimental

Crystallography

Data for **7b** and **7f** were collected at 100K on a Rigaku AFC11 quarter chi goniometer equipped with a Rigaku Hypix 6000 detector mounted at the window of 007 HF copper rotating anode generator with Varimax optics. Cell determination, Data collection, Data reduction and Absorption correction were performed with CrysAlisPro (Rigaku Oxford Diffraction, 2017, version 1.171.39.31c). Structures were solved using SHELXT [8] and refined with SHELXL-2014/7 within the Olex2 [9] software suite. Non-hydrogen atoms were refined anisotropically whilst hydrogen atoms were included isotropically in idealised positions based on the parent atom. Further data collection and refinement details can be found in Appendix 1 and full data, including structure factors, have been deposited with the Cambridge Crystallographic Data Centre (Deposition numbers CCDC2030901 and CCDC2030902 for **7b** and **7f** respectively).

General methods for the preparation of catalysts

Method A: The N-protected amino acid (1.0–1.6 equiv.) was dissolved in DMF (1–2.5 mL per mmol), CDI (1.2 equiv.) was added and the mixture stirred for 5 min to 24 h. After cooling (0 °C) the mixture, the required guanidine (1.0 equiv.) was added as a solid and the mixture stirred to rt over 16–168 h. After evaporation under reduced pressure (freeze dryer) or dilution with water and extracting with ethyl acetate. After drying ($MgSO_4$), filtering and evaporation under reduced pressure, the product was obtained and was purified by column chromatography (Et_2O/petroleum ether or EtOAc/petroleum ether), recrystallization or tritutation.

Method B: (C_2-catalysts): The N-alkyl-L-amino acid (1 equiv.) and CDI (1.20 equiv.) were added sequentially to dry DMF (0.5–2.5 mL per mmol) and the mixture stirred for 1–16 h. In a separate flask, NaH (0.60 equiv.) was suspended in dry DMF (1.0–2.0 mL per mmol) and dried (P_2O_5) guanidinium chloride (0.50 equiv.) was added. After stirring for 1 h the activated amino acid solution was transferred into this flask via cannula and the mixture stirred for 24–48 h. The mixture was diluted with water (100 mL) and EtOAc (100 mL), separated and the aqueous layer extracted with further EtOAc (2 × 100 mL) and the combined extracts washed with water (2 × 100 mL). After drying ($MgSO_4$), filtering and evaporation under reduced pressure the residue was co-evaporated with heptane to remove residual DMF and purified by silica gel chromatography (EtOAc in petroleum ether).

Benzyl (*S*)-2-((*N*-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-Carboxylate 5a.

Method A: *N*-Cbz-L-proline **9a** (1.51 g, 6.07 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (1.27 g, 7.83 mmol, 1.3 equiv.); 24 h; *N*-Cbz-guanidine **10a** (1.17 g, 6.07 mmol, 1.0 equiv.); 2 d, rt. Extraction with EtOAc; washed with water (3 × 150 mL) and brine (3 × 50 mL); column chromatography (0–30% EtOAc in petroleum ether) gave **5a** (1.73 g, 4.08 mmol) in 67% yield as a white solid. Rf 0.49 (EtOAc); Mp 47–49 °C; $[\alpha]_D^{20}$ -60.1 ($CHCl_3$, c = 2.0); δ_H ($CDCl_3$) (mixture of rotamers) 7.82–9.96 (3H, br s, 3 × NH), 7.16–7.45 (10H, m, 2 × Ph), 5.19 (1H, br d, *J* 11.7 Hz, CH), 5.14 (1H, d, *J* 12.5 Hz, CH), 5.10 (1H, d, *J* 12.4 Hz, CH), 5.02 (1H, br d, *J* 11.7 Hz, CH), 4.24–4.47 (1H, m, CH), 3.37–3.65 (2H, m, CH_2), 1.98–2.32 (2H, m, CH_2), 1.81–1.97 (2H, m, CH_2); δ_C ($CDCl_3$) (mixture of rotamers) 176.0, 162.7/162.1, 158.9/158.8, 155.6/154.4, 136.4/136.3/136.2 (2 × C), 128.5/128.1/128.1/128.0 (10 × CH), 67.6/67.4, 67.1, 61.7/61.4, 47.3/47.0, 31.2/29.6, 24.4/23.6; ν_{max} 3383, 3274, 3032, 2957, 2886, 1703, 1662, 1627, 1539, 1498, 1446, 1414, 1379, 1355, 1277, 1170, 1116, 1090, 1026, 989, 914, 806, 748 cm^{-1}; MS (ESI) *m/z* 425.2 (100%, $[M+H]^+$), HRMS (ESI) *m/z* found 425.1814, $C_{22}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 425.1819.

tert-Butyl (*S*)-2-((*N*-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-carboxylate 5b.

Method A: *N*-Boc-L-proline **9b** (1.52 g, 7.04 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (1.78 g, 10.1 mmol, 1.4 equiv.); 24 h; *N*-Cbz-guanidine **10a** (1.35 g, 6.97 mmol, 1.0 equiv.); 2 d, rt. Extraction with EtOAc; washed with water (150 mL × 3) and brine (50 mL × 2); column chromatography (0–20% EtOAc in petroleum ether) gave **5b** (1.10 g, 2.82 mmol) in 40% yield as a white solid. Rf 0.14 (30% EtOAc in hexane); Mp 64–66 °C; $[\alpha]_D^{20}$ -53.8 (c = 2.1, $CHCl_3$); δ_H ($CDCl_3$) (mixture of rotamers) 7.63–10.22 (3H, br. s, 3 × NH), 7.27–7.38 (5H, m, Ph), 5.11 (2H, s, CH_2), 4.11–4.46 (1H, m, CH), 3.28–3.62 (2H, m, CH_2), 1.94–2.30 (2H, m, CH_2), 1.76–1.94 (2H, m, CH_2), 1.44/1.40 (9H, 2 × s, 3 × CH_3); δ_C ($CDCl_3$) (mixture of rotamers) 175.9/176.7, 162.8, 158.8, 155.1/153.8, 136.5/136.3, 128.4, 128.0, 128.0, 80.9, 67.0, 61.8/61.4, 46.8/47.2, 31.3/29.7, 28.3, 24.5/23.8; ν_{max} 3380, 3275, 2976, 2883, 1697, 1661, 1628, 1541, 1497, 1477, 1446, 1392, 1367, 1279, 1161, 1120, 1090, 1045, 1026, 991, 927, 854, 806, 751, 698, 666 cm^{-1}; MS (ESI) *m/z* 391.2 (100%, $[M+H]^+$); HRMS (ESI) found 391.1980, $C_{19}H_{27}N_4O_5^+$ ($[M+H]^+$) requires 391.1976.

Di-tert-butyl 2,2'-(((iminomethylene)bis(azanediyl))bis(carbonyl))(2*S*,2'*S*)-bis(pyrrolidine-1-carboxylate) 6b.

Method B: *N*-Boc-L-proline **9b** (0.95 g, 4.40 mmol, 2.4 equiv.); DMF (10 mL); CDI (0.82 g, 5.13 mmol, 2.8 equiv.); 24 h; guanidinium hydrochloride (0.175 g, 1.83 mmol, 1.0 equiv.); DMF (10 mL); NaH (60%, 77.0 mg, 1.92 mmol, 1.05 equiv.); 2 d. Extraction with EtOAc; washed with water (3 × 100 mL) and brine (2 × 100 mL); column chromatography (75% Et_2O in hexane) gave **6b** (0.81 g, 1.78 mmol) as a white solid in 97% yield. Rf 0.28 (75% Et_2O in hexane); Mp 65–69 °C; $[\alpha]_D^{20}$ -77.1 ($CHCl_3$, c = 2.3); δ_H ($CDCl_3$) (mixture of rotamers) 9.11 (3H, br s, 3 × NH), 4.06–4.37 (2H, m, 2 × CH), 3.26–3.61 (4H, m, 2 × CH_2), 1.74–2.29 (8H, m, 4 × CH_2), 1.45/1.39/1.36 (18H, s, 6 × Me); δ_C ($CDCl_3$) (mixture of rotamers) 158.4/158.4, 155.2/155.1/154.2, 80.3/80.1, 62.9/62.1/62.0, 47.1/46.8, 31.2, 29.8/

29.7/29.6, 28.4/28.4, 24.4/23.7; ν_{max} 3366, 3231, 2976, 2932, 2879, 1692, 1643, 1520, 1477, 1451, 1392, 1365, 1249, 1158, 1122 cm^{-1}; MS (ESI) *m/z* 454.3 (100% $[M+H]^+$); HRMS (ESI) found 454.2654, $C_{21}H_{36}N_5O_6^+$ ($[M+H]^+$) requires 454.2660.

tert-Butyl (*S*)-(1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7a.

Method A: *N*-Boc-L-alanine **11a** (1.00 g, 5.29 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (0.94 g, 6.66 mmol, 1.26 equiv.); 30 min; *N*-Boc-guanidine **10b** (0.93 g, 5.95 mmol, 1.12 equiv.); DMF (15 mL); 3 d, rt; 2 d; 40 °C. Extraction with EtOAc (3 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (0–40% EtOAc in hexane) gave **7a** (1.10 g, 3.33 mmol) in 63% as a white solid. Rf 0.11 (25% EtOAc in hexane); $[\alpha]_D^{23}$ -24.0 ($CHCl_3$, c = 1.0); Mp 113 °C; δ_H ($CDCl_3$) (mixture of rotamers) 7.50–9.75 (3H, br s, 3 × NH), 5.56–5.81/5.21–5.48 (1H, 2 x br s, NH), 4.13–4.33/3.96–4.12 (1H, 2 × m, CH), 1.47 (9H, s, 3 × Me), 1.42 (9H, s, 3 × Me), 1.36 (3H, d, *J* 7.1 Hz, Me); δ_C ($CDCl_3$) (mixture of rotamers) 179.8, 164.2/158.9/156.6/155.2/152.0/149.7 (3 × C), 85.3/82.6, 79.9, 52.6, 28.5/28.2/28.1/28.0 (2 × *t*Bu), 19.3; ν_{max} 3382, 3282, 2978, 2934, 1712, 1643, 1539, 1496, 1447, 1148, 1047 cm^{-1}; MS (ESI) *m/z* 331.2 (100, $[M+H]^+$), HRMS (ESI) found 331.1973, $C_{14}H_{27}N_4O_5^+$ ($[M+H]^+$) requires 331.1976.

tert-Butyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7b.

Method A: *N*-Boc-L-alanine **11a** (1.00 g, 5.29 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (0.94 g, 6.66 mmol, 1.26 equiv.); 30 min; *N*-Cbz-guanidine **10a** (1.12 g, 5.81 mmol, 1.1 equiv.); DMF (15 mL); 3 d, rt. Extraction with EtOAc (3 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); Recrystallized from ethanol (ca. 15 mL) at −20 °C (2 days) to form white needles which were washed with ice-cold diethyl ether and dried under vacuum to give **7b** (1.37 g, 3.76 mmol) in 71% yield. Column chromatography (50% Et_2O in hexane) gave an analytical sample. Rf 0.11 (50% Et_2O in hexane); $[\alpha]_D^{25}$ -18.8 ($CHCl_3$, c = 1.15); Mp 138–140 °C; δ_H ($CDCl_3$) (mixture of rotamers) 7.77–10.41 (3H, br. s, 3 × NH), 7.24–7.37 (5H, m, Ph), 7.34/5.40 (1H, br s/d, *J* 5.8 Hz, NH), 5.09 (2H, s, CH_2), 4.24–4.39/3.86–3.99 (1H, 2 × br m, CH), 1.41 (9H, s, 3 × Me), 1.34/1/24 (3H, d/obscured d, *J* 6.5 Hz, Me); δ_C ($CDCl_3$) (mixture of rotamers) 177.9/176.7, 162.7/161.9, 159.2/159.1, 156.1/155.2, 136.1, 128.5, 128.2, 128.2, 81.5/80.3, 67.1, 52.7/51.7, 28.3, 18.3/17.2; ν_{max} 3383, 3282, 2978, 2928, 1695, 1629, 1542, 1498, 1436, 1165, 1069 cm^{-1}; MS (ESI) *m/z* 365.2 (100%, $[M+H]^+$); HRMS (ESI) found 365.1819, $C_{17}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 365.1820.

(*S*)-(1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7c.

Method A: *N*-Cbz-L-alanine **11b** (1.03 g, 4.48 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (0.91 g, 5.60 mmol, 1.25 equiv.); 90 min; *N*-Boc-guanidine **10b** (0.79 g, 4.93 mmol, 1.1 equiv.); 24 h, rt. Extraction with $CHCl_3$ (3 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (50% Et_2O in hexane) gave **7c** (1.37 g, 3.76 mmol) in 49% yield. Rf 0.13 (50% Et_2O in hexane); $[\alpha]_D^{28}$ -21.2 ($CHCl_3$, c = 1.0); Mp 64–66 °C; δ_H ($CDCl_3$) (mixture of rotamers) 8.03–9.41 (3H, br s, 3 × NH), 7.16–7.49 (5H, m, Ph), 5.92/5.87 (1H, 2 × d, J 6.6/7.2 Hz, NH), 5.03–5.20 (2H, m, CH_2), 4.25–4.33/4.07–4.14 (1H, 2 × m, CH), 1.50 (9H, s, 3 × Me), 1.41 (3H, d, *J* 7.0 Hz, Me); δ_C ($CDCl_3$) (mixture of rotamers) 179.8, 159.0/159.0, 156.7/156.2, 155.9/152.6, 136.4/136.6, 128.5/128.6, 128.2/128.1, 128.1/128.0, 84.4, 66.6/66.9, 52.0/53.0, 27.9/28.0, 19.1/19.2; ν_{max} 3374, 3101, 2976, 1720, 1639, 1524, 1500, 1236, 1146 cm^{-1}; MS (ESI) *m/z* 365.2 (100, $[M+H]^+$), HRMS (ESI) found 365.1819, $C_{17}H_{25}N_4O_5^+$ ($[M+H]^+$) requires 365.1819.

Benzyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7d.

Method A: *N*-Cbz-L-alanine **11b** (1.00 g, 5.48 mmol, 1.0 equiv.); DMF (5 mL), 0 °C; CDI (0.88 g, 5.40 mmol, 1.20 equiv.); 3 h; *N*-Cbz-guanidine **10a** (1.95 g, 4.93 mmol, 1.1 equiv.); DMF (5 mL); 3 d, rt. Extraction with $CHCl_3$ (3 × 50 mL); washed with HCl (aq. 0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); recrystallized from Et_2O (ca. 15 mL) at −20 °C (2 days) to form white needles which were washed with ice-cold diethyl ether and dried under vacuum to give **7d** (1.34 g, 3.36 mmol) in 75% yield. Column chromatography (70% Et_2O in hexane) gave an analytical sample. Rf 0.19 (70% Et_2O in hexane); $[\alpha]_D^{23}$ -17.5 ($CHCl_3$, c = 1.0); Mp 95–98 °C; δ_H ($CDCl_3$) (mixture of rotamers) 7.96–10.69 (3H, br s, 3 × NH), 7.19–7.58 (10H, m, 2 × Ph), 5.98/7.48 (1H, d/br s *J* 7.2 Hz, NH), 5.11 (2H, s, CH_2), 5.05–5.14 (2H, AB pattern, *J* 12.5 Hz, CH_2), 4.35–4.53/4.03–4.23 (1H, 2 × m, CH), 1.23/1.36 (3H, br d/d, J 5.4/7.0 Hz, Me); δ_C ($CDCl_3$) (mixture of rotamers) 178.4, 161.7/161.1, 159.1/158.8, 156.5/155.8, 136.2, 135.9/135.7, 128.5, 128.2, 128.2, 128.1, 127.9 (10 x CH) 67.5/67.2, 67.0, 52.5/52.0, 18.3/17.5; νmax 3332, 3272, 3033, 2951, 1708, 1687, 1627, 1526, 1259 cm^{-1}; MS (ESI) *m/z* 399.2 (100, $[M+H]^+$), HRMS (ESI) found 399.1664, $C_{20}H_{23}N_4O_5+$ ($[M+H]^+$) requires 399.16630.

tert-Butyl (*S*)-(1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7e.

Method A: *N*-Boc-L-alanine **11a** (1.01 g, 3.77 mmol, 1.0 equiv.); DMF (10 mL), 0 °C; CDI (0.77 g, 4.71 mmol, 1.25 equiv.); 90 min; *N*-Boc-guanidine **10b** (0.67 g, 4.15 mmol, 1.1 equiv.); DMF (15 mL); 2 d, rt. Extraction with $CHCl_3$ (3 × 50 mL); washed with (3 × 50 mL) and brine (2 × 50 mL); column chromatography (45% Et_2O in hexane) gave **7e** (0.68 g, 1.67 mmol) in 44% yield as a white solid. Rf 0.23 (50% Et_2O in hexane); $[\alpha]_D^{21}$ -21.0 ($CHCl_3$, c = 1.0); Mp 64–66 °C; δ_H ($CDCl_3$) (mixture of rotamers) 9.26 (2H, br s, 2 × NH), 8.81 (H, br s, NH) 7.14–7.25 (3H, m, 3 × CH), 7.07 (2H, br d, *J* 6.9 Hz, 2 × CH) 5.71–5.91/5.35 (2H, m/d, *J* 5.8 Hz, NH), 4.49–4.64/4.20–4.40 (1H, m/br m, CH), 3.15/3.00/2.75–3.21 (2H, dd J 5.0, 13.6/dd, J 5.6, 13.6/br m, 2 x CH), 1.43 (9H, s, 3 × Me), 1.34 (9H, s, 3 × Me); δ_C ($CDCl_3$) (mixture of rotamers) 182.4, 159.2, 155.0, 136.6, 129.5, 128.3, 126.7, 83.2, 80.3/79.4, 59.2/57.6, 39.2/38.5, 28.4, 27.9; νmax 3378, 3005, 2977, 2933, 1709, 1641, 1542, 1493, 1240, 1146 cm^{-1}; MS (ESI) *m/z* 407.2 (100, $[M+H]^+$); HRMS (ESI) found 407.2291, $C_{20}H_{31}N_4O_5+$ ($[M+H]^+$), requires 407.2289.

tert-butyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7f.

Method A: *N*-Boc-L-phenylalanine **11c** (1.00 g, 3.77 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (0.67 g, 4.75 mmol, 1.26 equiv.); 30 min; *N*-Cbz-guanidine **10a** (0.80 g, 4.15 mmol, 1.10 equiv.); DMF (15 mL); 3 d, rt, 2 d, 40 °C. Extraction with EtOAc (3 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); Recrystallized from ethanol (ca. 15 mL) at −20 °C (12 h) to form white needles which were washed with ice-cold Et_2O and dried under vacuum to give **7f** (1.20 g, 2.72 mmol) in 72% yield. Column chromatography (50% Et_2O in hexane) gave an analytical sample. Rf 0.15 (50% Et_2O in hexane); $[\alpha]_D^{25}$ -20.8 ($CHCl_3$, c = 1.27); Mp 151–154 °C; δ_H ($CDCl_3$) (mixture of rotamers) 8.89 (2H, br s, 2 × NH), 8.26 (1H, br s, NH), 7.07–7.44 (10H, m, 10 × CH), 5.20 (1H, br s, NH), 5.12/5.18 (2H, 2 × s, CH_2), 4.49–4.69/4.09–4.30 (1H, 2 × m, CH), 2.72–3.23 (2H, m, CH2) 1.39/1.30 (9H, 2 × s, 3 × Me); δ_C

($CDCl_3$) (mixture of rotamers) 178.5, 161.2/158.9/156.5/156.0/155.6/153.8 (3 × C), 137.5/136.5/136.2/136.0/134.5 (2 × C), 129.6/129.3/128.8/128.7/128.7/128.6/128.4/128.3/128.2/128.2/127.1/127.1 (10 × CH) 127.1/127.0/126.5, 81.4/80.4/79.4, 68.5/67.8/67.3, 58.6/56.9/56.2, 38.5/38.0/37.6, 28.4/28.3; ν_{max} 3395, 3350, 3271, 3059, 3033, 2985, 2956, 1708, 1684, 1620, 1543, 1511, 1439, 1378, 1316, 1294, 1252, 1201 cm^{-1}; MS (ESI) *m/z* 441.2 (100, $[M+H]^+$); HRMS (ESI) found 441.2134, $C_{23}H_{29}N_4O_5^+$ ($[M+H]^+$), requires 441.2132.

Benzyl (*S*)-(1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7g.

Method A: *N*-Cbz-L-phenylalanine **11d** (1.00 g, 3.34 mmol, 1.0 equiv.); DMF (15 mL); CDI (0.60 g, 3.74 mmol, 1.12 equiv.); 30 min; *N*-Boc-guanidine **10b** (0.59 g, 4.14 mmol, 1.24 equiv.); DMF (15 mL); 3 d, rt. Extraction with EtOAc; washed HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (50% Et_2O in hexane) gave **7g** (1.23 g, 2.79 mmol) in 84% yield as a white solid. Rf 0.23 (50% Et_2O in hexane); $[\alpha]_D^{21}$ -32.2 ($CHCl_3$, c = 1.54); Mp 123–125 °C; δ_H ($CDCl_3$) (mixture of rotamers) 8.75 (3H, br s, 3 × NH), 7.02–7.40 (10H, m, 2 × Ph), 5.60–5.71/5.58 (1H, m/d, *J* 6.6 Hz, NH), 4.96–5.10 (2H, m, CH_2), 4.57–4.65/4.37–4.51 (1H, 2 × m, CH), 2.92–3.22/3.12/3.26 (2H, m/dd/dd, J 13.6, 5.0/13.6, 5.2 Hz, 2 x CH) 1.47 (9H, s, 3 × Me); δ_C ($CDCl_3$) (mixture of rotamers) 182.6, 159.0, 155.7, 154.3, 136.7, 136.5. 129.6/128.5/128.4/128.2/126.8 (10 x CH), 83.7, 66.8/67.0, 58.1/59.0, 38.4/39.5, 28.0; ν_{max} 3378, 3031, 2977, 1721, 1641, 1542, 1497, 1145, 1081 cm^{-1}; MS (ESI) *m/z* 441.2 (100%, $[M+H]^+$); HRMS (ESI) found 441.2136, $C_{23}H_{29}N_4O_5^+$ ($[M+H]^+$), requires 441.2133.

Benzyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7h.

Method A: *N*-Cbz-L-phenylalanine **11d** (1.00 g, 3.34 mmol, 1.0 equiv.); DMF (15 mL), 0 °C; CDI (0.70 g, 4.98 mmol, 1.49 equiv.); 30 min; *N*-Cbz-guanidine **10a** (0.70 g, 3.67 mmol, 1.10 equiv.); DMF (15 mL); 3 d, rt; 2 d, 40 °C. Extraction with EtOAc (3 × 50 mL); washed with HCl (0.1 M, 50 mL), $NaHCO_3$ (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (45% Et_2O in hexane) gave **7h** (0.30 g, 0.63 mmol) in 19% as a white solid. Rf 0.35 (70% Et_2O in hexane); $[\alpha]_D^{25}$ -19.6° ($CHCl_3$, c = 1.0); Mp 83–86 °C; δ_H ($CDCl_3$) (mixture of rotamers) 8.80 (3H, br s, 3 × NH), 6.85–7.31 (15H, m, 3 × Ph), 7.33–7.50/5.48–5.59 (1H, br s/m, NH), 5.01 (2H, s, CH_2), 4.74–5.07 (2H, m, 2 × CH), 4.62–4.74/4.16–4.32 (1H, 2 × m, CH), 2.62–3.11 (2H, m, CH_2); δ_C ($CDCl_3$) (mixture of rotamers) 177.9, 160.2, 158.9/158.7, 156.7/155.9, 136.6, 136.2/136.0, 135.8/135.6, 129.3, 128.6, 128.6, 128.5, 128.3, 128.2, 128.2, 128.1, 127.9, 127.1, 127.0 (15 × CH), 67.4, 67.1, 58.4/57.3, 38.1/38.0/37.7; ν_{max} 3390, 3338, 3278, 3063, 3031, 2962, 1687, 1664, 1630, 1523, 1497, 1268, 1111, 1087 cm^{-1}; MS (ESI) *m/z* 475.2 (100, $[M+H]^+$); HRMS (ESI) , found 475.1977, $C_{26}H_{27}N_4O_5^+$ $[M+H]^+$), requires 475.1976.

Di-tert-butyl ((2*S*,2′*S*)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 8a.

Method B: *N*-Boc-L-alanine **11a** (1.78 g, 9.4 mmol, 2.2 equiv); DMF (5 mL); CDI (2.04 g, 12.7 mmol, 3.0 equiv); 0 °C, 90 min; guanidine hydrochloride (0.41 g, 4.3 mmol, 1.0 equiv); DMF (5 mL); NaH (60%, 0.16 g, 4.0 mmol, 0.93 equiv.), 24 h; 5 d; freeze dried then column chromatography (60% Et_2O in hexane) gave **8a** (1.05 g, 2.6 mmol) in 65% yield as a white solid. Rf 0.30 (75% Et_2Oin hexane); $[\alpha]_D^{21}$ -30 ($CHCl_3$, c = 1.0); Mp 76–78 °C; δ_H ($CDCl_3$) (mixture of rotamers) 9.18 (3H, br s, 3 × NH), 5.40–5.56/5.30–5.40 (2H, 2 × m, 2 × NH), 4.19–4.36/3.96–4.19 (2H, 2 × m, 2 × CH), 1.43 (18H, s, 6 × Me), 1.38 (6H, d, *J* 6.8 Hz, 2 × Me); δ_C ($CDCl_3$) 180.1, 158.7, 155.6, 80.3, 52.3, 28.4, 18.6; ν_{max} 3245, 3219, 3001, 2977, 2932, 1690, 1644, 1603, 1509, 1247; cm^{-1}; MS (ESI) *m/z* 402.2 (100, $[M+H]^+$); HRMS (ESI) found 402.2348, $C_{17}H_{32}N_5O_6^+$ ($[M+H]^+$) requires 402.2347.

Dibenzyl ((2*S*,2′*S*)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 8b.

Method B: *N*-Cbz-L-alanine **11b** (0.93 g, 4.16 mmol, 2.2 equiv.); DMF (5 mL); CDI (0.92 g, 5.7 mmol, 3.0 equiv.); 2 h; guanidine hydrochloride (0.18 g, 1.88 mmol, 1.0 equiv.); DMF (5 mL); NaH (60%, 0.07 g, 1.75 mmol, 0.93 equiv.); 24 h; 2 d; column chromatography (90–100% Et_2O in hexane) gave **8b** (0.71 g, 1.51 mmol) in 80% yield as a white solid. Rf 0.33 (Et_2O); $[\alpha]_D^{27}$ -22.7 ($CHCl_3$, c = 1.0); Mp 90–93 °C; δ_H ($CDCl_3$) (mixture of rotamers), 7.83 (1H, br s, 3 × NH), 7.27–7.39 (10H, m, 2 × Ph), 5.57–5.72 (2H, br m, 2 × NH), 5.13 (2H, d, *J* 12.3 Hz, 2 × CH), 5.08 (2H, d, *J* 12.3 Hz, 2 × CH), 4.29–4.41/4.14–4.29 (2H, m/m, 2 × CH), 1.42/1.40 (6H, 2 × d, *J* 7.0 Hz, 2 × Me); δ_C ($CDCl_3$) 176.0, 158.6, 156.0, 136.2, 128.7, 128.4, 128.3, 67.3, 52.8, 18.6; ν_{max} 3338, 3031, 2977, 1693, 1643, 1605, 1508, 1213 cm^{-1}; MS (ESI) *m/z* 470.2 (100, [M+H]+), HRMS (ESI) found 470.2040, $C_{23}H_{28}N_5O_6^+$ ($[M+H]^+$) requires 470.2034.

Di-tert-butyl ((2*S*,2′*S*)-((iminomethylene)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 8c.

Method B: *N*-Boc-L-phenylalanine **11c** (1.10 g, 4.15 mmol, 2.2 equiv); DMF (5 mL); CDI (0.92 g, 5.66 mmol, 3.0 equiv); 2 h; guanidine hydrochloride (0.19 g, 1.99 mmol, 1.0 equiv); DMF (5 mL); NaH (60%, 0.07 g, 1.75 mmol, 0.9 equiv.); 2 d; column chromatography (35% Et_2O in hexane) gave **8c** (0.78 g, 1.40 mmol) in 80% yield as a white solid. Rf 0.48 (70% Et_2O in hexane); $[\alpha]_D^{27}$ -21.4 ($CHCl_3$, c = 1.0); Mp 83–86 °C; δ_H (mixture of rotamers) 9.71 (3H, br s, 3 × NH), 7.09–7.33 (10H, m, 2 × Ph), 5.46–5.74/5.23–5.46 (2H, 2 × m, 2 × NH), 4.40–4.62/4.19–4.40 (2H, 2 × m, 2 × CH), 2.95–3.24 (4H, m, 2 × CH_2), 1.38 (18H, s, 6 × Me); δ_C (mixture of rotamers) 178.6, 158.3, 155.6, 136.4, 129.4, 128.6, 127.0, 80.6/80.3, 59.3/57.4, 38.7/38.1, 28.4; ν_{max} 3368, 3008, 2977, 2932, 1689, 1645, 1604, 1496 cm^{-1}; MS (ESI) *m/z* 554.3 (100, $[M+H]^+$), HRMS (ESI) found 554.2982, $C_{29}H_{40}N_5O_6^+$ ($[M+H]^+$) requires 554.2973.

Dibenzyl ((2*S*,2′*S*)-((iminomethylene)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 8d.

Method B: *N*-Cbz-L-phenylalanine **11d** (1.24 g, 4.15 mmol, 2.2 equiv); DMF (5 mL); CDI (0.92 g, 5.70 mmol, 3.0 equiv); 0 °C, 90 min; guanidine hydrochloride (0.18 g, 1.88 mmol, 1.0 equiv); DMF (5 mL); NaH (60%, 73.0 mg, 1.83 mmol, 0.97 equiv.), ; 4 d; column chromatography (50% Et_2O in hexane) gave **8d** (0.55 g, 0.89 mmol) in 49% yield as a white solid. Rf 0.26 (70% Et_2O in hexane); $[\alpha]_D^{28}$ -12.8 ($CHCl_3$, c = 1.0); Mp 150–152 °C; δ_H ($CDCl_3$) (mixture of rotamers) 9.07 (3H, br s, 3 × NH), 6.76–7.38 (20H, m, 4 × Ph), 5.52–5.87 (2H, m, 2 × NH), 4.91–5.14 (4H, m, 2 × CH_2), 4.52–4.91/4.29–4.50 (2H, 2 × m, 2 × CH), 2.75–3.20 (4H, m, 2 × CH_2); δ_C (mixture of rotamers) 178.4, 158.4/158.3, 156.2/156.1, 136.2, 136.0, 129.5, 129.4, 128.7, 128.6, 128.6, 128.3128.2, 127.1, 67.3/66.8, 59.0/57.8, 39.3/38.1; ν_{max} 3351, 3063, 3030, 2952, 1689, 1644, 1604, 1496, 1212 cm^{-1}; MS (ESI) *m/z* 622.3 (100, $[M+H]^+$), HRMS (ESI) found 622.2660, $C_{35}H_{36}N_5O_6^+$ ($[M+H]^+$) requires 622.2667.

Catalysed reactions of 2-hydroxy-1,4-napthoquinone 2 with β-nitrostyrene 3.

2-Hydroxy-1,4-napthoquinone **2** (100 mg, 0.574 mmol) and the required catalyst (0.04–0.1 equiv.) were dissolved in the requisite solvent and cooled to the required temperature (−20 to 0 °C). β-Nitrostyrene **3** (128.5 mg, 0.861 mmol, 1.5 equiv) was then added and the mixture stirred for the required time and temperature. Reaction progress was determined by sampling and determination by 1H NMR. 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 3 then CH_2Cl_2) to give **4** as a yellow solid. Enantiomeric excesses were determined either on a Chiralcel AS-H column (250 × 4.6 mm, mobile phase 96% hexane, 4% isopropanol, 0.1% TFA, 1.5 mL/min at 40 °C, detecting at 254 nm; R enantiomer 23.5 min, S enantiomer 26.2 min); or on a Phenomenex Lux Amylose-1 column (250 × 4.6 mm, mobile phase 70% hexane, 30% isopropanol, 0.5 mL/min at 40 °C, detecting at 254 nm; R enantiomer 13.2 min, S enantiomer 14.3 min).1.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132093.

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