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## *N*-Carbamate protected amino acid derived guanidine organocatalysts.

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### Abstract

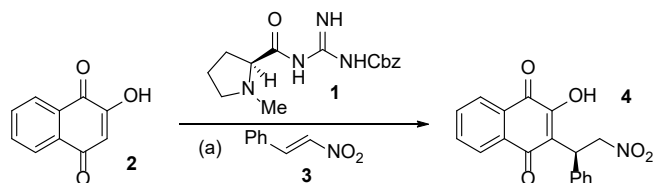
We report the preparation of a range of *N*-protected amino acid derived guanidine organocatalysts and their application to the Michael addition of 2-hydroxy-1,4-naphthoquinone to  $\beta$ -nitrostyrene, achieving a maximum ee of 26%. Whilst these catalysts gave poor ees, the structural variation together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

### Keywords

Organocatalysis, amino acids, guanidines, H-bonded extended networks.

### Introduction

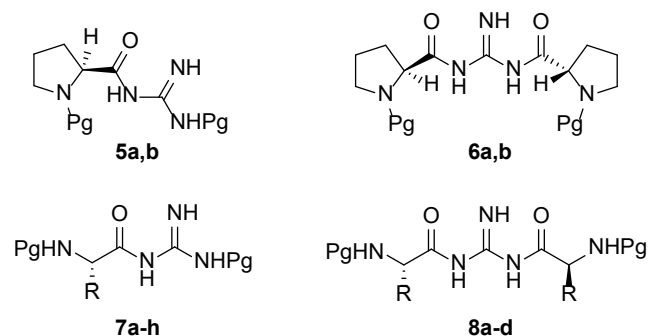
We recently reported<sup>1</sup> the preparation of a range of amino acid derived guanidines which were shown to have some potential as asymmetric organocatalysts however several problems were apparent from the work. This was supported by an investigation in the solid state demonstrating extensive intra- 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-naphthoquinone **2** to  $\beta$ -nitrostyrene **3**. (Scheme 1)



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

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-proliner with *N*-Cbz-guanidine in DMF. It was found that during the coupling the intermediate

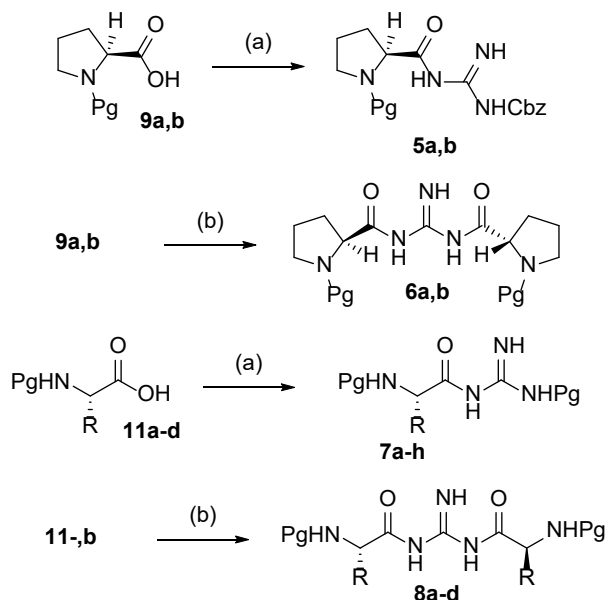
imidazole amide was prone to racemisation in the presence of even weakly basic guanidine reactants or the internal *N*-methyl functionality. In order to alleviate this problem and to investigate the role of the guanidine in the catalytic process we considered removing the internal amine base. We visualised 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.<sup>2</sup> 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. (Figure 1)



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

### Preparation of catalysts

The required *N*-protected amino acids and guanidines were available commercially or were prepared by literature methods.<sup>3,4</sup> 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 up and chromatography gave the **6b** in 97% yield. We attempted the preparation of the corresponding Cbz-catalyst **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 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).



**Scheme 2:** Preparation of catalysts **5-8** (a) METHOD A: 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.

Table 1: Preparation of catalysts **5-8**.

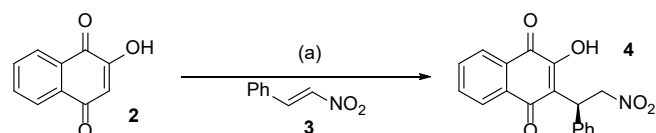
Entry	Catalyst	Yield	Method - SM	R	N-Pg	G-Pg
1	<b>5a</b>	67	A - <b>9a</b>	-	Cbz	Cbz
2	<b>5b</b>	40	A - <b>9b</b>	-	Boc	Cbz
3	<b>6a</b>	0	B - <b>9a</b>	-	Cbz	-
4	<b>6b</b>	97	B - <b>9b</b>	-	Boc	-
5	<b>7a</b>	63	A - <b>11a</b>	Me	Boc	Boc
6	<b>7b</b>	71	A - <b>11a</b>	Me	Boc	Cbz
7	<b>7c</b>	49	A - <b>11b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

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

### 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 8-18% ees but slower reactions. The *C*<sub>2</sub>-symmetric catalyst **6b** gave better 12-22% ees 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*<sub>2</sub>-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. Finally the *N*-Cbz-L-phenylalanine catalyst **8d** was 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%).



**Scheme 3:** Catalytic studies: Conditions: See Table 10, Catalyst (0.1 equiv.), 0 °C 7-8 h then rt.

Table 2: Catalytic studies<sup>(i)</sup>

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

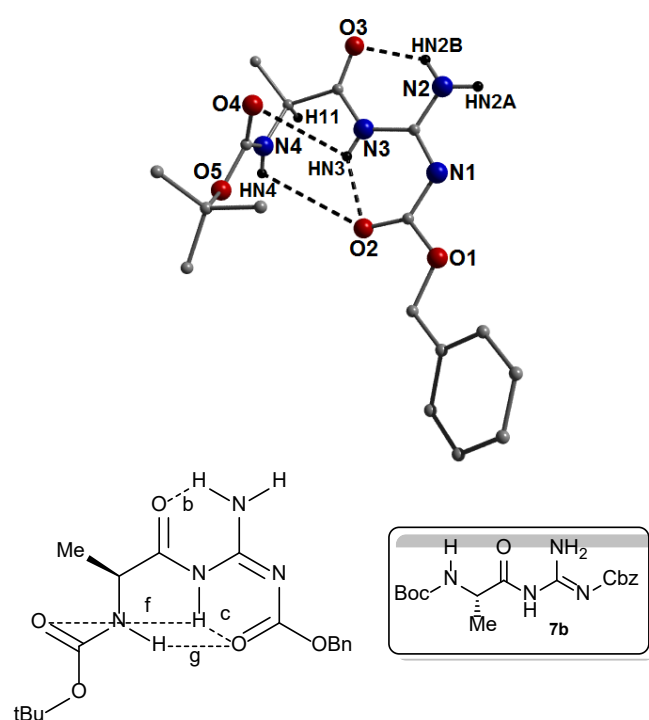
(i) Results are given as ee (time (d)/yield (%))

(ii) Benzoic acid (0.1 equiv.) was added

### 2.11 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 crystallise 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 ( $N4(HN4)\cdots O9 = 1.95 \text{ \AA}$ ), as well as a number of aliphatic C-H $\cdots$ O interactions (e.g.  $C34(H34A)\cdots O2 = 2.88 \text{ \AA}$ ,  $C16(H16A)\cdots O6 = 2.87 \text{ \AA}$  and  $C12(H12A)\cdots O8 = 2.69 \text{ \AA}$ ) (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<sup>1</sup> (bond b;  $N2(HN2B)\cdots O3 = 1.98 \text{ \AA}$  and bond c;  $N3(HN3)\cdots O2 = 1.97 \text{ \AA}$ ). Additionally an H-bond was observed between the guanidine NH and the Boc-protecting group (bond f;  $N3(HN3)\cdots O4 = 3.04 \text{ \AA}$ ) and possibly a weaker H-bond between the Boc-protecting group NH and the Cbz-protecting group carbonyl (bond g;  $N4(HN4)\cdots O2 = 3.40 \text{ \AA}$ ). This is an *E*-amide-bcf(g) pattern (Figure 2).

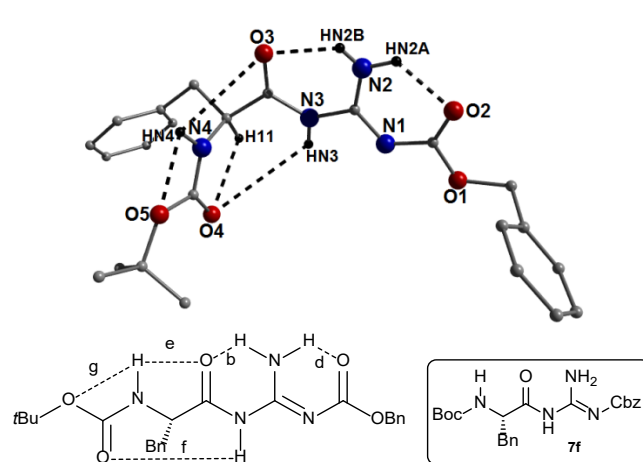


**Figure 2:** The X-ray crystal structure and corresponding ChemDraw representations of **7b**. The dashed lines represent intramolecular H-bonding at distances: (b)  $N2(HN2B)\cdots O3 = 1.98 \text{ \AA}$ ; (c)  $N3(HN3)\cdots O2 = 1.97 \text{ \AA}$  along with the long-contacts (f)  $N3(HN3)\cdots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

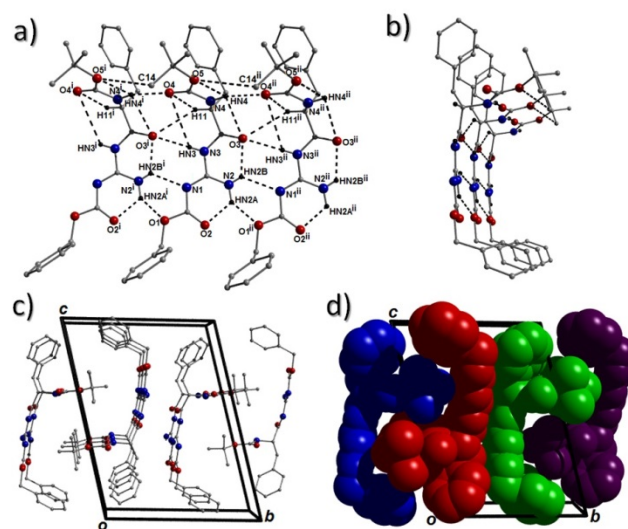
Organocatalyst **7f** crystallises in the  $P1$  space group and akin to **7b**, its asymmetric unit comprises two complete organocatalyst moieties (Fig. S3). In both molecules, extensive intramolecular H-bonds (e.g.  $N2(HN2A)\cdots O2 = 1.97 \text{ \AA}$ ,  $N4(HN4)\cdots O5 = 2.27 \text{ \AA}$  and  $N6(HN6B)\cdots O8 = 2.13 \text{ \AA}$ ) and C-H $\cdots$  $\pi$  interactions (e.g.  $[C18-C23]_{\text{centroid}}\cdots(H16C)C16 = 4.10 \text{ \AA}$  and  $[C41-C46]_{\text{centroid}}\cdots(H38B)C36 = 4.20 \text{ \AA}$ ) are observed (Figure 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;  $N3(HN3)\cdots O4 = 3.49 \text{ \AA}$ ) was observed. The guanidine  $NH_2$  had two H-bonds of the *E*-bd type (bond b;  $N2(HN2B)\cdots O3 = 2.17 \text{ \AA}$  and bond d;  $N2(HN2A)\cdots O2 = 1.97 \text{ \AA}$ ) and a H-bond between the NH of the Boc protecting group and the amide oxygen was also observed (bond e;  $N4(HN4)\cdots O3 = 3.12 \text{ \AA}$ ). Overall this is an *E*-amide-bde(f) pattern (Figure 3).

As highlighted in Figure 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 (Figure 5b). 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 $\cdots$  $\pi$  and C-H $\cdots$ O interactions at distance of  $3.80 \text{ \AA}$  ( $[C41-C46]_{\text{centroid}}\cdots(H7B)C7$ ) and  $2.54 \text{ \AA}$  ( $C23(H23)\cdots O7$ ), respectively. This packing efficiency is best shown in Figure 5d, whereby each H-bonded sheet is represented in space-fill mode and using a different colour.



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



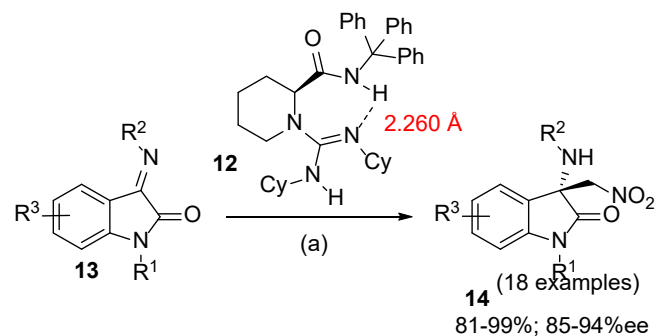
**Figure 4** A planar 2-D sheet comprising on individual **7f** units connected through numerous intermolecular hydrogen bonds (dashed lines) as viewed perpendicular (a) and parallel to the plane.

Intermolecular H-bond distances: N2(HN2A)<sup>i</sup>...O1 = 2.09 Å;  
 N2(HN2B)<sup>ii</sup>...N1 = 2.35 Å; N3(HN3)<sup>iii</sup>...O3 = 2.37 Å;  
 C11(H11)<sup>iiii</sup>...O3 = 2.93 Å; N4(HN4)<sup>v</sup>...O4 = 2.14 Å and  
 C14(H14B)<sup>vi</sup>...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 <sup>1</sup>H spectra of **7b** and **7f** in CDCl<sub>3</sub> displays a mixture of rotamers in both cases and the guanidine NH-protons are broadened. The corresponding <sup>1</sup>H spectra in DMSO-d<sub>6</sub> however gave separate and relatively sharp signals for each NH of the guanidines of **7b** (δ<sub>H</sub> = 11.30/8.90/8.86 (3 x 1H, 3 x br s)) and **7f** (δ<sub>H</sub> = 11.36/8.94/8.85 (3 x 1H, 3 x br s)). This might suggest the two catalysts which give reasonable ees in the catalytic reaction possess similar structures in solution.

## 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<sub>2</sub>-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.<sup>5</sup> 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<sup>1</sup> 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<sup>1</sup> to employ a simplified range of base catalysts might be more advantageous.<sup>6</sup> Interestingly, Liu *et al.* reported<sup>7</sup> 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 groups 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.<sup>†</sup>



**Scheme 4:** (a) i) **12** (10 mol %), **13**, MeNO<sub>2</sub>, PhMe, -30 °C, 72 h.  
 R<sup>1</sup> = Me, Bn; R<sup>2</sup> = Boc, EtO<sub>2</sub>C; R<sup>3</sup> = H, F, Cl, Br, I, Me, F<sub>3</sub>CO, CF<sub>3</sub>.

## Acknowledgements

We would like to thank Dr Daniel Evans for his invaluable help with this project, the BEACON II scheme (ERDF; PJM) and the Iraqi government (ZSSA-T). We also thank the EPSRC National Crystallography Service at the University of Southampton and Rolf Kraehenbuehl (Bangor University) for MS data.

## 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**,<sup>3</sup> *N*-Cbz-guanidine **10a**<sup>4</sup> and *N*-Boc-guanidine **10b**<sup>4</sup>) were prepared according to literature procedures. Flash column chromatography was performed on Davisil<sup>®</sup> silica gel (35-70 microns) with the eluent specified in each case, TLC was conducted on precoated E. Merck silica gel 60 F<sub>254</sub> glass plates. <sup>1</sup>H and <sup>13</sup>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<sub>H</sub> 7.26 and δ<sub>C</sub> 77.016 ppm for CDCl<sub>3</sub>, δ<sub>H</sub> 3.31 and δ<sub>C</sub> 49.0 ppm for CD<sub>3</sub>OD. 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<sup>8</sup> and refined with SHELXL-2014/7 within the Olex2<sup>9</sup> 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<sub>4</sub>), filtering and evaporation under reduced pressure, the product was obtained and was purified by column chromatography (Et<sub>2</sub>O/petroleum ether or EtOAc/petroleum ether), recrystallization or trituration.

**Method B:** (*C*<sub>2</sub>-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<sub>2</sub>O<sub>5</sub>) 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<sub>4</sub>), 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)carbamoyle)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. **R<sub>f</sub>** 0.49 (EtOAc); **Mp** 47-49 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -60.1 (CHCl<sub>3</sub>, *c* = 2.0);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 1.98-2.32 (2H, m, CH<sub>2</sub>), 1.81-1.97 (2H, m, CH<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (mixture of rotamers) 176, 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;  $\nu_{\text{max}}$  3383, 3274, 3032, 2957, 2886, 1703, 1662, 1627, 1539, 1498, 1446, 1414, 1379, 1355, 1277, 1170, 1116, 1090, 1026, 989, 914, 806, 748 cm<sup>-1</sup>; **MS (ESI) m/z** 425.2 (100%, [M+H]<sup>+</sup>), **HRMS (ESI) m/z** found 425.1814, C<sub>22</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 425.1819.

#### *tert*-Butyl (*S*)-2-((*N*-((benzyloxy)carbonyl)carbamimidoyl)carbamoyle)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. **R<sub>f</sub>** 0.14 (30% EtOAc in hexane); **Mp** 64-66 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -53.8 (*c* = 2.1, CHCl<sub>3</sub>);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (mixture of rotamers) 7.63-10.22 (3H, br s, 3 × NH), 7.27-7.38 (5H, m, Ph), 5.11 (2H, s, CH<sub>2</sub>), 4.11-4.46 (1H, m, CH), 3.28-3.62 (2H, m, CH<sub>2</sub>), 1.94-2.30 (2H, m, CH<sub>2</sub>), 1.76-1.94 (2H, m, CH<sub>2</sub>), 1.44/1.40 (9H, 2 × s, 3 × CH<sub>3</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  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<sup>-1</sup>; **MS (ESI) m/z** 391.2 (100%, [M+H]<sup>+</sup>); **HRMS (ESI) found** 391.1980, C<sub>19</sub>H<sub>27</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>2</sub>O in hexane) gave **6b** (0.81 g, 1.78 mmol) as a white solid in 97% yield. **R<sub>f</sub>** 0.28 (75% EtOAc in hexane); **Mp** 65-69 °C; [ $\alpha$ ]<sub>D</sub><sup>20</sup> -77.1 (CHCl<sub>3</sub>, *c* = 2.3);  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 1.74-2.29 (8H, m, 4 × CH<sub>2</sub>), 1.45/1.39/1.36 (18H, s, 6 × Me);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3366, 3231, 2976, 2932, 2879, 1692, 1643, 1520, 1477, 1451, 1392, 1365, 1249, 1158, 1122; **MS (ESI) m/z** 454.3 (100% [M+H]<sup>+</sup>); **HRMS (ESI) found** 454.2654, C<sub>21</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>3</sub> (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. **R<sub>f</sub>** 0.11 (25% EtOAc in hexane); [ $\alpha$ ]<sub>D</sub><sup>23</sup> -24.0 (CHCl<sub>3</sub>, *c* = 1.0); **Mp** 113 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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 x m, CH), 1.47 (9H, s, 3 × Me), 1.42 (9H, s, 3 × Me), 1.36 (3H, d, *J* 7.1 Hz, Me);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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 × tBu), 19.3;  $\nu_{\text{max}}$  3382, 3282, 2978, 2934, 1712, 1643, 1539, 1496, 1447, 1148, 1047 cm<sup>-1</sup>; **MS (ESI) m/z** 331.2 (100, [M+H]<sup>+</sup>), **HRMS (ESI) found** 331.1973, C<sub>14</sub>H<sub>27</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>3</sub> (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<sub>2</sub>O in hexane) gave an analytical sample. **R<sub>f</sub>** 0.11 (50% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -18.8 (CHCl<sub>3</sub>, c = 1.15); **Mp** 138-140 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 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, CH<sub>3</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3383, 3282, 2978, 2928, 1695, 1629, 1542, 1498, 1436, 1165, 1069 cm<sup>-1</sup>; **MS (ESI) m/z** 365.2 (100%, [M+H]<sup>+</sup>); **HRMS (ESI)** found 365.1819, C<sub>17</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>3</sub> (3 × 50 mL); washed with HCl (0.1 M, 50 mL), NaHCO<sub>3</sub> (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (50% Et<sub>2</sub>O in hexane) gave **7c** (1.37 g, 3.76 mmol) in 49% yield. **R<sub>f</sub>** 0.13 (50% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>28</sup> -21.2 (CHCl<sub>3</sub>, c = 1.0); **Mp** 64-66 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3374, 3101, 2976, 1720, 1639, 1524, 1500, 1236, 1146 cm<sup>-1</sup>; **MS (ESI) m/z** 365.2 (100, [M+H]<sup>+</sup>), **HRMS (ESI)** found 365.1819, C<sub>17</sub>H<sub>25</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>3</sub> (3 × 50 mL); washed with HCl (aq. 0.1 M, 50 mL), NaHCO<sub>3</sub> (aq. sat. 50 mL) and brine (2 × 50 mL); recrystallized from Et<sub>2</sub>O (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<sub>2</sub>O in hexane) gave an analytical sample. **R<sub>f</sub>** 0.19 (70% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>23</sup> -17.5 (CHCl<sub>3</sub>, c = 1.0); **Mp** 95-98 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 5.05-5.14 (2H, AB pattern, *J* 12.5 Hz, CH<sub>2</sub>), 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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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 × CH) 67.5/67.2, 67.0, 52.5/52.0, 18.3/17.5;  $\nu_{\text{max}}$  3332, 3272, 3033, 2951, 1708, 1687, 1627, 1526, 1259 cm<sup>-1</sup>; **MS (ESI) m/z** 399.2 (100, [M+H]<sup>+</sup>), **HRMS (ESI)** found 399.1664, C<sub>20</sub>H<sub>23</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>) 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<sub>3</sub> (3 × 50 mL); washed with (3 × 50 mL) and brine (2 × 50 mL); column chromatography (45% Et<sub>2</sub>O in hexane) gave **7e** (0.68 g, 1.67 mmol) in 44% yield as a white solid. **R<sub>f</sub>** 0.23 (50% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>21</sup> -21.0 (CHCl<sub>3</sub>, c = 1.0); **Mp** 64-66 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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 × CH), 1.43 (9H, s, 3 × Me), 1.34 (9H, s, 3 × Me);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3378, 3005, 2977, 2933, 1709, 1641, 1542, 1493, 1240, 1146 cm<sup>-1</sup>; **MS (ESI) m/z** 407.2 (100, [M+H]<sup>+</sup>); **HRMS (ESI)** found 407.2291, C<sub>20</sub>H<sub>31</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>), 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<sub>3</sub> (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<sub>2</sub>O and dried under vacuum to give **7f** (1.20 g, 2.72 mmol) in 72% yield. Column chromatography (50% Et<sub>2</sub>O in hexane) gave an analytical sample. **R<sub>f</sub>** 0.15 (50% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -20.8 (CHCl<sub>3</sub>, c = 1.27); **Mp** 151-154 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 4.49-4.69/4.09-4.30 (1H, 2 × m, CH), 2.72-3.23 (2H, m, CH<sub>2</sub>) 1.39/1.30 (9H, 2 × s, 3 × Me);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3395, 3350, 3271, 3059, 3033, 2985, 2956, 1708, 1684, 1620, 1543, 1511, 1439, 1378, 1316, 1294, 1252, 1201 cm<sup>-1</sup>; **MS (ESI) m/z** 441.2 (100, [M+H]<sup>+</sup>); **HRMS (ESI)** found 441.2134, C<sub>23</sub>H<sub>29</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>), 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<sub>3</sub> (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (50% Et<sub>2</sub>O in hexane) gave **7g** (1.23 g, 2.79



mmol) in 84% yield as a white solid. **R<sub>f</sub>** 0.23 (50% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>21</sup> -32.2 (CHCl<sub>3</sub>, c = 1.54); **Mp** 123-125 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 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 × CH) 1.47 (9H, s, 3 × Me);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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 × CH), 83.7, 66.8/67.0, 58.1/59.0, 38.4/39.5, 28.0;  $\nu_{\text{max}}$  3378, 3031, 2977, 1721, 1641, 1542, 1497, 1145, 1081 cm<sup>-1</sup>; **MS (ESI) m/z** 441.2 (100%, [M+H]<sup>+</sup>); **HRMS (ESI)** found 441.2136, C<sub>23</sub>H<sub>29</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> ([M+H]<sup>+</sup>), 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<sub>3</sub> (aq. sat. 50 mL) and brine (2 × 50 mL); column chromatography (45% Et<sub>2</sub>O in hexane) gave **7h** (0.30 g, 0.63 mmol) in 19% as a white solid. **R<sub>f</sub>** 0.35 (70% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>25</sup> -19.6° (CHCl<sub>3</sub>, c = 1.0); **Mp** 83-86 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 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<sub>2</sub>);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) (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;  $\nu_{\text{max}}$  3390, 3338, 3278, 3063, 3031, 2962, 1687, 1664, 1630, 1523, 1497, 1268, 1111, 1087; **MS (ESI) m/z** 475.2 (100, [M+H]<sup>+</sup>); **HRMS (ESI)** C<sub>26</sub>H<sub>27</sub>N<sub>4</sub>O<sub>5</sub><sup>+</sup> [M+H]<sup>+</sup>, requires 475.1976, found 475.1977.

#### **Di-tert-butyl ((2S,2'S)-((iminomethylene)bis(azanediy))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<sub>2</sub>O in hexane) gave **8a** (1.05 g, 2.6 mmol) in 65% yield as a white solid. **R<sub>f</sub>** 0.30 (75% Et<sub>2</sub>O/PE); [ $\alpha$ ]<sub>D</sub><sup>21</sup> -30 (CHCl<sub>3</sub>, c = 1.0); **Mp** 76-78 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 180.1, 158.7, 155.6, 80.3, 52.3, 28.4, 18.6;  $\nu_{\text{max}}$  3245, 3219, 3001, 2977, 2932, 1690, 1644, 1603, 1509, 1247; cm<sup>-1</sup>; **MS (ESI) m/z** 402.2 (100, [M+H]<sup>+</sup>); **HRMS (ESI)** found 402.2348, C<sub>17</sub>H<sub>32</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 402.2347.

#### **Dibenzyl ((2S,2'S)-((iminomethylene)bis(azanediy))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<sub>2</sub>O in hexane) gave **8b** (0.71 g, 1.51 mmol) in 80% yield as a white solid. **R<sub>f</sub>** 0.33 (Et<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>27</sup> -22.7 (CHCl<sub>3</sub>, c = 1.0); **Mp** 90-93 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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);  $\delta_{\text{C}}$  (CDCl<sub>3</sub>) 176.0, 158.6, 156.0, 136.2, 128.7, 128.4, 128.3, 67.3, 52.8, 18.6;  $\nu_{\text{max}}$  3338, 3031, 2977, 1693, 1643, 1605, 1508, 1213 cm<sup>-1</sup>; **MS (ESI) m/z** 470.2 (100, [M+H]<sup>+</sup>), **HRMS (ESI)** found 470.2040, C<sub>23</sub>H<sub>28</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 470.2034.

#### **Di-tert-butyl ((2S,2'S)-((iminomethylene)bis(azanediy))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<sub>2</sub>O in hexane) gave **8c** (0.78 g, 1.40 mmol) in 80% yield as a white solid. **R<sub>f</sub>** 0.48 (70% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>27</sup> -21.4 (CHCl<sub>3</sub>, c = 1.0); **Mp** 83-86 °C;  $\delta_{\text{H}}$  (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<sub>2</sub>), 1.38 (18H, s, 6 × Me);  $\delta_{\text{C}}$  (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;  $\nu_{\text{max}}$  3368, 3008, 2977, 2932, 1689, 1645, 1604, 1496 cm<sup>-1</sup>; **MS (ESI) m/z** 554.3 (100, [M+H]<sup>+</sup>), **HRMS (ESI)** found 554.2982, C<sub>29</sub>H<sub>40</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 554.2973.

#### **Dibenzyl ((2S,2'S)-((iminomethylene)bis(azanediy))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.), 24 min; 4 d; column chromatography (50% Et<sub>2</sub>O in hexane) gave **8d** (0.55 g, 0.89 mmol) in 49% yield as a white solid. **R<sub>f</sub>** 0.26 (70% Et<sub>2</sub>O in hexane); [ $\alpha$ ]<sub>D</sub><sup>28</sup> -12.8 (CHCl<sub>3</sub>, c = 1.0); **Mp** 150-152 °C;  $\delta_{\text{H}}$  (CDCl<sub>3</sub>) (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<sub>2</sub>), 4.52-4.91/4.29-4.50 (2H, 2 × m, 2 × CH), 2.75-3.20 (4H, m, 2 × CH<sub>2</sub>);  $\delta_{\text{C}}$  (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, 128.3, 128.2, 127.1, 67.3/66.8, 59.0/57.8, 39.3/38.1;  $\nu_{\text{max}}$  3351, 3063, 3030, 2952, 1689, 1644, 1604, 1496, 1212 cm<sup>-1</sup>; **MS (ESI) m/z** 622.3 (100, [M+H]<sup>+</sup>), **HRMS (ESI)** found 622.2660, C<sub>35</sub>H<sub>36</sub>N<sub>5</sub>O<sub>6</sub><sup>+</sup> ([M+H]<sup>+</sup>) requires 622.2667.

#### **Catalysed reaction of 2-hydroxy-1,4-naphthoquinone 2 with $\beta$ -nitrostyrene 3**

2-Hydroxy-1,4-naphthoquinone **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).  $\beta$ -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 <sup>1</sup>H 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<sub>2</sub>Cl<sub>2</sub>) 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).<sup>1</sup>

† Note added in proof. A communication<sup>10</sup> 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 compound, afforded predominantly syn diastereoselectivity and high ee. MMFF modelling suggested the presence of extensive hydrogen bonding network between the acylguanidinium group and the reaction intermediates.

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**Appendix 1: Slow catalysts – insights into structural dependency of amino acid derived Guanidine catalysts (P. J. Murphy et al).**

**Supporting information**

**X-Ray data**

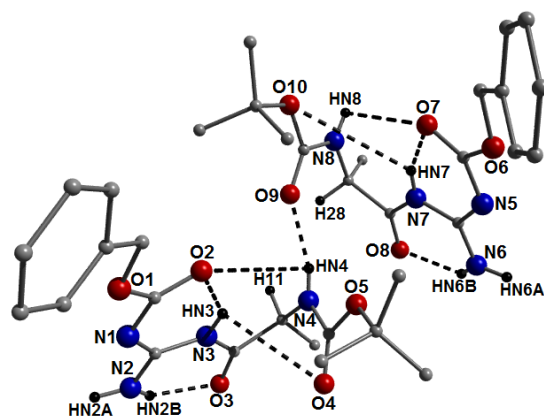
**Table S1.** Crystal data and structure refinement details for **7b**.

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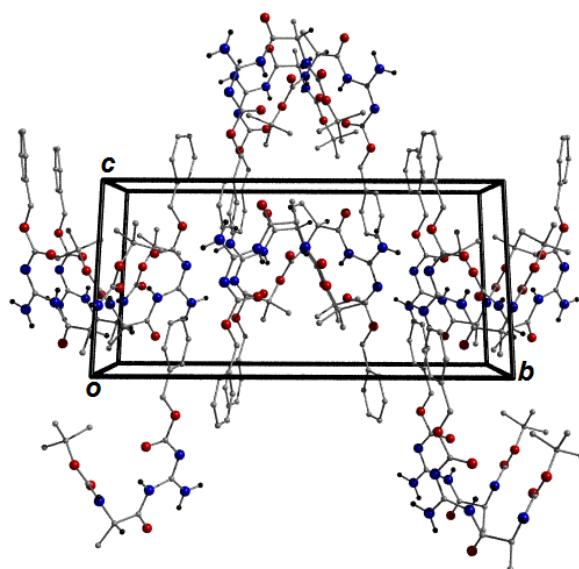
Empirical formula	C <sub>17</sub> H <sub>24</sub> N <sub>4</sub> O <sub>5</sub>
Formula weight	364.40
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	<i>P</i> 2 <sub>1</sub>
Unit cell dimensions	<i>a</i> = 9.3046(3) Å $\alpha = 90^\circ$ <i>b</i> = 20.5570(6) Å $\beta = 109.461(3)^\circ$ <i>c</i> = 10.3928(3) Å $\gamma = 90^\circ$
Volume	1874.31(10) Å <sup>3</sup>
<i>Z</i>	4
Density (calculated)	1.291 Mg / m <sup>3</sup>
Absorption coefficient	0.802 mm <sup>-1</sup>
<i>F</i> (000)	776
Crystal	plate; colourless
Crystal size	0.1 × 0.05 × 0.025 mm <sup>3</sup>
$\theta$ range for data collection	4.301 – 70.508°
Index ranges	-11 ≤ <i>h</i> ≤ 11, -25 ≤ <i>k</i> ≤ 24, -12 ≤ <i>l</i> ≤ 12
Reflections collected	34589
Independent reflections	7018 [ <i>R</i> <sub>int</sub> = 0.1316]
Completeness to $\theta = 67.684^\circ$	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.48398
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>
Data / restraints / parameters	7018 / 13 / 509
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.053
Final <i>R</i> indices [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )]	<i>R</i> 1 = 0.0746, <i>wR</i> 2 = 0.1866
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0874, <i>wR</i> 2 = 0.1971
Absolute structure parameter	-0.03(19)
Extinction coefficient	0.0036(8)
Largest diff. peak and hole	0.735 and -0.303 e Å <sup>-3</sup>
CCDC Deposition Number	CCDC2030901

**Table S2.** Crystal data and structure refinement details for **7f**.

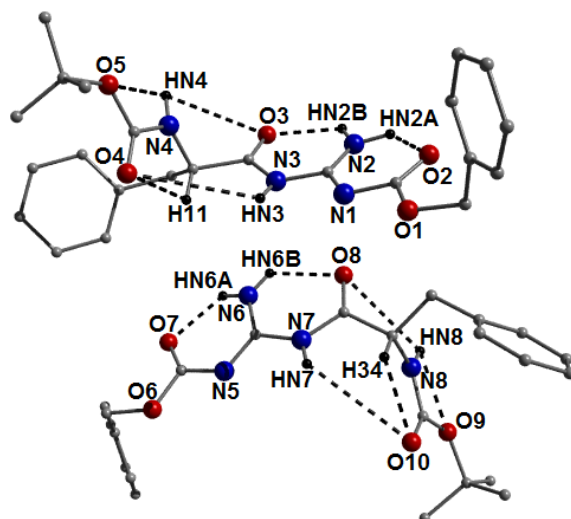
Empirical formula	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>5</sub>
Formula weight	440.49
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Triclinic
Space group	<i>P</i> 1
Unit cell dimensions	$a = 5.21590(10)$ Å $\alpha = 76.385(2)^\circ$ $b = 12.9476(2)$ Å $\beta = 83.401(2)^\circ$ $c = 17.1996(4)$ Å $\gamma = 88.849(2)^\circ$
Volume	1121.40(4) Å <sup>3</sup>
<i>Z</i>	2
Density (calculated)	1.305 Mg / m <sup>3</sup>
Absorption coefficient	0.767 mm <sup>-1</sup>
<i>F</i> (000)	468
Crystal	plate; colourless
Crystal size	0.3 × 0.05 × 0.01 mm <sup>3</sup>
$\theta$ range for data collection	3.512 – 70.456°
Index ranges	–5 ≤ <i>h</i> ≤ 6, –15 ≤ <i>k</i> ≤ 15, –20 ≤ <i>l</i> ≤ 20
Reflections collected	52890
Independent reflections	7847 [ <i>R</i> <sub>int</sub> = 0.0926]
Completeness to $\theta = 67.684^\circ$	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.31940
Refinement method	Full-matrix least-squares on <i>F</i> <sup>2</sup>
Data / restraints / parameters	7847 / 3 / 609
Goodness-of-fit on <i>F</i> <sup>2</sup>	1.071
Final <i>R</i> indices [ <i>F</i> <sup>2</sup> > 2σ( <i>F</i> <sup>2</sup> )]	<i>R</i> 1 = 0.0572, <i>wR</i> 2 = 0.1564
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0606, <i>wR</i> 2 = 0.1592
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.252 and –0.235 e Å <sup>-3</sup>
CCDC Deposition Number	CCDC2030902



**Figure S1** The two guanidine molecules comprising the asymmetric unit in **7b**. The dashes lines represent hydrogen bonding intra- and intermolecular interactions. Hydrogen bond distances: N2(HN2B)···O3 = 1.978 Å; N3(HN3)···O2 = 1.973 Å; N7(HN7)···O7 = 1.867 Å; N6(HN6B)···O8 = 2.035 Å; N4(HN4)···O9 = 1.953 Å along with the long-contacts N3(HN3)···O4 = 3.041 Å and N4(HN4)···O2 = 3.402 Å; N7(HN7)···O10 = 3.538 Å and N8(HN8)···O7 = 3.490 Å. The labels H11 and H28 represent the chiral protons in **7b**.



**Figure S2** Packing configuration observed in the crystal structure of **7b** as viewed along the *a* unit cell direction. All aromatic and *tert*-Butyl protons have been omitted for clarity.



**Figure S3** The two guanidine molecules that make up the asymmetric unit in **7f**. The dashes lines represent the H-bonds: N2(HN2A)···O2 = 1.97 Å; N2(HN2B)···O3 = 2.17 Å; N4(HN4)···O5 = 2.27 Å; C11(H11)···O4 = 2.42 Å; N6(HN6A)···O7 = 2.01 Å; N6(HN6B)···O8 = 2.13 Å; N8(HN8)···O9 = 2.36 Å; C34(H34)···O10 = 2.41 Å along with the long contacts with distances of 3.49 Å (N3(HN3)···O4); 3.12 Å (N4(HN4)···O3); 3.41 Å ((N7(HN7)···O10) and 3.02 Å (N8(HN8)···O8). The chiral protons have been labelled H11 and H34.

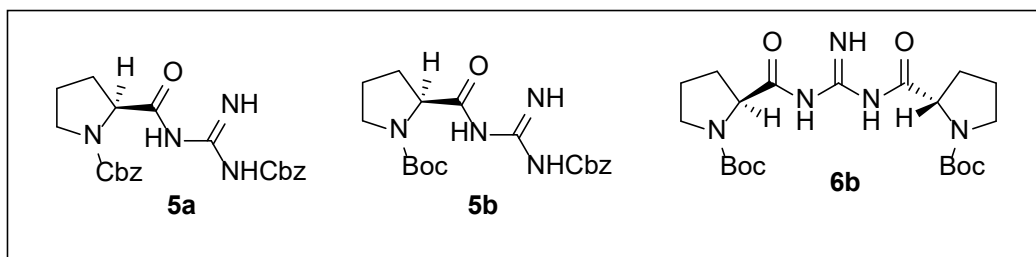
## Appendix 2: Carbamate protected amino acid derived guanidine organocatalysts.

(P. J. Murphy et al).

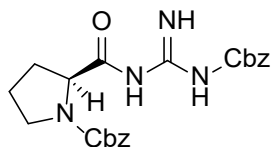
### Supporting information

### NMR Spectra

#### Cbz- and Boc-L-proline catalysts



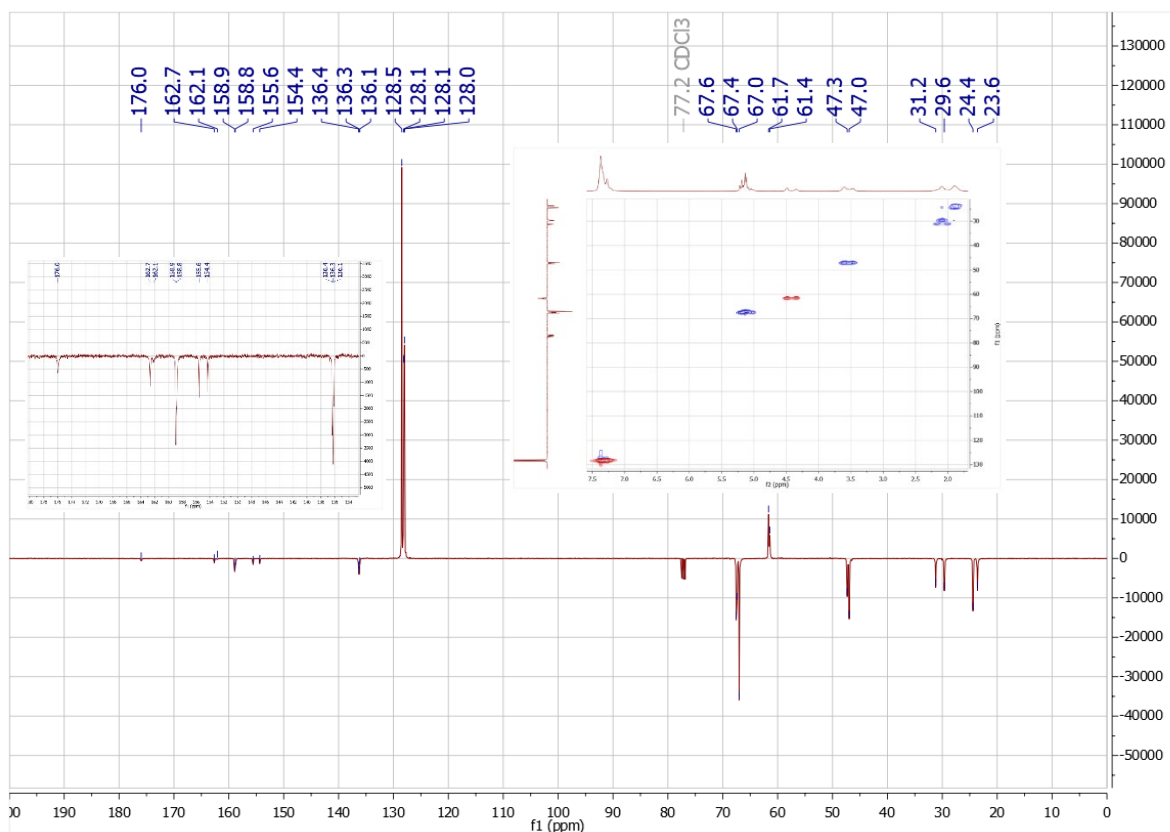
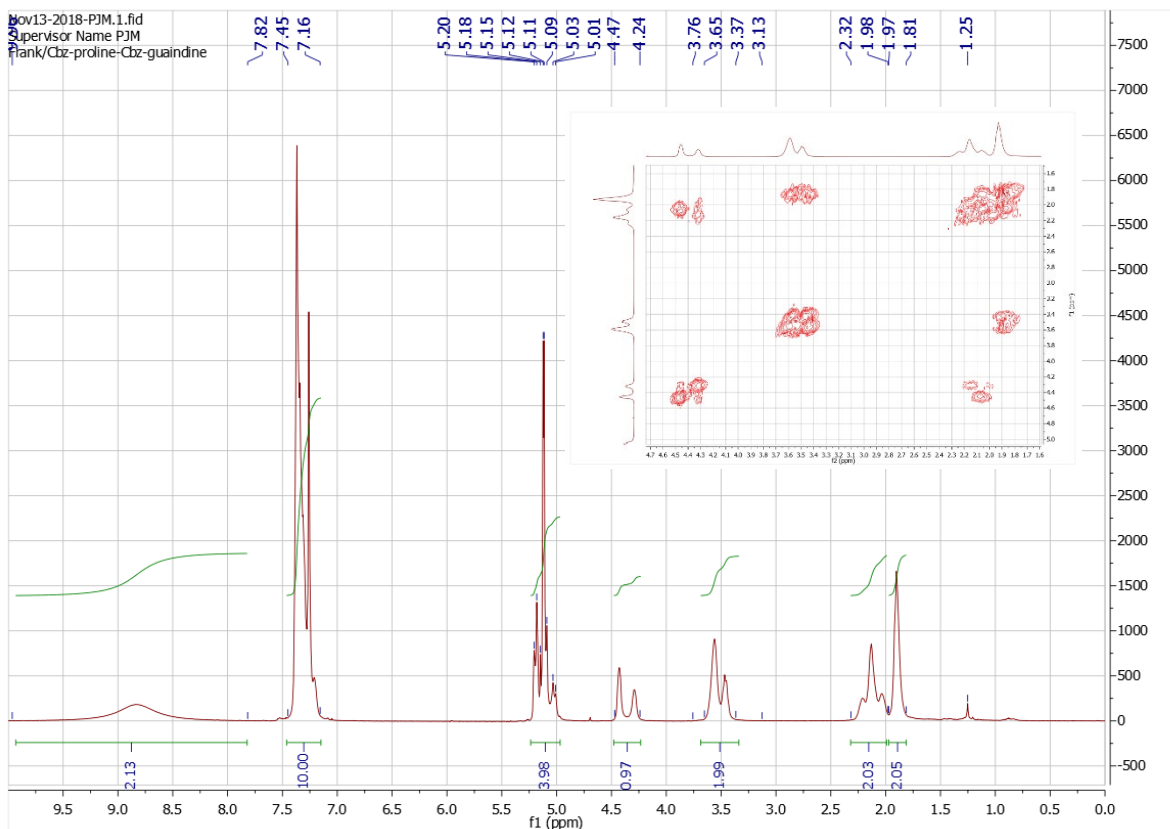
**Benzyl (S)-2-((N-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-Carboxylate 5a.**



Chemical Formula: C<sub>22</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>

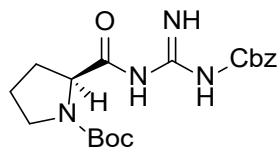
Exact Mass: 424.1747

Molecular Weight: 424.4570





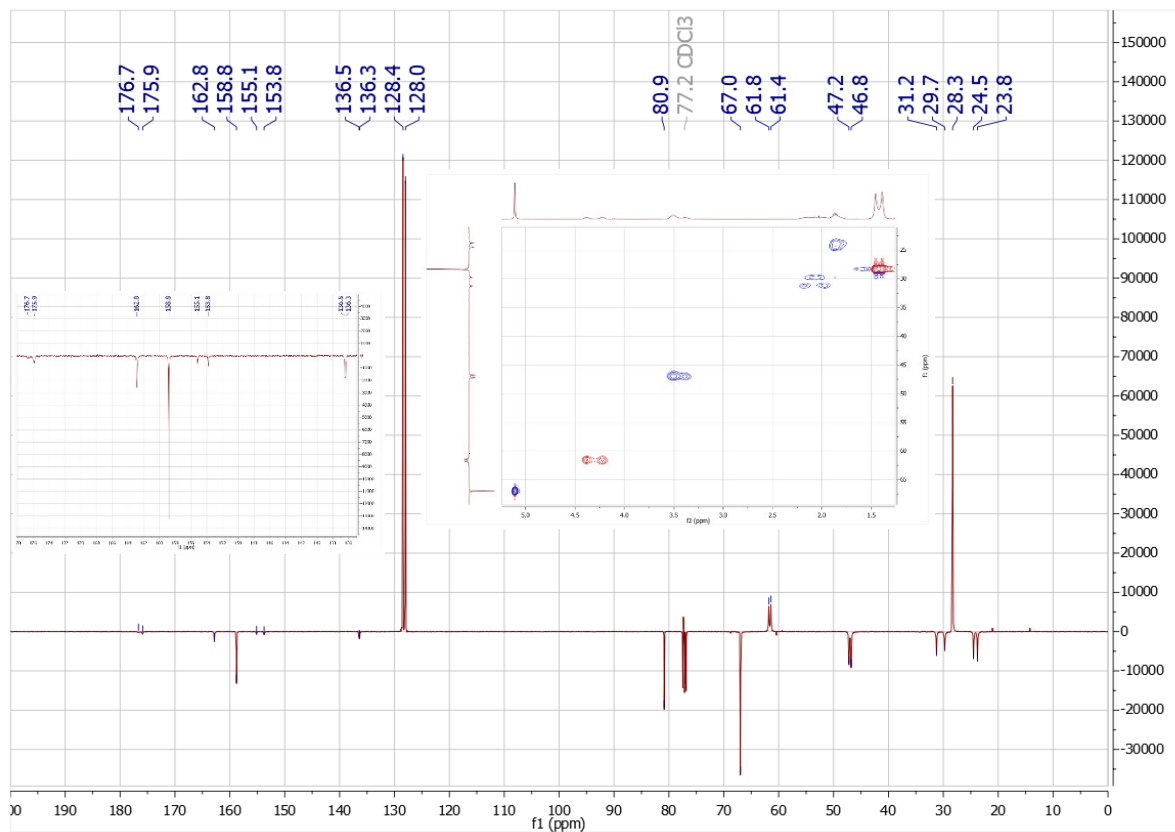
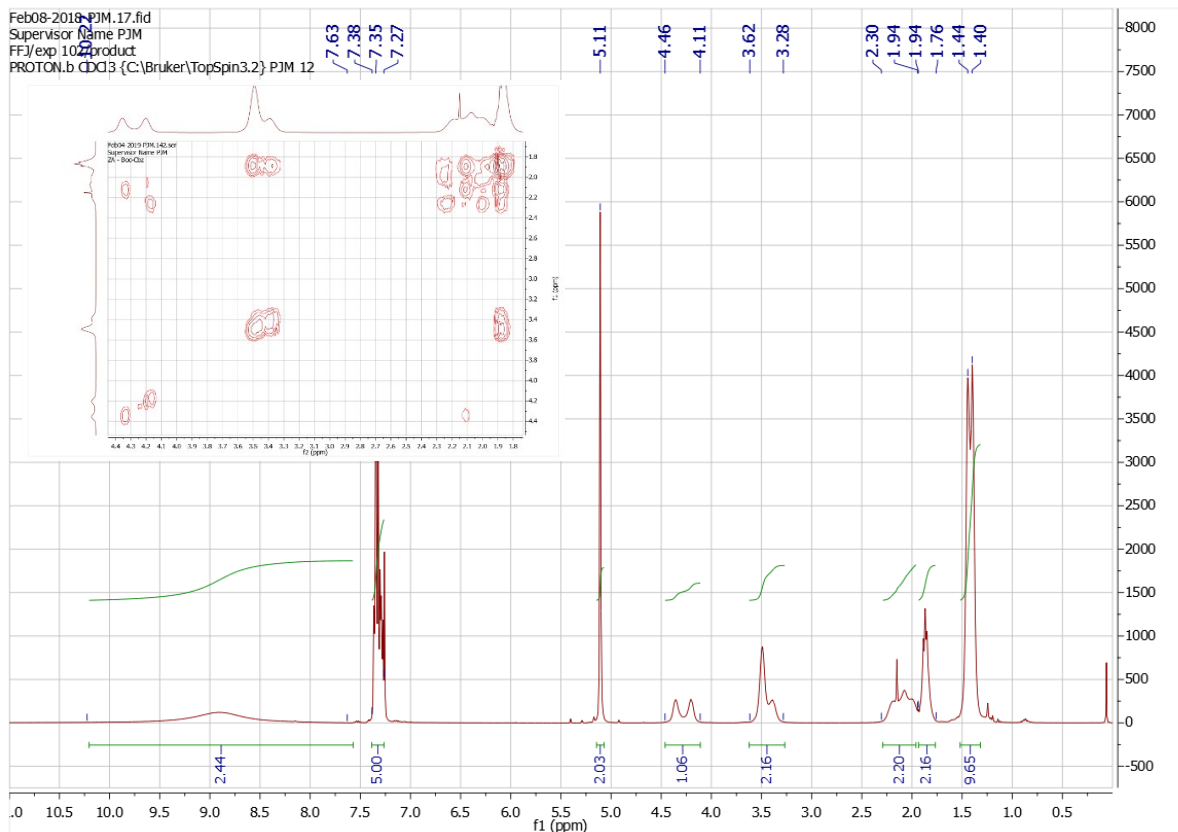
***tert*-Butyl (*S*)-2-((*N*-((benzyloxy)carbonyl)carbamimidoyl)carbamoyl)pyrrolidine-1-carboxylate 5b.**



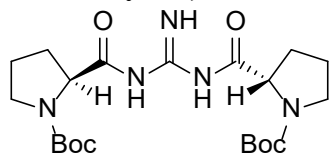
Chemical Formula: C<sub>19</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>

Exact Mass: 390.1903

Molecular Weight: 390.4400



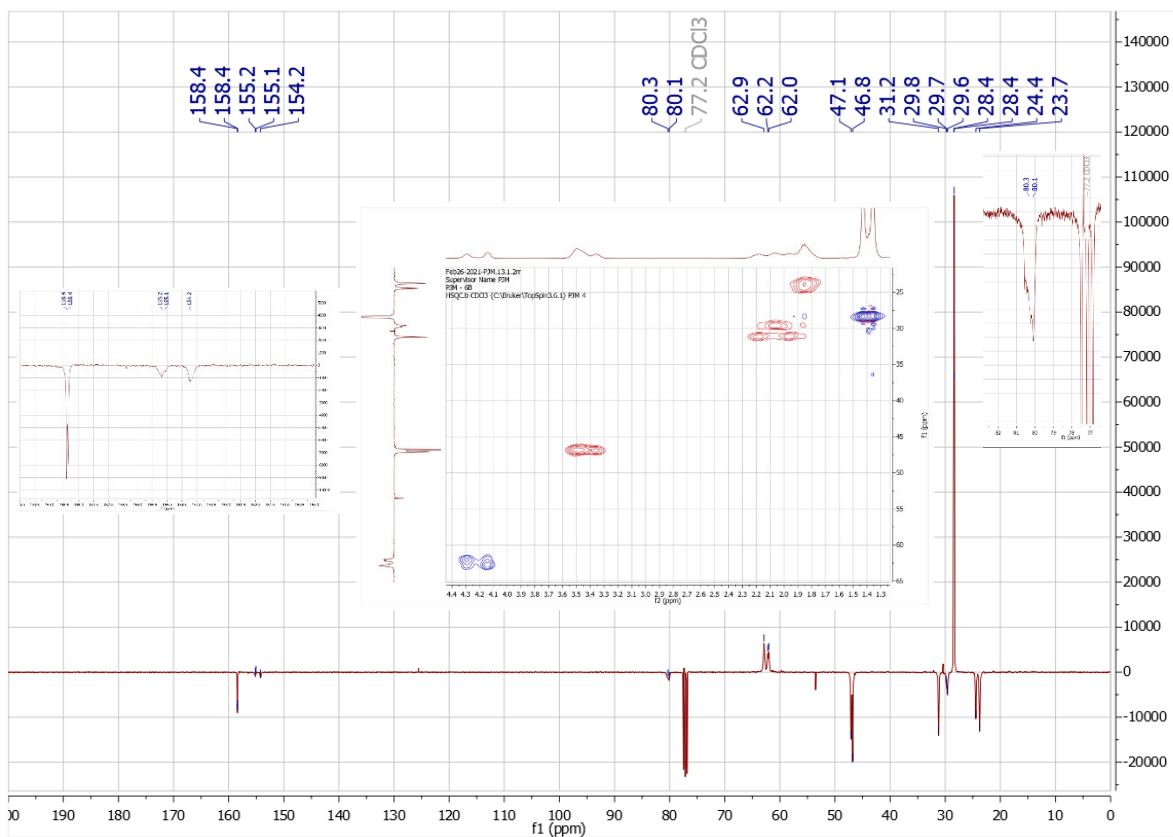
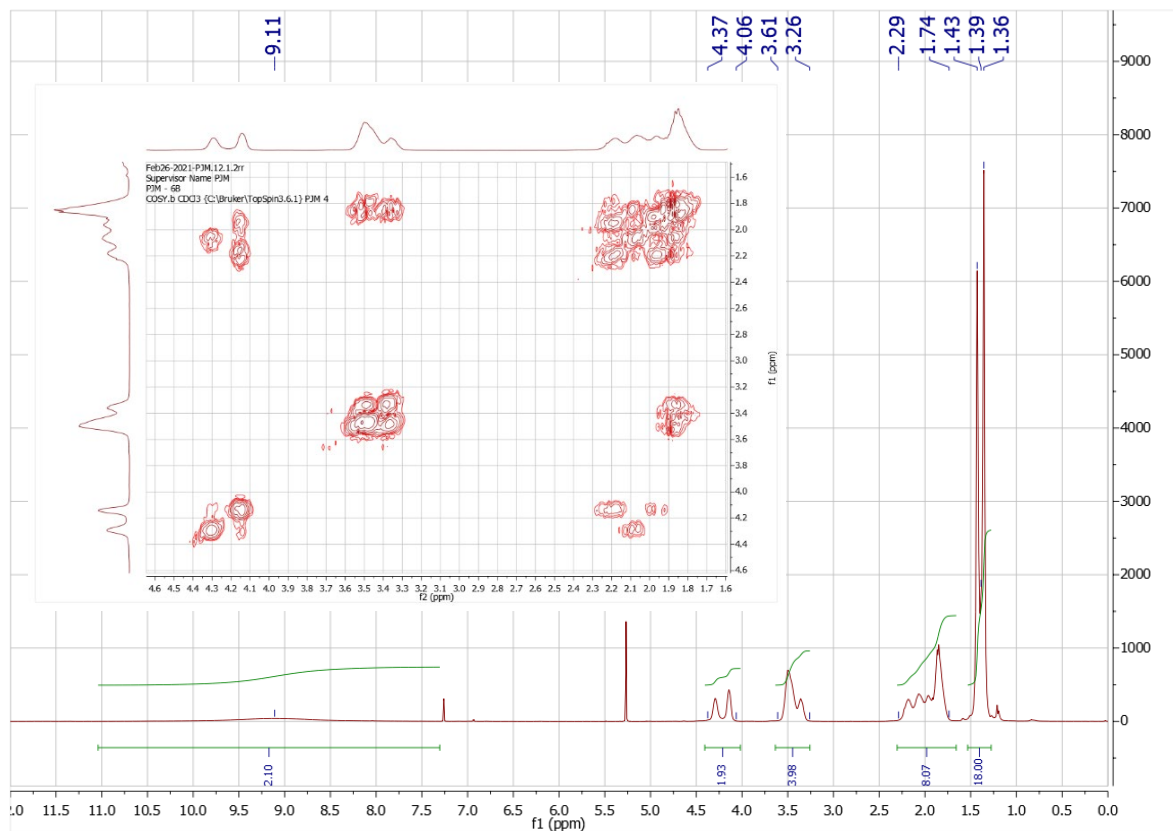
**Di-tert-butyl 2,2'-(((iminomethylene)bis(azanediyl))bis(carbonyl))(2*S*,2'*S*)-bis(pyrrolidine-1-carboxylate) 6b.**



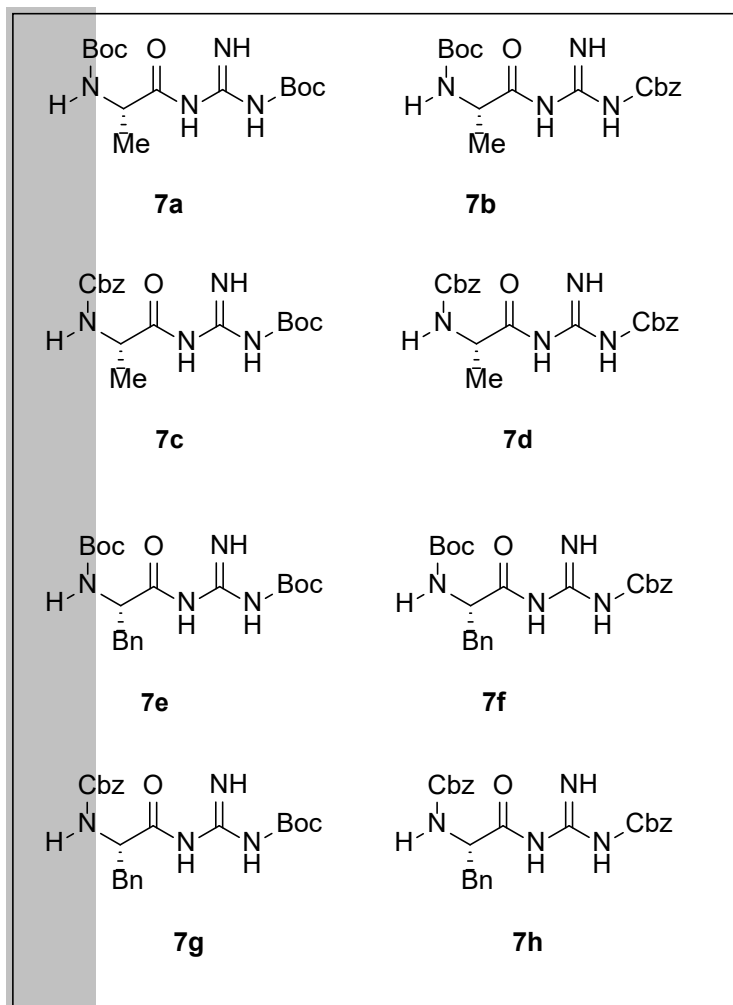
Chemical Formula: C<sub>21</sub>H<sub>35</sub>N<sub>5</sub>O<sub>6</sub>

Exact Mass: 453.2587

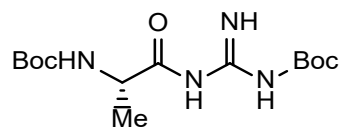
Molecular Weight: 453.5400



*N*-Cbz-, *N*-Boc-L-alanine and *N*-Cbz-, *N*-Boc-L-phenylalanine catalysts.



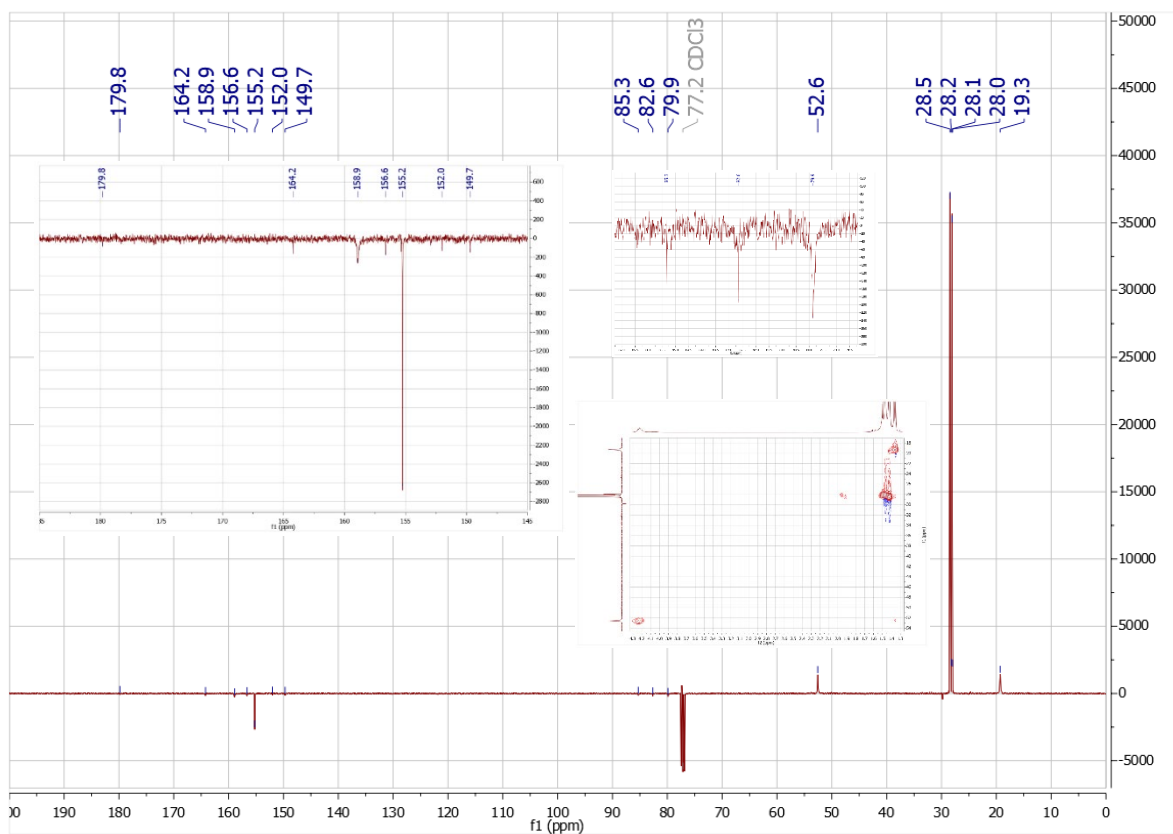
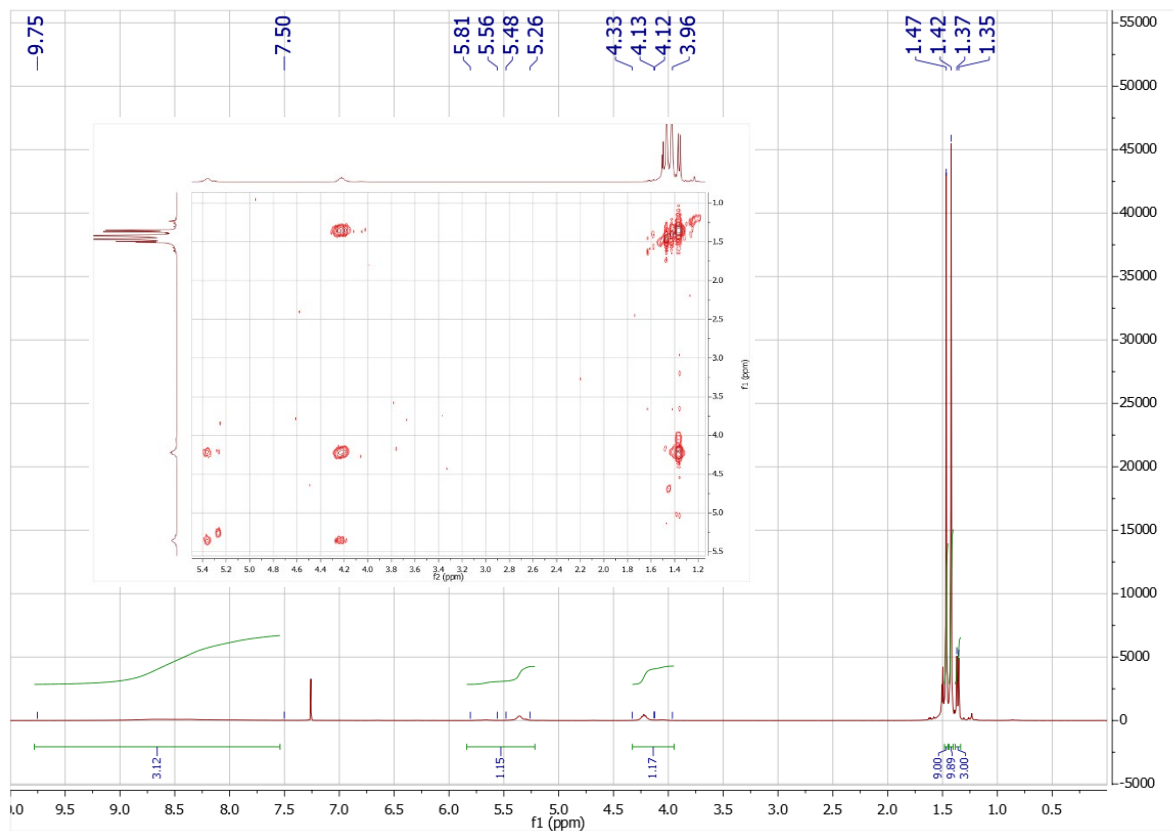
***tert*-Butyl (*S*)-1-(3-(*tert*-butyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7a.**



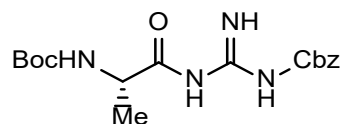
Chemical Formula: C<sub>14</sub>H<sub>26</sub>N<sub>4</sub>O<sub>5</sub>

Exact Mass: 330.19

Molecular Weight: 330.39



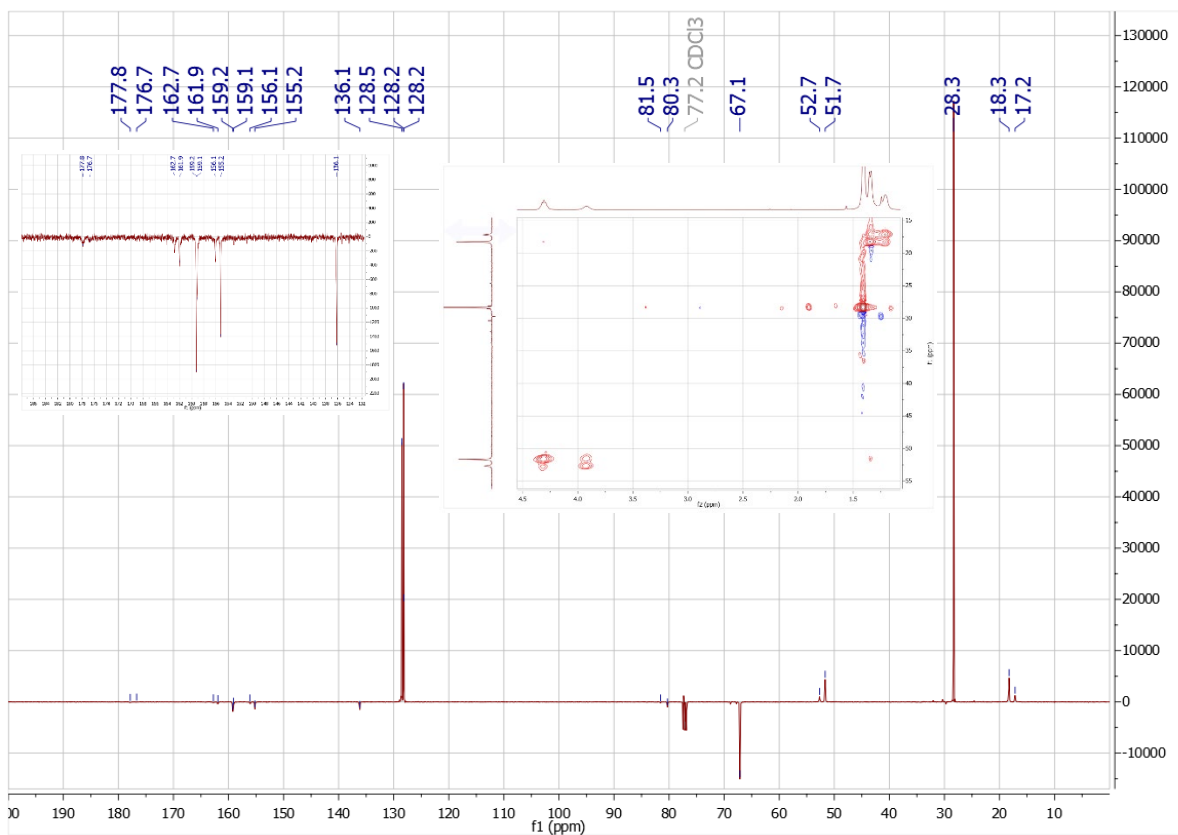
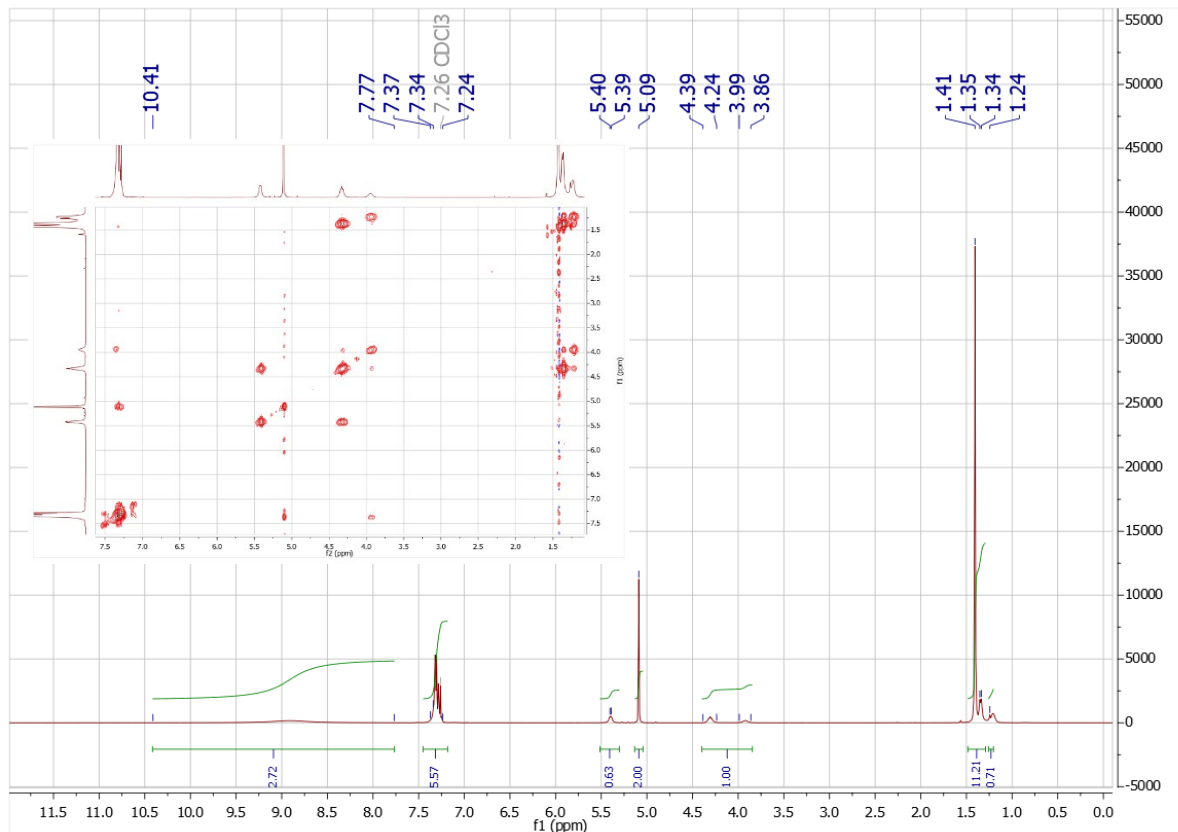
**tert-Butyl (S)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7b.**



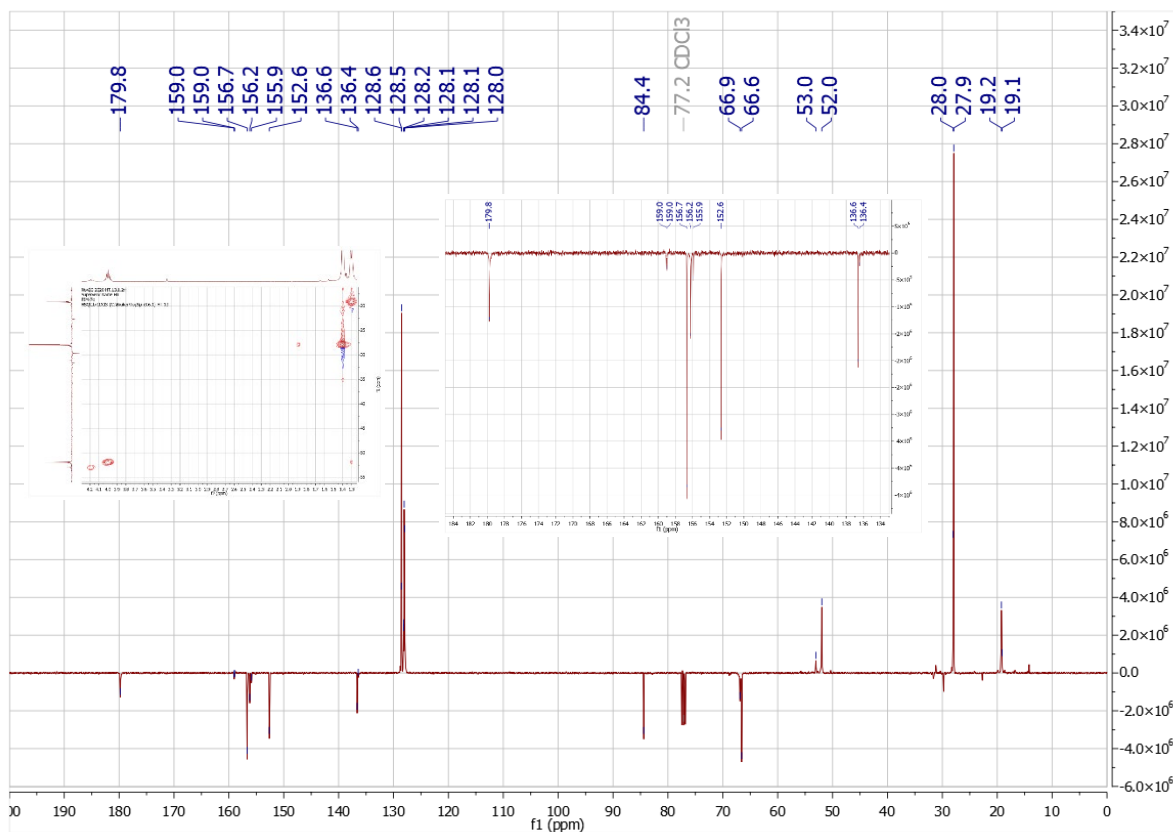
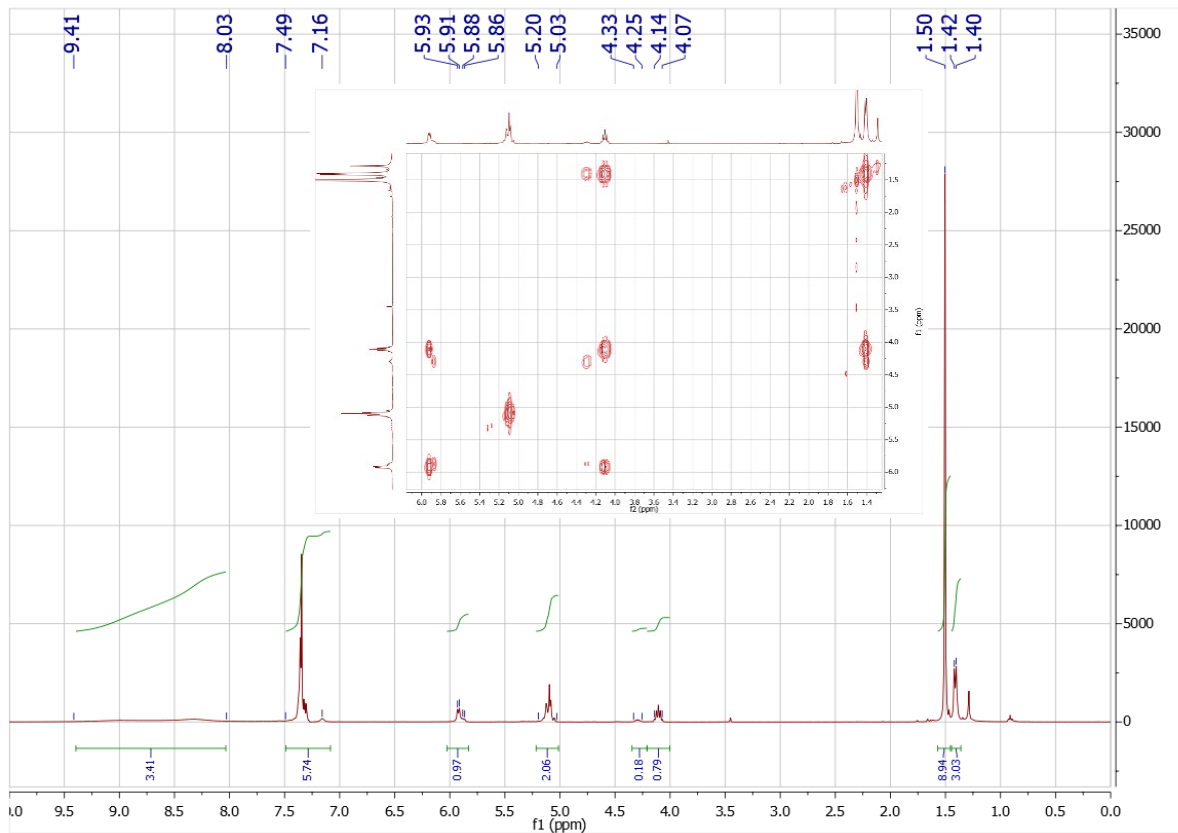
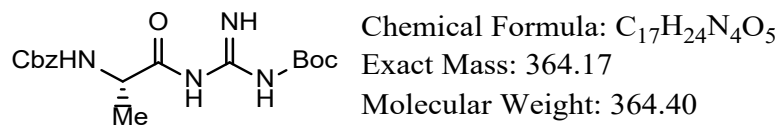
Chemical Formula: C<sub>17</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>

Exact Mass: 364.17

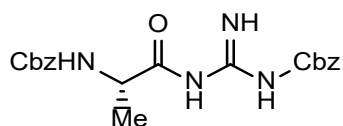
Molecular Weight: 364.40



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



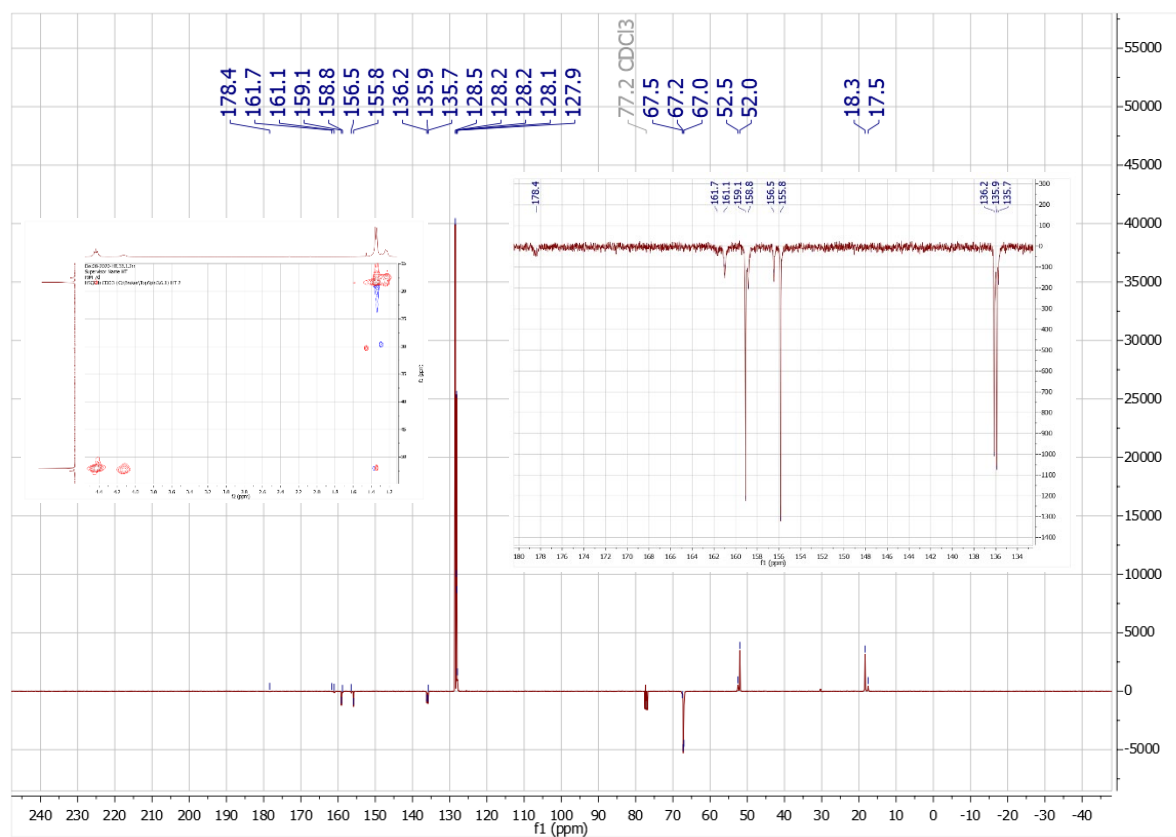
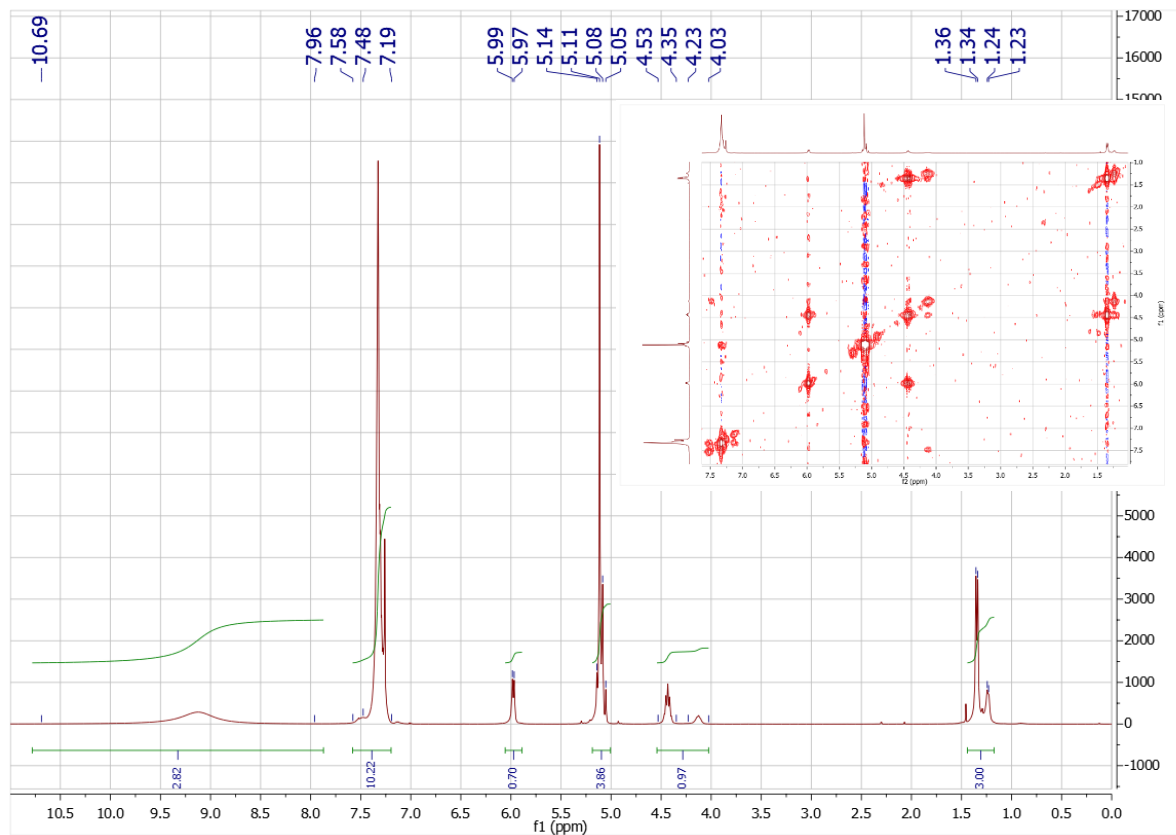
**Benzyl (S)-1-(3-(benzyloxycarbonyl)guanidino)-1-oxopropan-2-yl)carbamate 7d.**



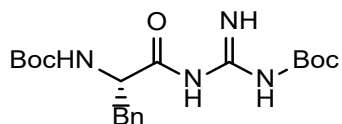
Chemical Formula:  $C_{20}H_{22}N_4O_5$

Exact Mass: 398.16

Molecular Weight: 398.42



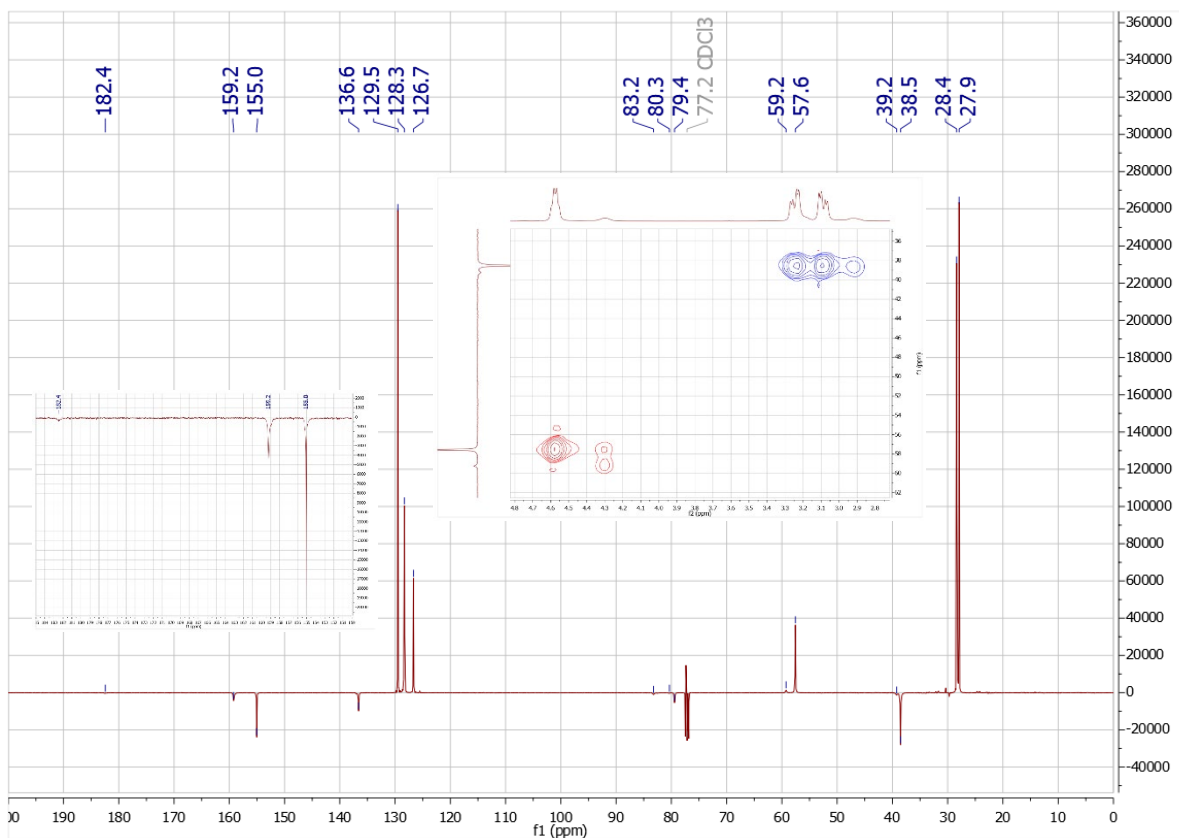
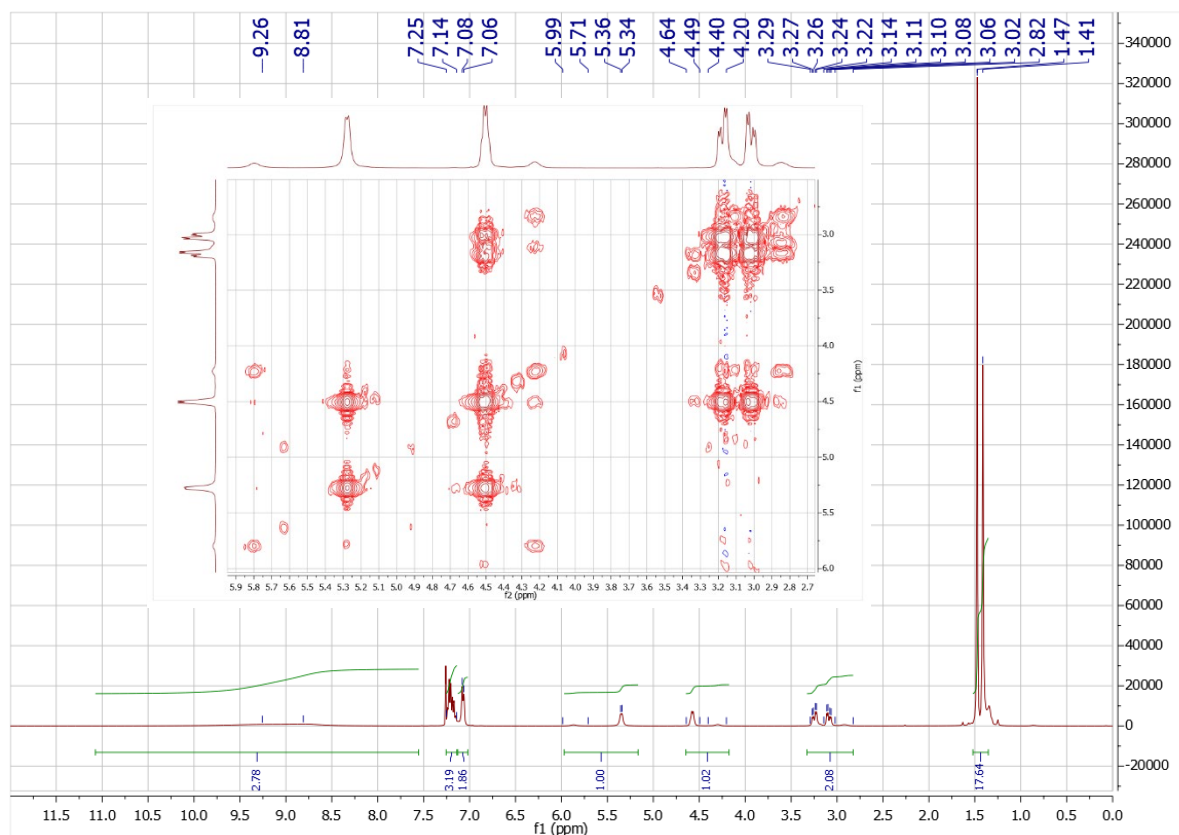
***tert*-Butyl (*S*)-1-(3-(*tert*-butyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate **7e**.**



Chemical Formula: C<sub>20</sub>H<sub>30</sub>N<sub>4</sub>O<sub>5</sub>

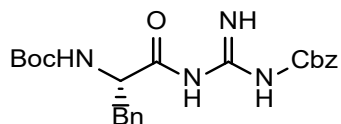
Exact Mass: 406.22

Molecular Weight: 406.48





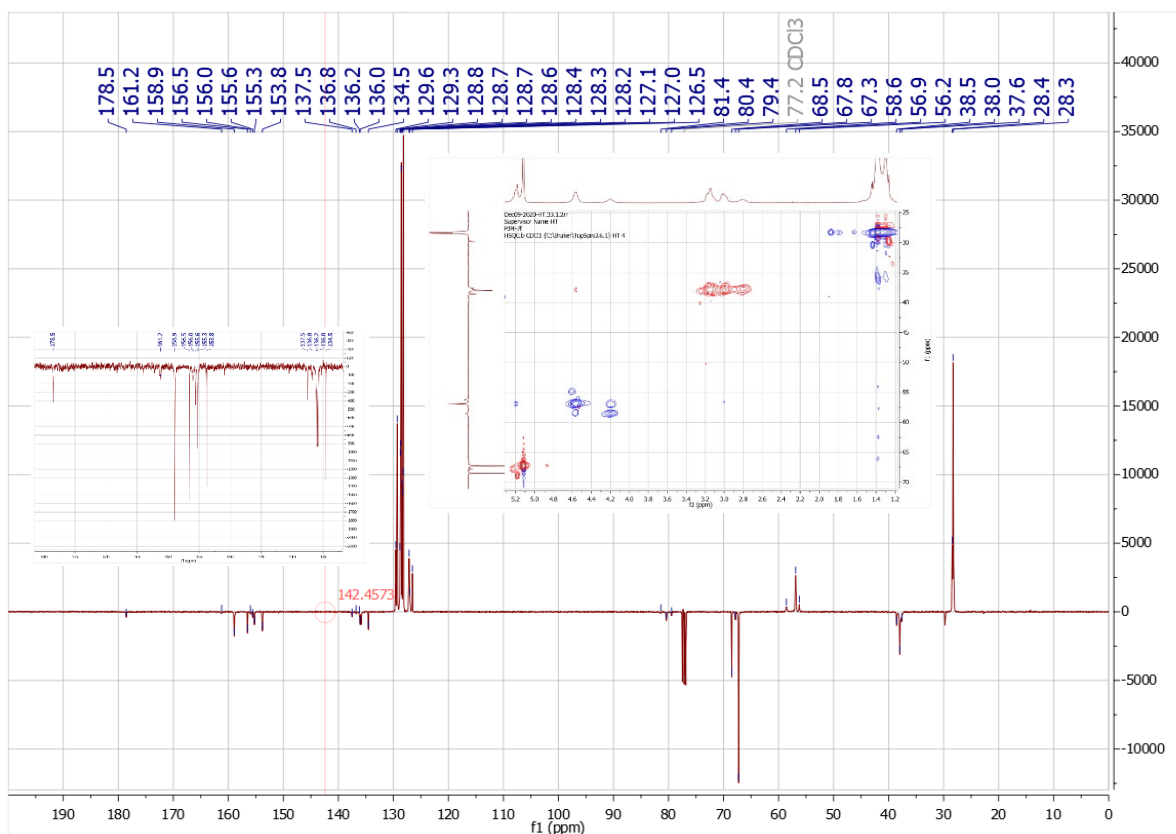
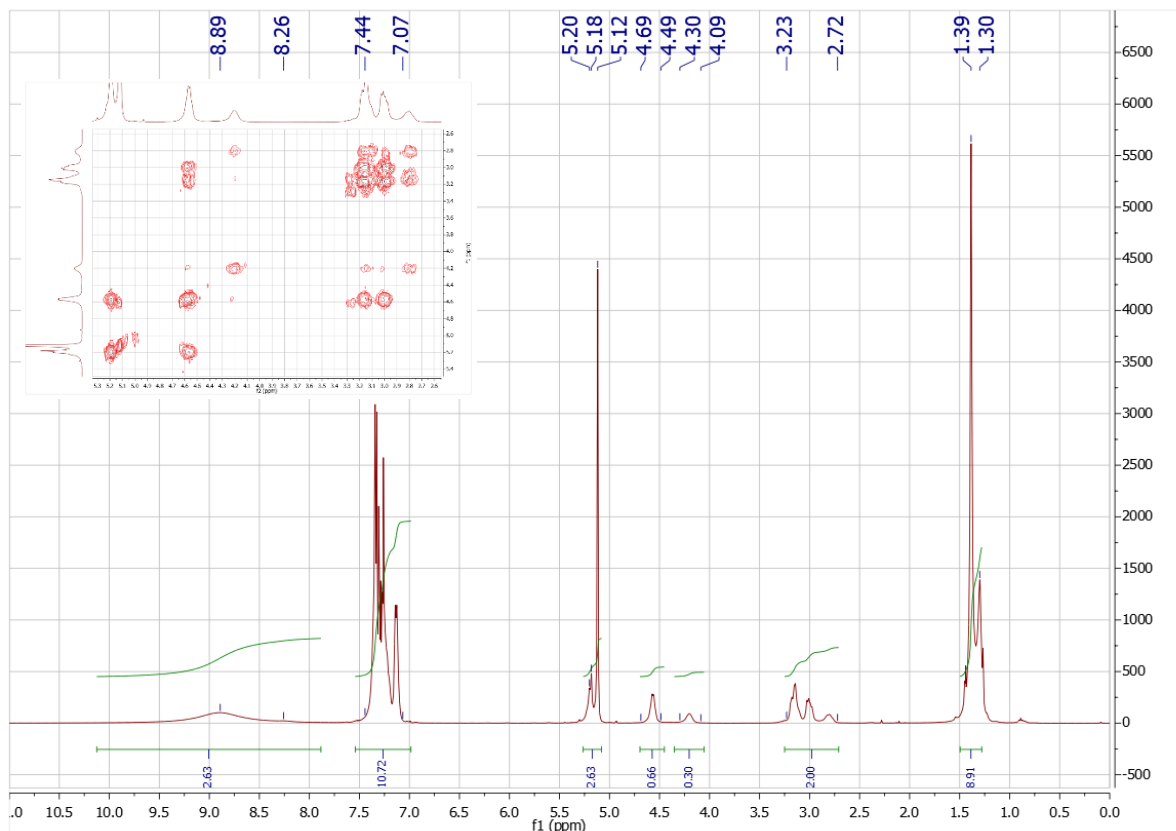
***tert*-butyl (*S*)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7f.**



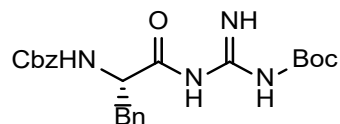
Chemical Formula:  $C_{23}H_{28}N_4O_5$

Exact Mass: 440.2060

Molecular Weight: 440.5000



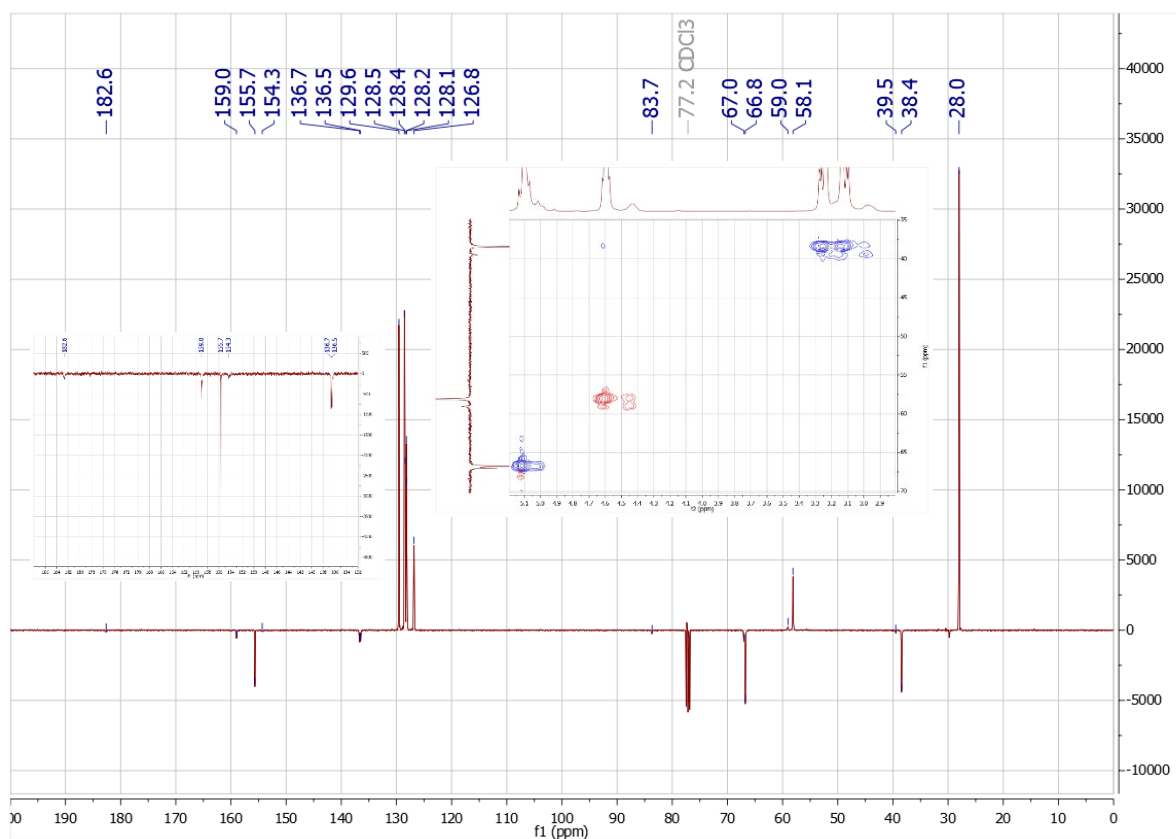
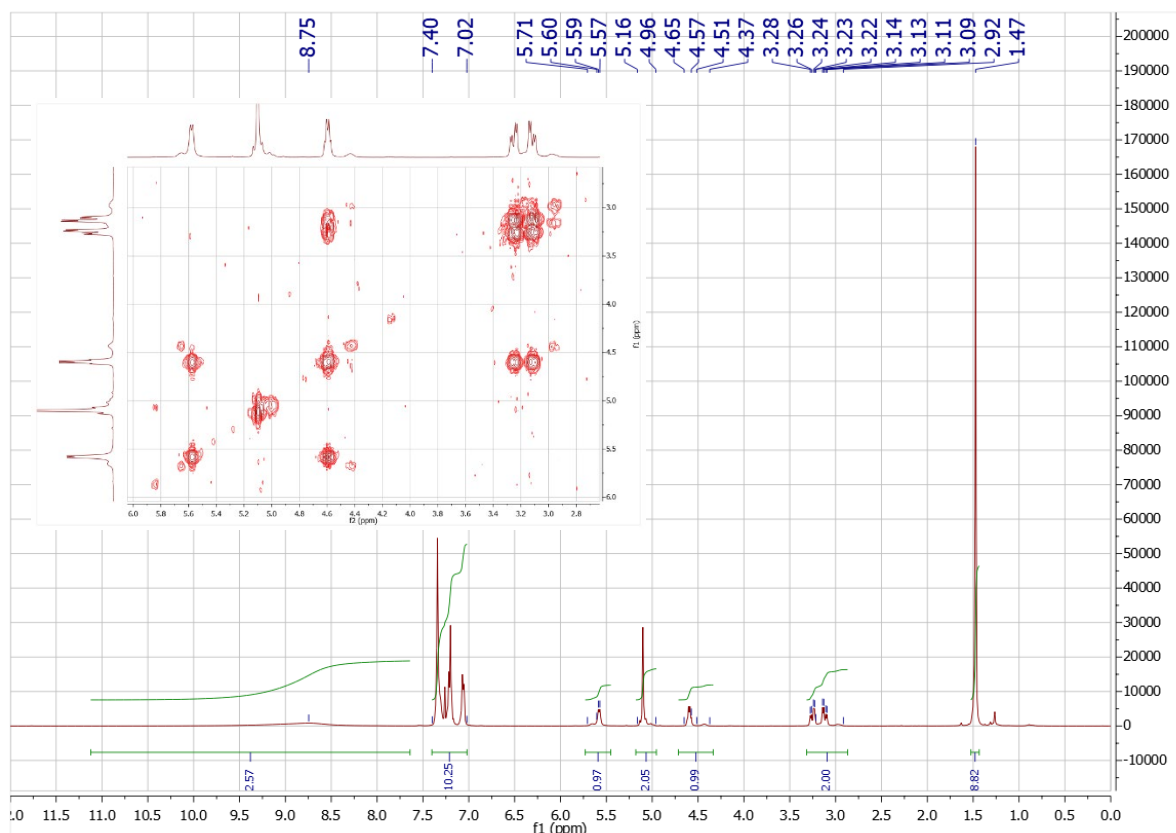
**Benzyl (S)-1-(3-(tert-butyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate 7g.**



Chemical Formula:  $C_{23}H_{28}N_4O_5$

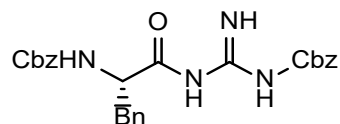
Exact Mass: 440.21

Molecular Weight: 440.50



# Benzyl (S)-(1-(3-(benzyloxycarbonyl)guanidino)-1-oxo-3-phenylpropan-2-yl)carbamate

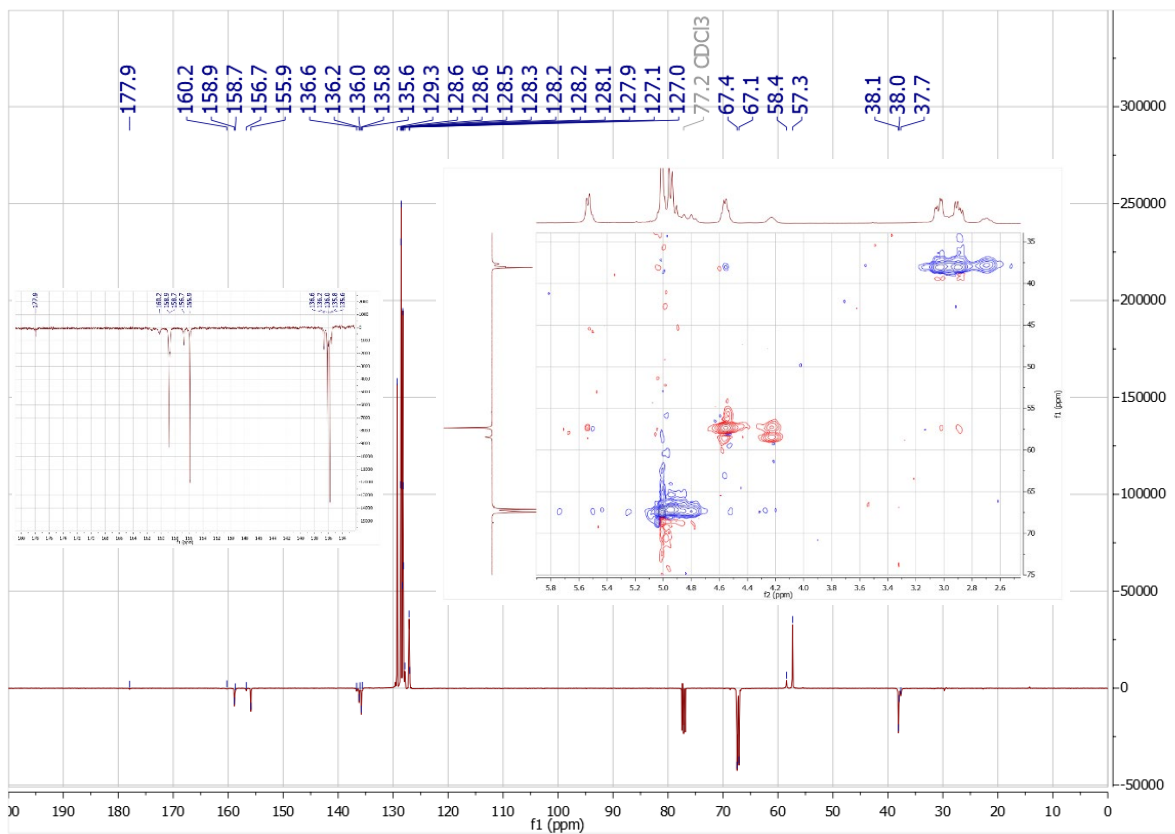
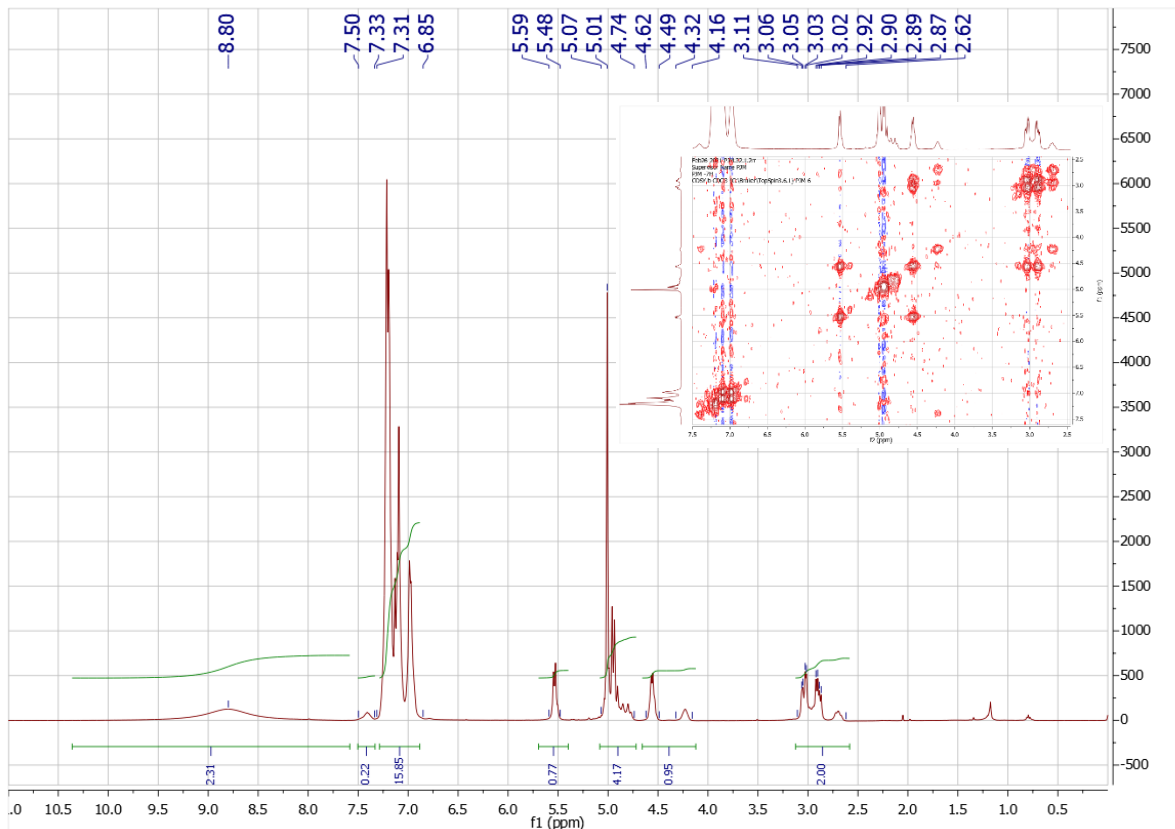
7h.



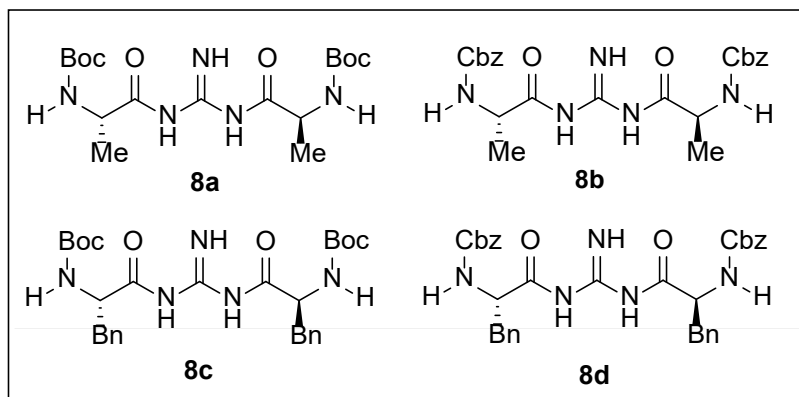
Chemical Formula:  $C_{26}H_{26}N_4O_5$

Exact Mass: 474.19

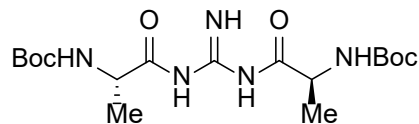
Molecular Weight: 474.52



**N-Cbz- and N-Boc-L-alanine and L-phenylalanine C<sub>2</sub>-symmetric catalysts.**



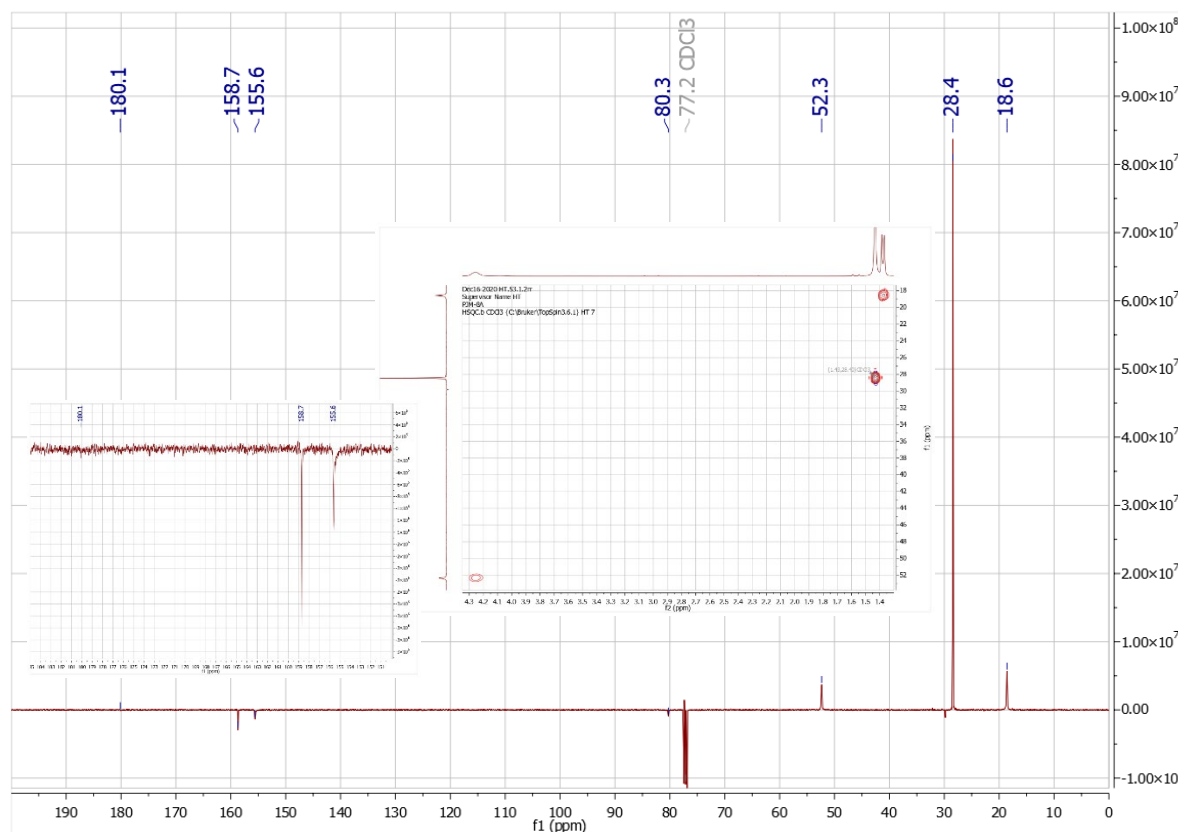
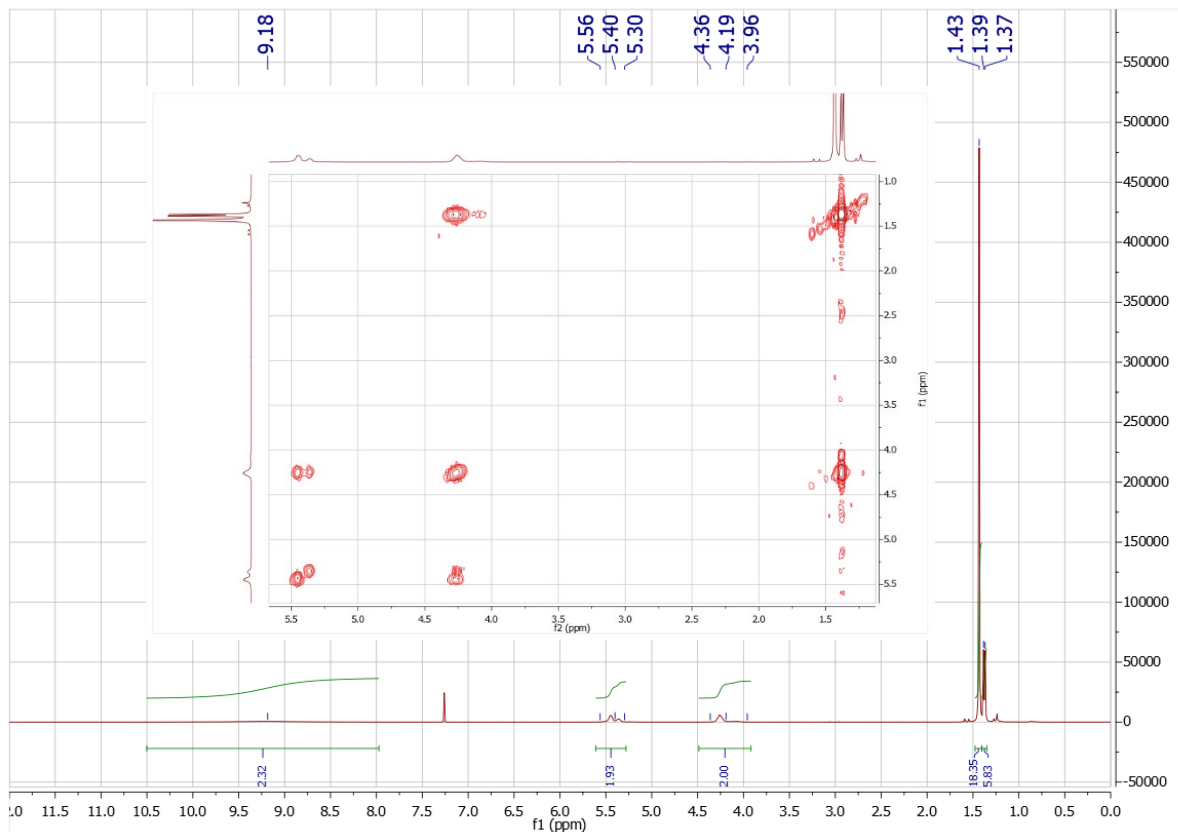
**Di-*tert*-butyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediyl))bis(1-oxopropane-1,2-diyl))dicarbamate 8a.**



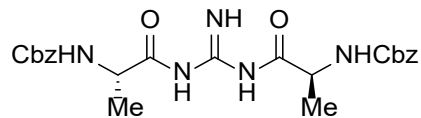
Chemical Formula: C<sub>17</sub>H<sub>31</sub>N<sub>5</sub>O<sub>6</sub>

Exact Mass: 401.2274

Molecular Weight: 401.4640



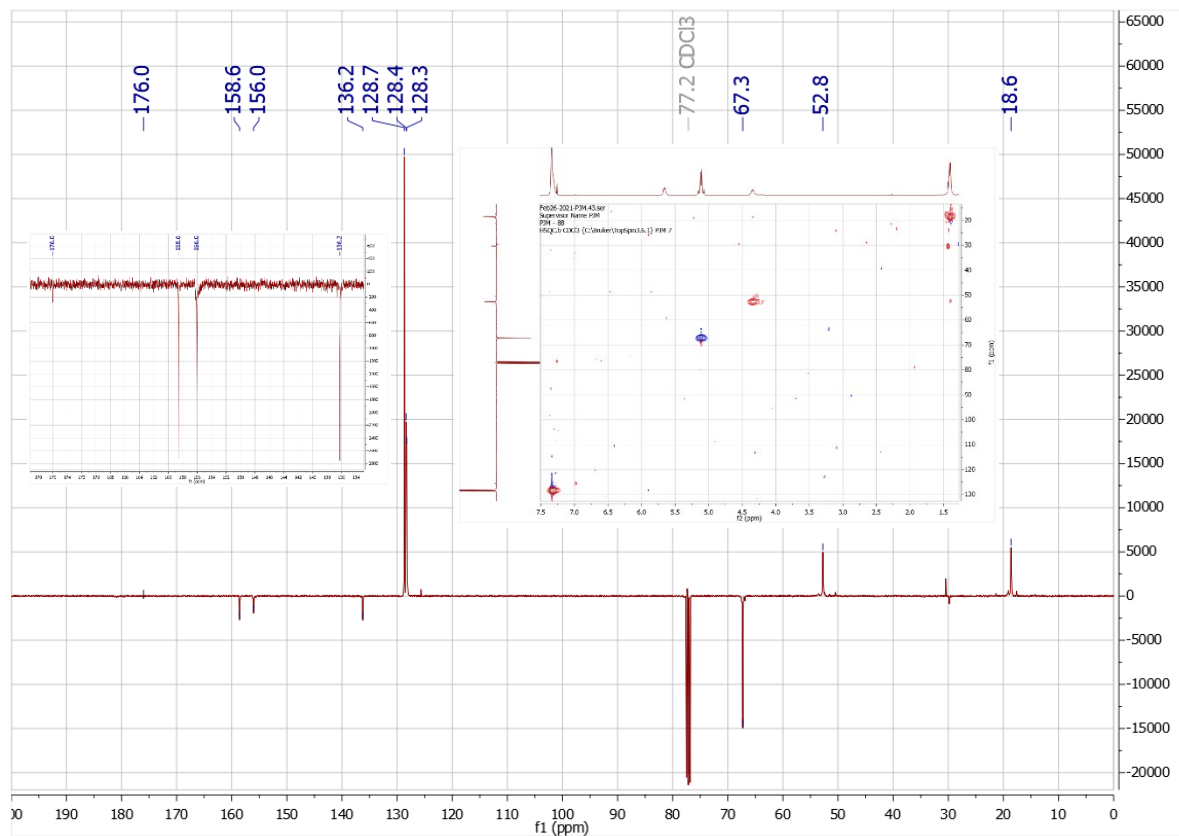
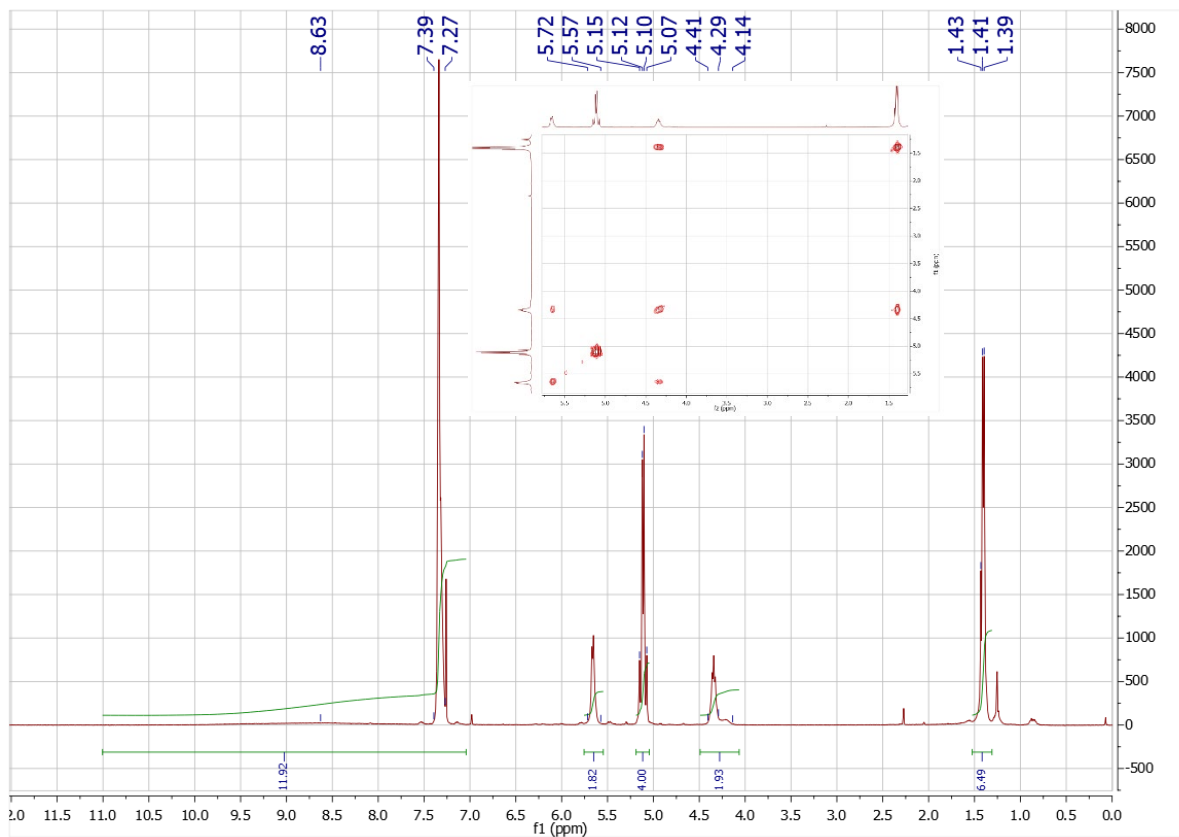
**Dibenzyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediy))bis(1-oxopropane-1,2-diyl))dicarbamate 8b.**



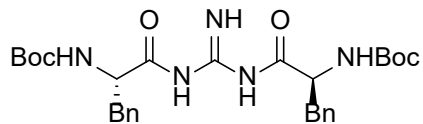
Chemical Formula: C<sub>23</sub>H<sub>27</sub>N<sub>5</sub>O<sub>6</sub>

Exact Mass: 469.1961

Molecular Weight: 469.4980



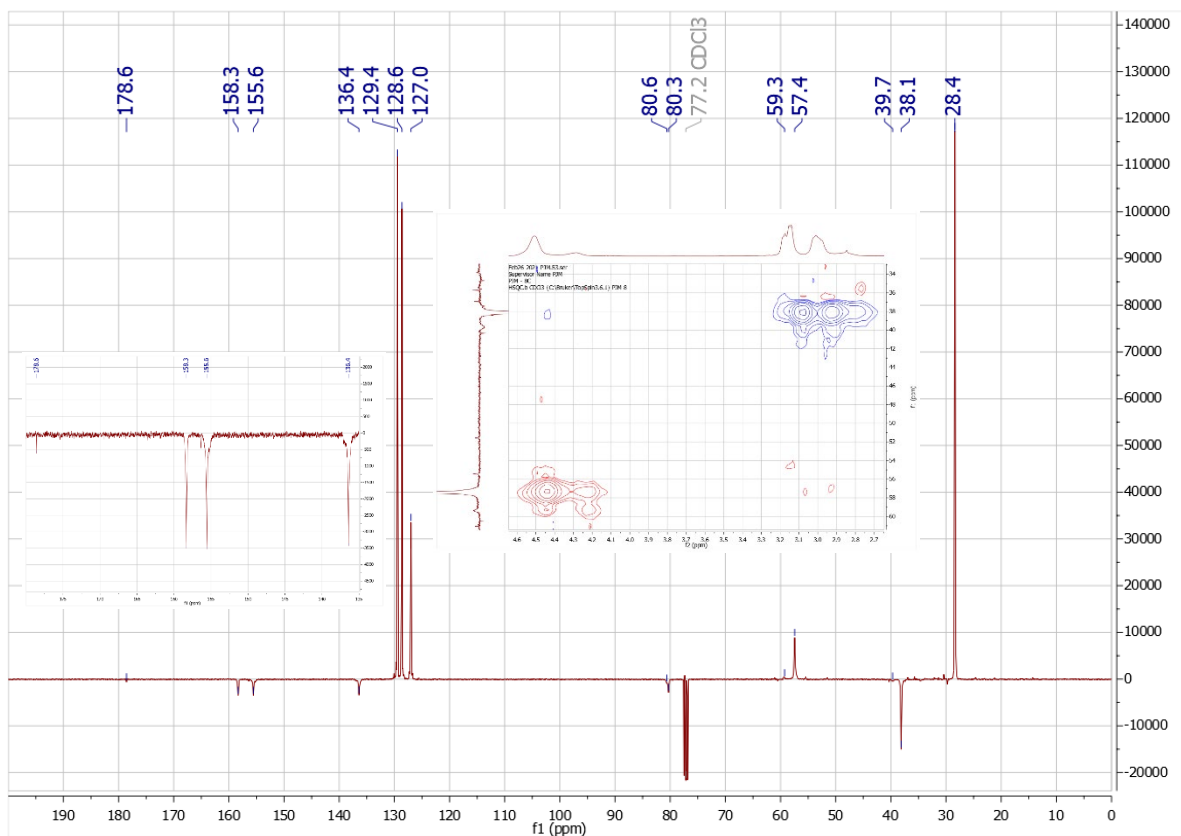
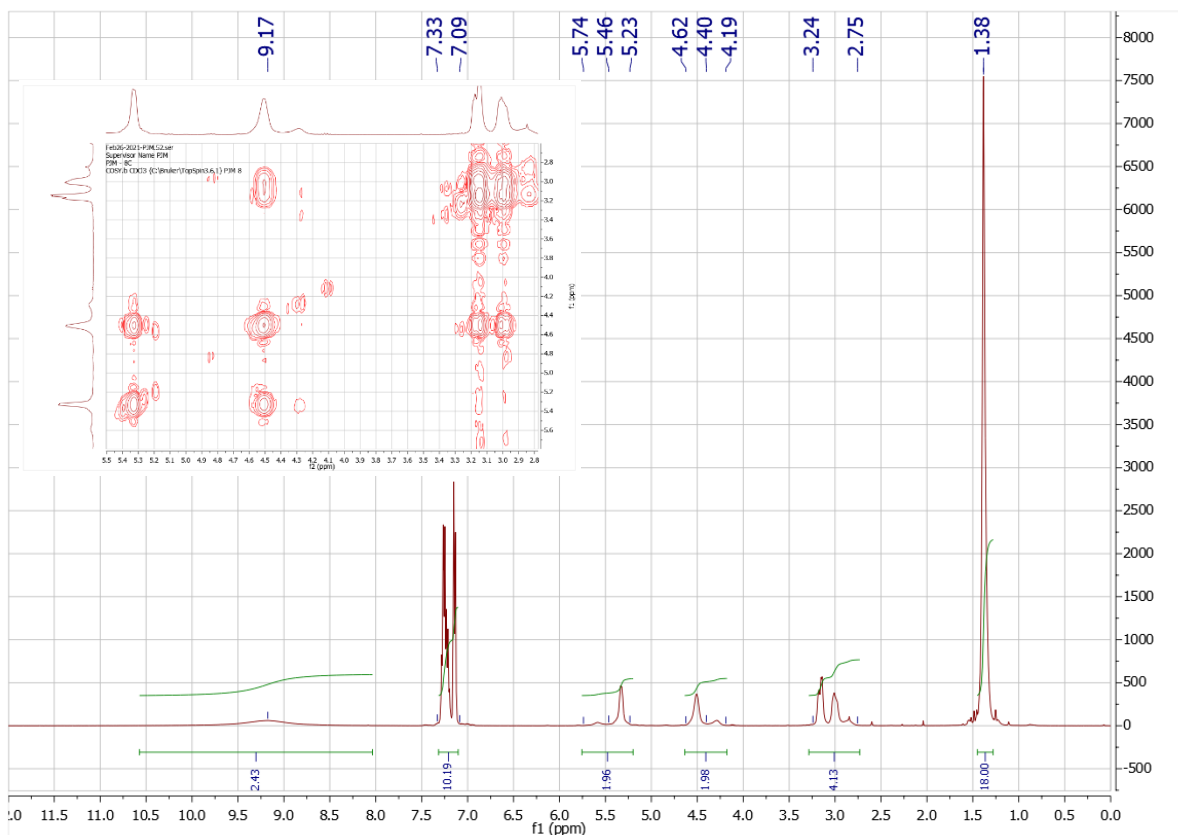
**Di-tert-butyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediy))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 8c.**



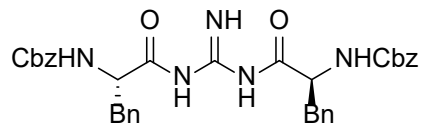
Chemical Formula: C<sub>29</sub>H<sub>39</sub>N<sub>5</sub>O<sub>6</sub>

Exact Mass: 553.2900

Molecular Weight: 553.6600



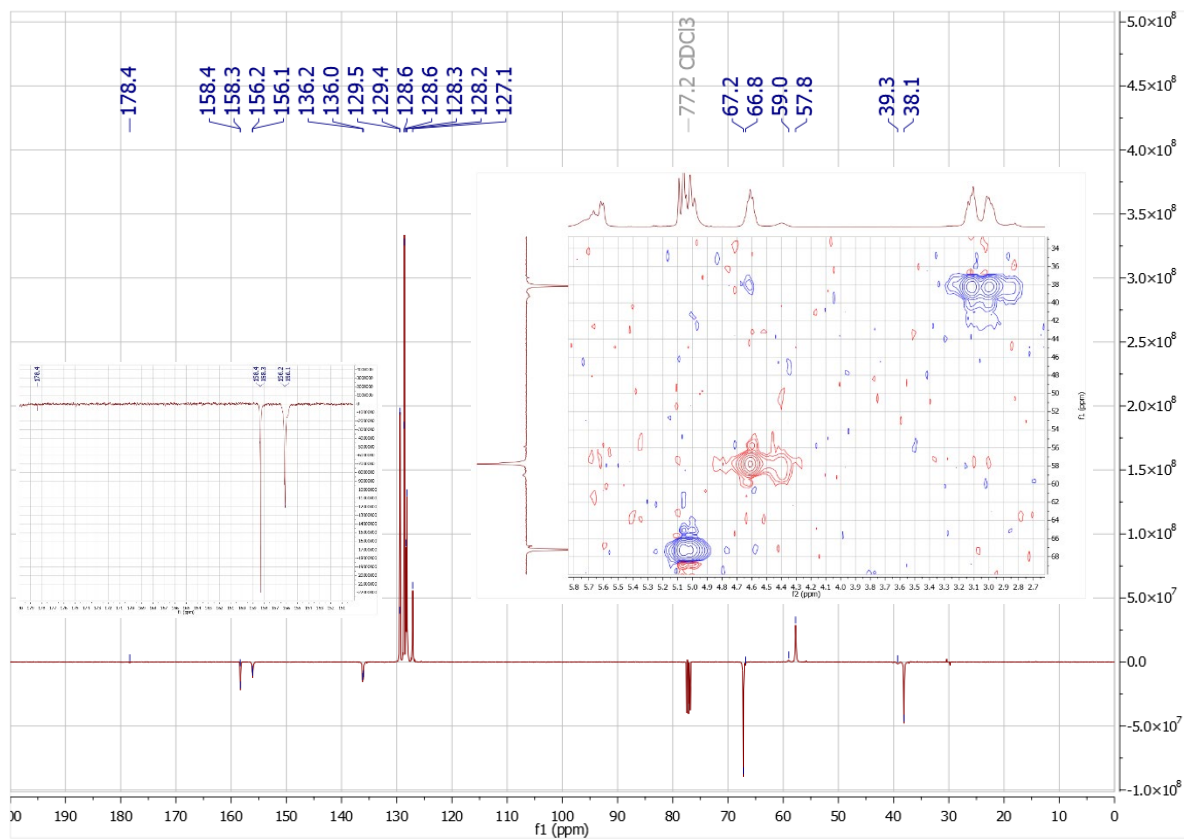
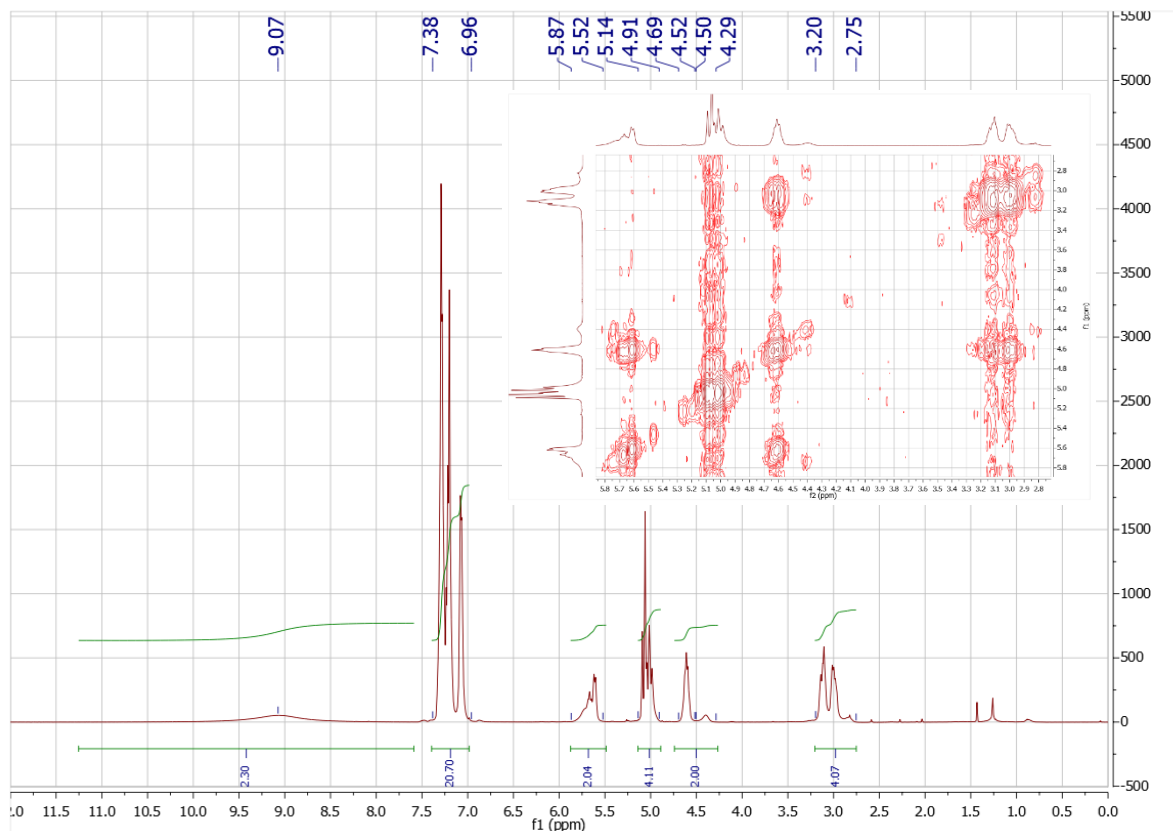
**Dibenzyl ((2*S*,2'*S*)-((iminomethylene)bis(azanediyl))bis(1-oxo-3-phenylpropane-1,2-diyl))dicarbamate 8d.**



Chemical Formula: C<sub>35</sub>H<sub>35</sub>N<sub>5</sub>O<sub>6</sub>

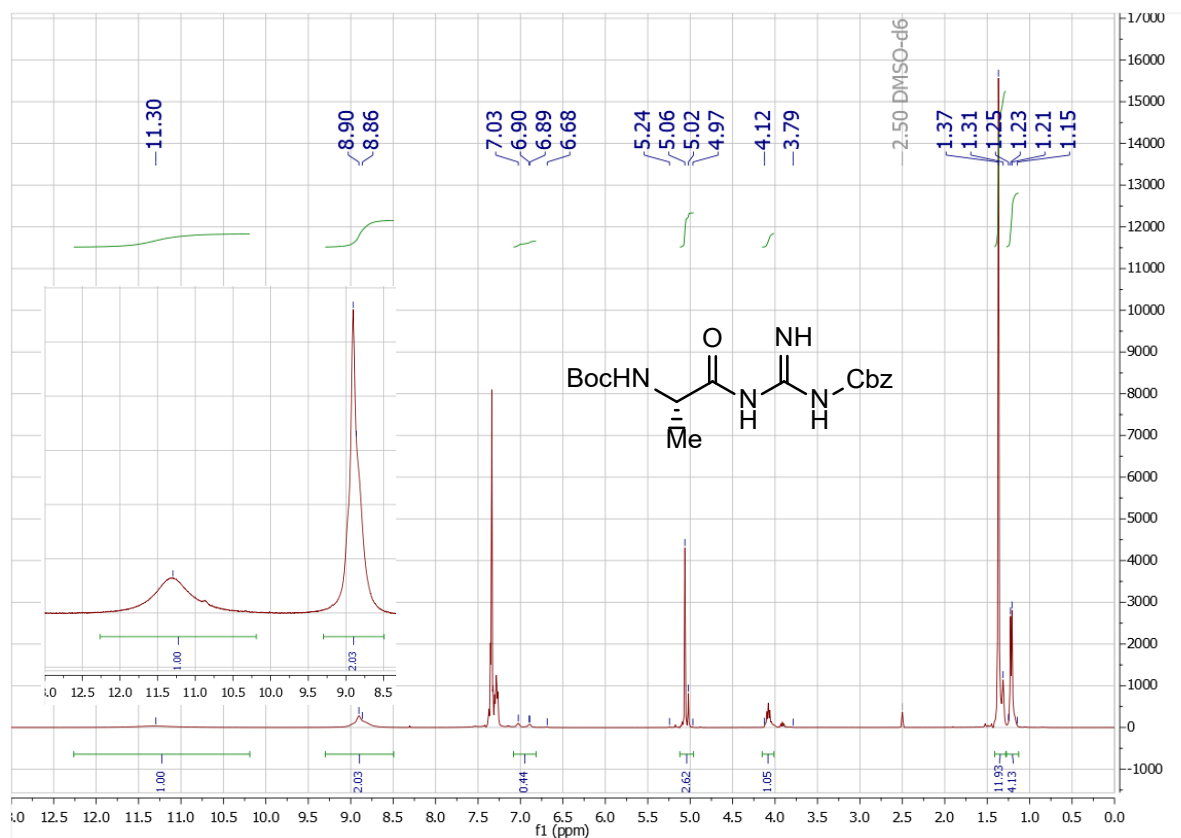
Exact Mass: 621.2587

Molecular Weight: 621.6940





<sup>1</sup>H NMR spectrum of 7b in DMSO-d6.



<sup>1</sup>H NMR spectrum of 7f in DMSO-d6.

