

Synthesis and application of L-serine derivative ligands in Diels-Alder reaction between CPD and methyl acrylate

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Abstract

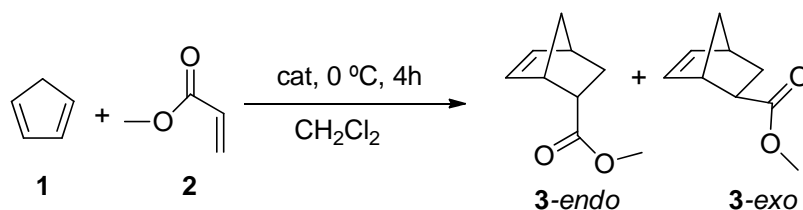
New L-serine derivative ligands were prepared and tested as co-catalyst in the Diels-Alder reactions between cyclopentadiene (CPD) and methyl acrylate in the presence of several Lewis acids. The catalytic potential of the *in situ* formed complexes was evaluated based on the reaction yield. Bidentate serine ligands showed good ability to coordinate medium strength Lewis acids, thus boosting their catalytic activity. The synthesis of the L-serine ligands proved to be highly efficient and straightforward. Silylated serines were also prepared for posterior grafting onto inorganic materials for application in heterogeneous catalysis.

1. Introduction

The synthesis of bicyclic compounds has detained large significance due to their use as synthetic intermediates in the preparation of a vast variety of compounds of chemical, biological, and pharmaceutical interest.[1-2] The most efficient and widely used method for the preparation of bicyclic compounds is the Diels-Alder reaction. Generally, activation by an electron-withdrawing group and a Lewis acid is required in order to achieve good conversion rates.

The acid catalyzed Diels-Alder reactions, namely between cyclopentadiene (CPD) and acrylates, is well documented,[1,3-15] the most important used Lewis acids being Al(III), Fe(III) or boron complexes. The use of such strong acids is needed because ester dienophiles (as acrylate ones) are not very reactive.[15-16] Depending on the reactions, the solvent used is also a factor to consider regarding both the Lewis acid solubility and the reaction media's polarity, the most common being dichloromethane.

In this work, we studied the use of moderate strength Lewis acids as catalysts for Diels-Alder reaction between CPD (**1**) and methyl acrylate (**2**) in dichloromethane (scheme 1), by complexing insoluble metal ions with novel L-serine derivative ligands, as alternative of the usual strong Lewis acids.



Scheme 1. Lewis acid catalyzed Diels-Alder reaction between CPD (**1**) and methyl acrylate (**2**).

2. Results and discussion

The work started with the study of several Lewis acids tested as catalysts in the Diels-Alder reaction between CPD (**1**) and methyl acrylate (**2**) using dichloromethane as solvent; the results are summarized in table 1, as well as the reaction conditions.

Table 1. Results of the Diels-alder reaction between **1** and **2**, yield and *endo/exo* ratio of adduct **3**.

entry	catalyst	reaction time / h	η / %	<i>endo/exo</i> ratio ^c
1	-	4	-	-
2	AlCl ₃		87	95/5
3	AlMe ₃		70	93/7

4	FeCl ₃		75	95/5
5	TiCl ₄		80	94/6
6	SnCl ₄		67	94/6
7	Cu(OTf) ₂		35	98/2
8	ZnI ₂		11	94/6
9	Cu(OTf) ₂ ^a	20	38	85/15
10	ZnI ₂ ^a		16	92/8
11	Cu(OTf) ₂ ^b	2	32	94/6
12	AlCl ₃	20	53	91/9

The reactions were performed with 10 % of catalyst, at 0 °C in dichloromethane, except in the mentioned cases. *a*- 0 °C to room temp.; *b*- 30 % of catalyst; *c*- measured by ¹H-NMR;

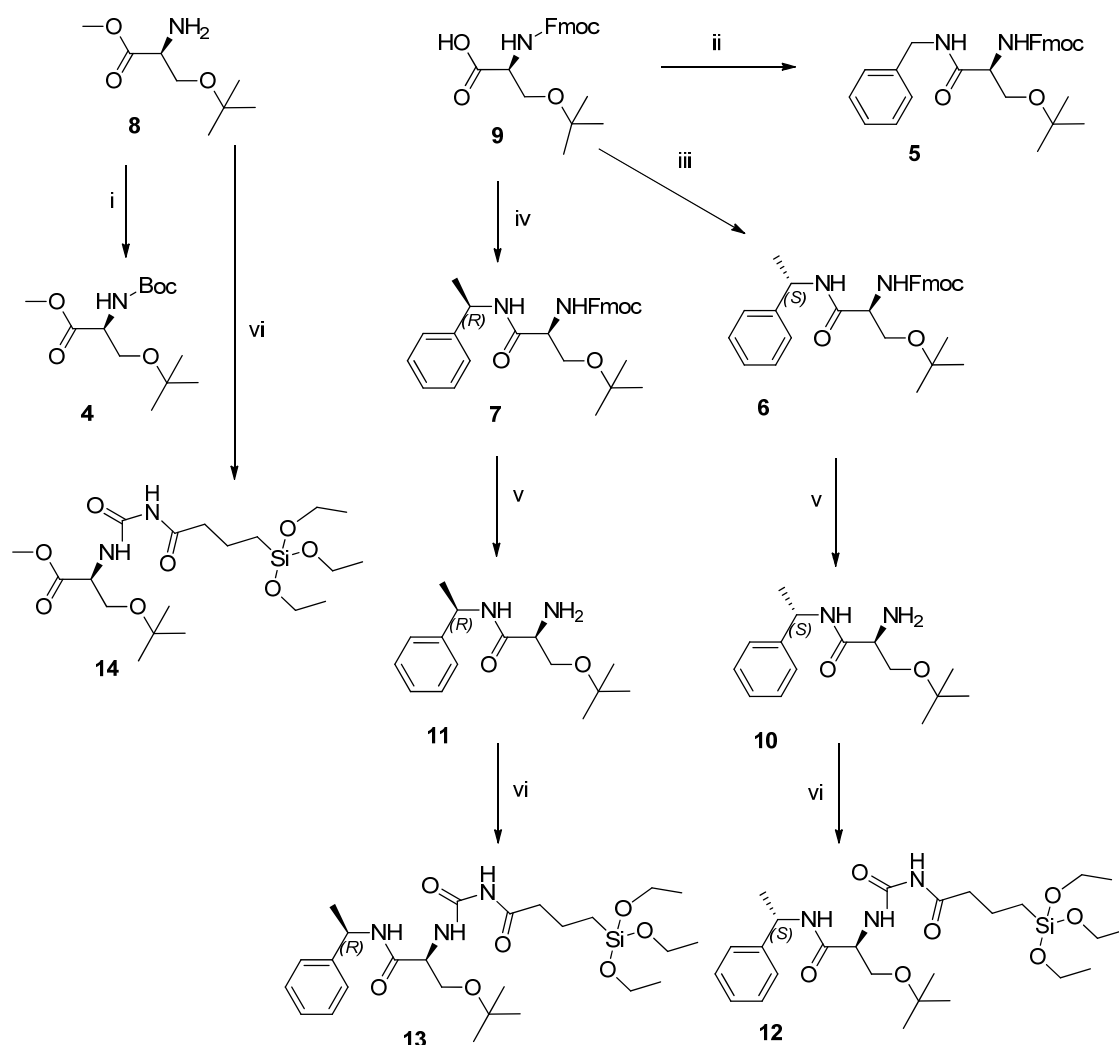
As expected, in the absence of catalyst the reaction did not take place (entry 1). It is noteworthy the correlation observed between the Lewis acid strength and the yield of the reaction: the best results were achieved when the stronger Lewis acids AlCl₃, FeCl₃ and TiCl₄ were employed (entries 2, 4 and 5, respectively). On comparison to AlCl₃, a slight decrease in the reaction yield was observed when AlMe₃ was used (entry 3). SnCl₄ originated a lower yield than the previous mentioned strong Lewis acids (entry 6). For Cu(OTf)₂ and ZnI₂, which are moderate Lewis acids, the yields were quite low (entries 7, 8); nevertheless, their poor solubility in the solvent used (dichloromethane) may also explain these results. The increasing of the reaction time (entries 9, 10) and of the amount of catalyst employed (entry 11) did not significantly changed the results in terms of yield. In fact, similar results were observed in a previous work comprising the catalytic cycloaddition reaction between CPD and methyl glyoxylate oxime.[17] It is possible, however, that the increasing of reaction time when strong acids were used decreased the yield of Diels-Alder reactions, probably due to decomposition of the final adduct (entry 12).[17-18]

Considering this, we synthesized new L-serine derivative ligands as inexpensive ligands for application on the Diels-Alder reactions. Serine has two major advantages for this purpose: is cheap and readily available and has three functional groups that may be easily functionalized, thus allowing chemical and structural design. In fact, serine was earlier used for other purposes as evaluation as ligand for complex formation with Cd(II), complexation with Cu(II) for antibacterial studies and used as recyclable catalyst for asymmetric aldol reactions.[19-21] In this work, L-serine derivative ligands were designed and used to coordinate the Lewis acids, in order to form *in situ* metal

complexes that would be more soluble in dichloromethane than the original Lewis acids. In this context, only Cu(II) and Zn(II) salts (Cu(OTf)₂ and ZnI₂) were considered in the catalytic reaction. In fact, complexes of Zn(II) and Cu(II) are widely used as Lewis acids in Diels-Alder reactions.[1]

The chemical structures of the prepared L-serine derivative ligands **4-14** either from **8** or **9** (commercially available) are depicted in scheme 2. Ligand **4** was effectively obtained by protecting the amine group of serine **8** with Boc; ligands **5-7** were prepared in excellent yields by reacting the respective amine with serine **9** in the presence of DIPEA and TBTU. After removing the Fmoc group from serines **6/7**, the resultant amines, as well as **8**, were efficiently silylated with 3-(triethylsilyl)propyl isocyanate, affording serines **12-14**.

The Diels-Alder reaction represented in scheme 1 was then tested in the presence of the ligands **4-14** and the results are summarized in table 2. The reaction conditions were those represented in scheme 1, except in the indicated cases.



Scheme 2. L-serine derivative ligands used in the Diels-Alder reaction between **1** and **2**. Reagents and conditions: *i*- Boc₂O, CH₂Cl₂, r.t., 2 h, *ii*- benzylamine, DIPEA, TBTU, CH₂Cl₂, r.t., 2 h, 99%; *iii*- (S)-1-phenylethylamine, DIPEA, TBTU, CH₂Cl₂, r.t., 2 h,

100%; *iv*- (*R*)-1-phenylethylamine, DIPEA, TBTU, CH₂Cl₂, r.t., 2 h, 100%; *v*- piperidine, DMF, room temp. 2 h, 100 %; *vi*- OCN(CH₂)₃Si(OEt)₃, CH₂Cl₂, reflux, overnight, 90-98 %.

Table 2. Results of the Diels-alder reaction between **1** and **2**, yield, *endo/exo* ratio of adduct **3** and enantiomeric excess (e.e.).

entry	catalyst	ligand	reaction time / h	η / %	<i>endo/exo</i> ratio ²	e.e. / % ³
1	AlCl ₃	8	4	traces	-	-
2	FeCl ₃	8	4	< 5	-	-
3	Cu(OTf) ₂ ¹	8	20	-	-	-
4	Cu(OTf) ₂ ¹	4	20	< 5	-	-
5	Cu(OTf) ₂ ¹	9	20	31	90/10	< 1
6	Cu(OTf) ₂ ¹	5	20	59	82/18	< 1
7	ZnI ₂	5	4	23	87/13	< 1
8	ZnI ₂ ¹	5	20	58	87/13	< 1
9	Cu(OTf) ₂ ¹	6	20	21	86/14	12 (<i>R</i>)
10	ZnI ₂ ¹	6	20	30	83/17	24 (<i>R</i>)
11	Cu(OTf) ₂ ¹	7	20	57	82/18	8 (<i>R</i>)
12	ZnI ₂ ¹	7	20	56	88/12	10 (<i>R</i>)
13	Cu(OTf) ₂ ⁴	7	20	51	83/17	8 (<i>R</i>)
14	Cu(OTf) ₂ ¹	10	20	2	85/15	18 (<i>R</i>)
15	ZnI ₂ ¹	10	20	1	85/15	16 (<i>R</i>)
16	Cu(OTf) ₂ ¹	11	20	traces	-	-
17	ZnI ₂ ¹	11	20	2	81/19	72 (<i>S</i>)
18	Cu(OTf) ₂ ¹	13	20	12	84/16	7 (<i>R</i>)

19	ZnI ₂ ¹	13	20	13	85/15	9 (<i>R</i>)
20	Cu(OTf) ₂ ¹	12	20	14	85/15	8 (<i>R</i>)
21	ZnI ₂ ¹	12	20	18	85/15	10 (<i>R</i>)
22	Cu(OTf) ₂ ¹	14	20	58	82/18	< 1
23	ZnI ₂ ¹	14	20	58	87/13	< 1

The reactions were performed with 10 % of both catalyst and ligand, at 0 °C in dichloromethane, except in the mentioned cases. 1- 0 °C to room temp.; 2- measured by ¹H-NMR; 3- measured by chiral gaseous chromatography. The absolute configuration was determined by comparison with the [α]_D value of an authentic sample;^[15] 4- 10 % of catalyst and 20 % of ligand.

It is noteworthy that ligand **8** completely deactivated the metal catalyst (entries 1, 2, 3), the strong catalytic effect of AlCl₃ and FeCl₃ (entries 2 and 4, table 1) being totally suppressed. This suggests that the cation coordinates to the basic amine group of **6** and the resulting complex is not sufficiently acidic to catalyze the Diels-Alder reaction. The Boc-protection of serine **8** led to serine ligand **4**. The addition of **4** to a suspension of Cu(OTf)₂ in dichloromethane did not result in a colored homogeneous solution, indicating that the complex **4**-Cu was not formed. Consequently, the reaction yield was drastically decreased (entry 4, table 2) when compared with the use of Cu(OTf)₂ alone (entry 9, table 1), as the acid character of the Lewis catalyst was compensated with the basic character of amide **4**. The same reaction was performed with serine **9** and Cu(OTf)₂. Similarly, the **9**-Cu complex was not formed, as indicated by the non homogenization of the solution. However, in this case the reaction yield was not significantly changed when compared with the use of Cu(OTf)₂ alone (entry 5, table 2 and entry 9, table 1, respectively). This is in agreement with the acid character of **9**.

The bidentate serine derivative ligands **5-7** were also tested as co-catalysts. The complete solubilization and coloring subsequent to the addition of ligands **5-7** to a suspension of the Lewis acids [yellow for Zn(II) and blue for Cu(II)] points to a good metal to ligand complexation. By analyzing table 2, it is possible to verify that the use of ligands **5** significantly improved the reaction yield (when compared with the use of Lewis acid alone). We further studied the influence of steric effects near to the ligand binding atom on the catalytic performance, by comparing the performance of **5** (ligand with a benzylamine moiety) with **6** [(*S*)-phenylethylamine moiety] and **7** [(*R*)-phenylethylamine moiety]. The results clearly showed that the methyl group of the phenylethyl moiety slightly blocks the approximation of the CPD to the dienophile-metal-ligand complex when it is at *S* configuration. On the other hand, the e.e. were slightly higher for **6** than for **7** (entries 9-12, table 2). No significant effect was observed when it is at *R* configuration. The *endo/exo* ratio of **3** does not seem to significantly change with the used ligand. The use of metal:ligand molar ratio of 1:2 led to similar

results to the usual 1:1 molar ratio (entries 11 and 13, table 2), suggesting that each metal ion coordinates to only one serine derivative ligand, contrarily to what occurs with C_2 symmetry ligands.[22] In fact, BOX ligands proved to be quite ineffective in this reaction, leading to very low yields and low e.e.; at the best of our knowledge, there are not reported any results concerning good e.e. obtained in the catalyzed Diels-Alder reaction between CPD and methyl acrylate.

By removing the Fmoc group of **6** and **7**, we obtained the ligands **10** and **11**, respectively, which were also tested as ligands. Similarly to what happened with ligand **8**, the metal catalysts were deactivated, the yields of the reactions being too low (entries 14-17). The e.e. obtained with **10** remained similar as the preceding serine **6**. However, the e.e. obtained with the use of **11** was 72%, the configuration of adduct **3** being *S* (entry 14, table 2). Even though the reaction yields were negligible, this result proves that the configuration of the phenylethylamine moiety of the serine derivative ligand may influence the reaction enantioselectivity, which encouraged us to keep our investigation on these serine derivative ligands. We used the amino free group of serines **8**, **10** and **11** to prepare the corresponding silylated serines in order to allow posterior grafting onto inorganic materials for posterior employment in heterogeneous catalysis. For this, we reacted the referred serines with 3-(triethylsilyl)propyl isocyanate, affording serines **14**, **12** and **13**, respectively. It is worthy to note that serine **14** led to yields similar to those obtained when serines **5** and **7** were used (entries **22** and **23**, table 2); on the other hand, the e.e. were negligible, as expected. Silylated serines **12/13** showed low yields (entries 18-21), probably due to the existence of 3 coordination nitrogen atoms, which will encapsulate the metal ion thus difficulting the coordination of the catalytic complex to the dienophile. These observations confirm that the serine derivative ligands should be bidentated in order to effectively form complexes that efficiently catalyse the Diels Alder reaction between **2** and **3**.

3. Conclusions

Bidentated L-serine based ligands showed good potential to be applied in Diels-Alder reactions, particularly if coordinated to moderate-strength Lewis acids such as $\text{Cu}(\text{OTf})_2$ and ZnI_2 . This is an alternative to the usage of strong Lewis acids such as AlCl_3 or FeCl_3 , as serine derivative ligands proved to allow good yields at mild conditions, are cheap and easy to prepare.

The results also anticipate that the change of the serine carboxylic residue by a chiral group may influence the stereochemistry of the Diels-Alder reaction, this subject being currently under study and development in our laboratory, as well as additional design optimization. The possibility of easily silylating of the referred serines with alkoxysilanes was also confirmed, which will allow posterior grafting onto inorganic materials for application in heterogeneous catalysis.

4. Materials and Methods

4.1 General notes

All solvents were distilled and dried using standard methods. CPD was freshly bi-distilled prior to use. All starting material and reagents were from commercial suppliers (Aldrich, Fluka, Bachem) and used without purification. Serine 6 was obtained by treatment of its commercial hydrochloride with triethylamine.

Flash column chromatography was performed on silica gel (60Å, 230,240 mesh) and analytical thin-layer chromatography (TLC) on pre-coated silica gel 60 F254 plates using iodine vapor and/or UV light (254 nm) for visualization. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. Optical rotations were measured on a conventional thermostated polarimeter using a sodium lamp.

4.2 Experimental procedure for Diels-Alder reactions

To a suspension of catalyst (0.10 eq) in anhydrous dichloromethane (10 ml) at the conditions referred in table 1, methyl acrylate (0.136 ml, 1.50 mmol) and CPD (0.125 ml, 1.51 mmol) were added. The mixture was left to react with stirring under argon atmosphere. After the reaction period, the mixture was treated by either the methods: a) filtration through celite/silica with dichloromethane; b) extraction from water with dichloromethane, followed by drying with anhydrous Na₂SO₄. The solvent was eliminated at reduced pressure. Whenever necessary, methanol was added to the dry crude in order to polymerize unreacted CPD. The formed polymer was triturated, filtered off and washed with methanol. After evaporation of the volatiles, the crude was weight and analyzed by NMR in order to evaluate both the reaction yield and the *endo/exo* ratio.

For Diels-Alder reaction catalyzed by a serine-metal complex: to a suspension of catalyst (0.10 eq) in anhydrous dichloromethane (10 ml) at the conditions referred in table 2, the ligand (0.10 eq) was added and the mixture was left to react under argon atmosphere into an ice bath during 30 min. After this period, methyl acrylate (0.136 ml, 1.50 mmol) and CPD (0.125 ml, 1.51 mmol) were added, the subsequent procedure being similar to the previously described.

(±)-*methyl bicyclo[2.2.1]hept-5-ene-2-endo-carboxylate (3-endo)*: ¹H NMR (400 MHz, CDCl₃): δ = 8.71 (dd, *J* = 5.7, 3.1 Hz, 1H, 5-H), 5.95 (dd, *J* = 5.7, 2.8 Hz, 1H, 6-H), 3.65 (s, 3H, OCH₃), 3.20-3.24 (m, 1H, 1-H), 2.97 (dt, *J* = 9.3, 3.8 Hz, 1H, 2-H), 2.90-2.95 (m, 1H, 4-H), 1.93 (ddd, *J* = 12.0, 9.3, 3.7 Hz, 1H, 3-H), 1.41-1.48 (m, 1H, 3-H + 7_{syn}-H), 1.27-1.23 (m, 1H, 7_{anti}-H);

(±)-*methyl bicyclo[2.2.1]hept-5-ene-2-exo-carboxylate (3-exo)*: ¹H NMR (400 MHz, CDCl₃): δ = 6.16 (dd, *J* = 5.6, 2.9 Hz, 1H, 5-H), 6.13 (dd, *J* = 5.5, 3.0 Hz, 1H, 6-H), 3.72 (s, 3H, OCH₃), 3.05-3.08 (m, 1H, 4-H), 2.23-2.28 (m, 1H), 1.53-1.57 (m, 1H) (other signals are superimposed);

4.3 Synthesis of L-serine derivative ligands

(S)-methyl 3-(*tert*-butoxy)-2-((*tert*-butoxycarbonyl)amino)propanoate (**4**): A solution of **8** (0.200 g, 0.945 mmol) and Boc₂O (0.207 g, 0.948 mmol) in anhydrous dichloromethane (5 ml), was stirred at room temperature under argon atmosphere overnight. 10 ml of water was added and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 × 10 ml). The organic extracts were rinsed with brine, dried over anhydrous Na₂SO₄ and evaporated at reduced pressure, yielding a colorless oil that was purified by chromatographic column (eluent: Hex/AcOEt 1:1). Traces of Boc₂O were eliminated by leaving the oil under high vacuum overnight. η = 86 %.

¹H NMR (400 MHz, CDCl₃): δ = 5.35 (d, *J* = 8.4 Hz, 1H, NH), 4.33-4.43 (m, 1H, CH), 3.79 (dd, *J* = 2.8, 8.9 Hz, 1H, OCH_aCH_b), 3.73 (s, 3H, OCH₃), 3.56 (dd, *J* = 3.2, 9.0 Hz, 1 H, OCH_aCH_b), 1.45 (s, 9H, C(CH₃)₃), 1.13 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): δ = 171.6 (COO), 155.7 (HNCOO), 79.9 (C(CH₃)₃), 73.4 (C(CH₃)₃), 62.2 (OCH₂), 54.4 (CH), 52.3 (OCH₃), 28.4 (C(CH₃)₃), 27.4 (C(CH₃)₃); ESI-MS: calculated for [C₁₃H₂₅NO₅ + H]⁺ (M + H⁺) 276.17, obtained 276.22;

Bidentated Serines (5-7): To a solution of **9** (0.50 g, 1.3 mmol) in anhydrous dichloromethane (25 ml), TBTU (0.63 g, 2.0 mmol), DIPEA (0.34 ml, 2.0 mmol) and the corresponding amine (1.3 mmol) were added. The mixture was left to react at room temperature under argon atmosphere for 2 h. 10 ml of water was added and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3 × 10 ml). The organic extracts were rinsed with brine, dried over anhydrous Na₂SO₄ and evaporated at reduced pressure, affording the expected serine derivative ligands **5**, **6** or **7** with 99% yield. No further purifications were needed.

(S)-(9*H*-fluoren-9-yl)methyl (1-(benzylamino)-3-(*tert*-butoxy)-1-oxopropan-2-yl)carbamate (**5**): ¹H NMR (400 MHz, CDCl₃): δ = 7.79 (d, *J* = 7.5 Hz, 2H, H_{ar-Fluoren}), 7.62 (d, *J* = 7.4 Hz, 2H, H_{ar-Fluoren}), 7.39-7.45 (m, 2H_{ar}), 7.28-7.38 (m, 7H_{ar}), 6.91 (bs, 1H, NH), 5.79 (bs, 1H, NH), 4.47-4.57 (sl, 2H, CH₂Ph), 4.44 (d, *J* = 6.8 Hz, 2H, COOCH₂), 4.28 (sl, 1H, COCH), 4.24 (t, *J* = 7.0 Hz, 1H, CH_{Fluoren}), 3.87 (dd, *J* = 8.6, 3.7 Hz, 1H, OCH_aCH_b), 3.42 (t, *J* = 8.0 Hz, 1H, OCH_aCH_b), 1.17 (s, 9 H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): δ = 170.2 (COO), 156.1 (HNCOO), 143.8 and 143.7 (2 × C_{Fluoren}), 141.3 (2 × C_{Fluoren}), 137.9 (C_{ipso Ph}), 128.7 (2 × C_{meta Ph}), 127.8 (2 × CH_{Fluoren}), 127.6 (2 × C_{ortho Ph}), 127.5 (C_{para Ph}), 127.1 (2 × CH_{Fluoren}), 125.0 and 125.1 (2 × CH_{Fluoren}), 120.0 (2 × CH_{Fluoren}), 74.2 (C(CH₃)₃), 67.0 (COOCH₂), 61.9 (OCH₂), 54.6 (CH), 47.2 (CH_{Fluoren}), 43.6 (CH₂Ph), 27.4 (C(CH₃)₃); ESI-MS: calculated for [C₂₉H₃₂N₂O₄ + H]⁺ (M + H⁺) 473.24, obtained 473.28; m.p. = 125-130 °C; [α]_D^{24°C} = +25.0 (*c* 1, CHCl₃).

(9H-fluoren-9-yl)methyl ((*S*)-3-(*tert*-butoxy)-1-oxo-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)carbamate (**6**): ¹H NMR (400 MHz, CDCl₃): δ = 7.78 (d, *J* = 7.5 Hz, 2H, H_{ar-Fluoren}), 7.61 (d, *J* = 7.4 Hz, 2H, H_{ar-Fluoren}), 7.29-7.45 (m, 9H_{ar}), 7.03 (bs, 1H, NH), 5.83 (bs, 1H, NH), 5.17-5.07 (m, 1H, CHPh), 4.41 (d, *J* = 7.5 Hz, 2H, COOCH₂), 4.20-4.28 (m, 2H, COCH + CH_{Fluoren}), 3.81 (dd, *J* = 8.5, 4.1 Hz, 1H, OCH_aCH_b), 3.32 (t, *J* = 8.2 Hz, 1H, OCH_aCH_b), 1.53 (d, *J* = 6.9 Hz, 3H, CH₃), 1.15 (s, 9H, C(CH₃)₃); ¹³C NMR

(100 MHz, CDCl₃): δ = 169.2 (COO), 156.0 (HNCOO), 143.9 (C_{ipso} Ph), 143.7 (2 × C_{Fluoren}), 141.3 (2 × C_{Fluoren}), 128.7 (2 × C_{meta} Ph), 127.7 (2 × CH_{Fluoren}), 127.4 (C_{para} Ph), 127.1 (2 × CH_{Fluoren}), 126.1 (2 × C_{ortho} Ph), 125.1 (2 × CH_{Fluoren}), 120.0 (2 × CH_{Fluoren}), 74.3 (C(CH₃)₃), 67.0 (COOCH₂), 61.8 (OCH₂), 54.0 (CH), 49.2 (CHCH₃), 47.1 (CH_{Fluoren}), 27.3 (C(CH₃)₃), 22.0 (CHCH₃); calculated for [C₃₀H₃₄N₂O₄ + H]⁺ (M + H⁺) 487.25, obtained 487.26; wax; $[\alpha]_D^{24^\circ\text{C}} = -2.9$ (c 1, CHCl₃).

(9H-fluoren-9-yl)methyl ((S)-3-(tert-butoxy)-1-oxo-1-((R)-1-phenylethylamino)propan-2-yl)carbamate (**7**): ¹H NMR (400 MHz, CDCl₃): δ = 7.78 (d, *J* = 7.5 Hz, 2H, H_{ar-Fluoren}), 7.61 (d, *J* = 7.5 Hz, 2H, H_{ar-Fluoren}), 7.28-7.45 (m, 9H_{ar}), 6.96 (bs, 1 H, NH), 5.80 (bs, 1H, NH), 5.20-5.09 (m, 1H, CHPh), 4.43 (d, *J* = 6.9 Hz, 2H, COOCH₂), 4.24 (m, 2H, COCH + CH_{Fluoren}), 3.86 (dd, *J* = 8.1, 3.4 Hz, 1H, OCH_aCH_b), 3.41 (t, *J* = 8.2 Hz, 1H, OCH_aCH_b), 1.52 (d, *J* = 6.9 Hz, 3H, CH₃), 1.23 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃): δ = 169.3 (COO), 156.0 (HNCOO), 143.9 and 143.7 (2 × C_{Fluoren}), 143.0 (C_{ipso} Ph), 141.3 (2 × C_{Fluoren}), 128.7 (2 × C_{meta} Ph), 127.7 (2 × CH_{Fluoren}), 127.4 (C_{para} Ph), 127.1 (2 × CH_{Fluoren}), 126.0 (2 × C_{ortho} Ph), 125.1 (2 × CH_{Fluoren}), 120.0 (2 × CH_{Fluoren}), 74.3 (C(CH₃)₃), 67.1 (COOCH₂), 62.0 (OCH₂), 54.4 (CH), 49.0 (CHCH₃), 47.2 (CH_{Fluoren}), 27.5 (C(CH₃)₃), 22.1 (CHCH₃); calculated for [C₃₀H₃₄N₂O₄ + H]⁺ (M + H⁺) 487.25, obtained 487.26; m.p. = 147-148 °C; $[\alpha]_D^{24^\circ\text{C}} = +48.7$ (c 1, CHCl₃).

Serines (10, 11): Piperidine (2 eq.) was added to a solution of serines **6/7** in anhydrous DMF (5 ml). The mixture was left to react for 2 h at room temperature, under argon atmosphere. After water (10 ml) and dichloromethane (10 ml) addition to the mixture, the phases were separated. The aqueous phase was extracted with dichloromethane (3 × 10 ml) and the organic phases washed with brine. After evaporation of the volatiles at reduced pressure, the mixture was purified by chromatographic column (eluent: Hexane/AcOEt 1:1), affording serines **10/11** with 100 % yield.

(S)-2-amino-3-(tert-butoxy)-N-((S)-1-phenylethyl)propanamide (**10**): ¹H NMR (400 MHz, CDCl₃): δ = 7.65 (d, *J* = 7.2 Hz, 1 H, NH), 7.33-7.39 (m, 4 H_{ar}), 7.25-7.31 (m, 1 H_{para}), 5.13 (dt, 15.0, 6.9 Hz, 1 H, CHPh), 3.62 (dd, *J* = 11.4, 8.1 Hz, 1 H, NH₂CH), 3.48-3.54 (m, 2 H, OCH₂), 1.83 (bs, 2 H, NH₂), 1.51 (d, *J* = 6.9 Hz, 3 H, CH₃), 1.19 (s, 9 H, C(CH₃)₃);

(S)-2-amino-3-(tert-butoxy)-N-((R)-1-phenylethyl)propanamide (**11**): ¹H NMR (400 MHz, CDCl₃): δ = 7.72 (d, *J* = 7.8 Hz, 1 H, NH), 7.31-7.37 (m, 4 H_{ar}), 7.22-7.28 (m, 1 H_{para}), 5.12 (dt, 15.0, 7.0 Hz, 1 H, CHPh), 3.50-3.63 (m, 3 H, OCH₂CH), 2.06 (bs, 2 H, NH₂), 1.51 (d, *J* = 6.9 Hz, 3 H, CH₃), 1.19 (s, 9 H, C(CH₃)₃);

Ethoxysilylated serines (12, 13, 14): To a solution of serine **8/10/11** in anhydrous dichloromethane, 1 eq. of 3-(triethylsilyl)propyl isocyanate was added dropwise. The reaction was left with stirring overnight at reflux under argon atmosphere. The solvent was evaporated at reduced pressure and the residue was purified by chromatographic column (eluent: dichloromethane), affording serines **14/12/13** with 98%, 90% and 90% yields, respectively.

N-(((*S*)-3-(*tert*-butoxy)-1-oxo-1-(((*S*)-1-phenylethyl)amino)propan-2-yl)carbamoyl)-4-(triethoxysilyl)butanamide (**12**): ^1H NMR (400 MHz, CDCl_3): δ = 7.31-7.36 (m, 4 H_{ar}), 7.25-7.27 (m, 1 H_{para}), 7.18 (d, J = 7.7 Hz, 1 H, NH), 5.55 (d, J = 6.0 Hz, 1 H, NH), 5.07 (m, 1 H, NHCH), 4.96-5.02 (m, 1 H, NH), 4.34 (ddd, J = 8.9, 5.9, 4.3 Hz, 1 H, CHPh), 3.83 (q, J = 7.0 Hz, 6 H, 3 \times SiOCH₂), 3.78 (dd, J = 8.5, 4.3 Hz, 1 H, OCH_aCH_b), 3.28 (t, J = 8.6 Hz, 1 H, OCH_aCH_b), 3.12-3.20 (m, 2 H, OCH₂), 1.56-1.66 (m, 2 H, CH₂CH₂ CH₂), 1.50 (d, J = 6.9 Hz, 3 H, CH₃), 1.24 (t, J = 7.0 Hz, 9 H, 3 \times OCH₂CH₃), 1.13 (s, 9 H, C(CH₃)₃), 0.61-0.61 (m, 2 H, SiCH₂);

N-(((*S*)-3-(*tert*-butoxy)-1-oxo-1-(((*R*)-1-phenylethyl)amino)propan-2-yl)carbamoyl)-4-(triethoxysilyl)butanamide (**13**): ^1H NMR (400 MHz, CDCl_3): δ = 7.18-7.35 (m, 6 H, NH + H_{ar}), 5.68 (d, J = 6.3 Hz, 1 H, NH), 5.25 (t, J = 5.6 Hz, 1 H, NH), 5.06 (m, 1 H, NHCH), 4.35 (ddd, J = 8.3, 6.3, 4.2 Hz, 1 H, CHPh), 3.81 (q, J = 7.0 Hz, 6 H, 3 \times SiOCH₂), 3.78-3.84 (m, 1 H, OCH_aCH_b), 3.36 (t, J = 8.4 Hz, 1 H, OCH_aCH_b), 3.11 (ddd, J = 13.1, 7.1, 2.1 Hz, 2 H, OCH₂), 1.53-1.62 (m, 2 H, CH₂CH₂ CH₂), 1.48 (d, J = 6.9 Hz, 3 H, CH₃), 1.21 (t, J = 7.0 Hz, 9 H, 3 \times OCH₂CH₃), 1.21 (s, 9 H, C(CH₃)₃), 0.57-0.64 (m, 2 H, SiCH₂);

(*S*)-methyl 12-(*tert*-butoxymethyl)-4,4-diethoxy-8,10-dioxo-3-oxa-9,11-diaza-4-silatridecan-13-oate (**14**): ^1H NMR (400 MHz, CDCl_3): δ = 5.28 (d, J = 8.6 Hz, 1 H, NH), 4.96 (t, J = 5.5 Hz, 1 H, NH), 4.58 (dt, J = 8.6, 3.2 Hz, 1 H, CH), 3.81 (q, J = 7.0 Hz, 6 H, 3 \times SiOCH₂), 3.78 (dd, J = 9.0, 3.2 Hz, 1 H, OCH_aCH_b), 3.72 (s, 3 H, OCH₃), 3.56 (dd, J = 9.0, 3.2 Hz, 1 H, OCH_aCH_b), 3.10-3.25 (m, 2 H, COCH₂), 1.57-1.66 (m, 2 H, CH₂CH₂ CH₂), 1.22 (t, J = 7.0 Hz, 9 H, 3 \times OCH₂CH₃), 1.13 (s, 9 H, C(CH₃)₃), 0.60-0.68 (m, 2 H, SiCH₂); ^{13}C NMR (100 MHz, CDCl_3): δ = 173.2 (CH(CO)O + CH₂(CO)NH), 158.6 (NHCONH), 74.2 (C(CH₃)₃), 63.6 (OCH₂), 59.3 (3 \times SiOCH₂), 54.8 (CH), 53.1 (OCH₃), 43.9 (COCH₂), 28.2 (C(CH₃)₃), 24.3 (SiCH₂), 19.2 (OCH₂CH₃), 8.6 (CH₂CH₂ CH₂);

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