

N-Tfa- and N-Fmoc- $(\alpha$ -aminoacyl)benzotriazoles as Chiral C-Acylating Reagents under Friedel-Crafts Reaction Conditions

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Chiral N-Tfa- and N-Fmoc-protected (a-aminoacyl)benzotriazoles 1a-j undergo Friedel-Craftstype reactions with indole, N-methylindole, pyrrole, N-methylpyrrole, and benzene in the presence of AlCl₃ in efficient two-step sequences leading to enantiomerically pure α -amino N-heterocyclic ketones 2, 3, 5, 6, and 7 or diketone 4. In the absence of a reactive partner, Phe- and Trp-derivatives **1a**, **1d** undergo intramolecular cyclization to afford **12** and **13**, again with retention of chirality.

Introduction

Chiral N-protected α-amino ketones are useful precursors to many biologically active compounds including chiral α -amino alcohols,¹ pharmaceutically important chiral heterocycles,^{2,3} and diamines.^{1c,4} Preparations of α -amino aliphatic ketones and α -amino aryl ketones have been thoroughly investigated,⁵ but much less attention has been directed toward the synthesis of α -aminoalkyl heterocyclic ketones and to our knowledge, no general method has been reported. Previous syntheses of chiral α -amino ketones utilized N-protected α -amino acids, esters, and amides (i) with organometallic reagents for nucleophilic substitution⁶ or (ii) with AlCl₃ for Friedel-Crafts acylations.⁷ The methods using organometallic reagents, though well-established, sometimes suffer from drawbacks such as tedious purification^{6a} and competition between nucleophilic addition and nucleophilic substitution.^{6b} Moreover, N-protected α-amino acid chlorides are often unstable and prone to racemization.8

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N-Acylbenzotriazoles, which are easily prepared from carboxylic acids by (i) thionyl chloride and 1H-benzotriazole at 20 °C^{9a} or (ii) BtSO₂Me in the presence of Et_3N ,^{9b} are efficient *C*-acylating agents for heterocycles such as indoles, pyrroles,^{10a} furan, and thiophene^{10b} under Friedel-Craft conditions. Recently, we converted amino acids into enantiomerically pure N-protected (aminoacyl)benotriazoles, which were then coupled with chiral amines,^{11a} amino acids, and peptides.^{11b-d} We now report the first syntheses of C-acylated indoles and pyrroles utilizing N-(Tfa- and Fmoc- α -aminoacyl)benzotriazoles under Friedel-Crafts conditions to obtain the corre-

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SCHEME 1. Preparation of N-Protected Aminoacylbenzotriazoles



sponding α -amino ketones with complete retention (>99%) of chirality.

Results and Discussion

Preparation of N-(Tfa- and Fmoc- α -aminoacyl)benzotriazoles. The amino group of L-alanine and L-phenylalanine were protected with the N-trifluoroacetyl (Tfa) group using ethyl trifluoroacetate in the presence of Et₃N in methanol to generate the N-Tfa-α-amino acids. $^{\rm 12}$ The resultant N-Tfa-protected amino acids were treated with thionyl chloride and 4 equiv of benzotriazole to give N-(Tfa- α -aminoacyl)benzotriazoles **1a** and **1b** (Scheme 1). Racemic N-(Tfa-α-aminoacyl)benzotriazoles 1i and 1j were prepared similarly from DL-alanine and DL-phenylalanine, respectively. N-(Fmoc- α -aminoacyl)benzotriazoles 1c-h were prepared by the above method from commercially available N-Fmoc-L-phenylalanine, L-tryptophan, and L-methionine.^{11d} The Z-protected aminoacylbenzotriazole 1k was prepared by a previously reported method.^{11b}

Friedel-Crafts Acylations of Pyrrole and N-**Methylpyrrole.** Reactions of 1a-e in CH₂Cl₂ with 1.2 equiv of pyrrole in the presence of 3 equiv of anhydrous AlCl₃ under nitrogen at 20 °C for 3 h produced the corresponding amino ketones 2a-e; reactions of 1a-ewith *N*-methylpyrrole under similar conditions also gave the corresponding amino ketones 3a-e (Table 1). The C-acylations occurred specifically at C-2, and no 3-acylated products were observed.

When compounds with an Fmoc group and bulky aromatic side chains such as Fmoc-Phe-Bt (1c) and Fmoc-Trp-Bt (1d) were used, the corresponding ketones were obtained in lower yields than the ketones with aliphatic side chains. For the reaction of **1d** with *N*-methylpyrrole, the 45% yield was not improved even when the reaction time was extended to 24 h.

Furthermore, we extended this method to the preparation of the bis(acyl)-pyrrole 4 by using N-(Fmoc-aminodiacyl)benzotriazole 1h (prepared from N-Fmoc-glutamic acid) in 35% yield (Scheme 2). The yield of the aminodiketone 4 was not as good as those from the monoacylation reactions, presumably due to the lack of solubility of **1h** in CH₂Cl₂. No mono-acylated compounds were observed during the purification of 4 by column chromatography.



However, attempted C-acylation of pyrrole with Z-Ala-Bt (1k) resulted in the loss of the Z group as indicated by their crude NMR spectra and no desired product was isolated.

Friedel-Crafts Acylations of Indole and N-Methylindole. Utilizing the procedure developed above for the acylation of pyrrole and N-methylpyrrole, C-acylations of indole to give $5\mathbf{a} - \mathbf{e}$ and of *N*-methylindole to give 6a-g were carried out in the presence of 3 equiv of AlCl₃. Most of the expected products were thus obtained in good to moderate yields (Table 2). Exceptionally, the reaction of Fmoc-Trp-Bt (1d) with indole failed to give expected product 5d, and 1d decomposed under the reaction conditions. However, N-TMS-indole readily reacted with 1d in the presence of $TiCl_4$ or $AlCl_3$ in 15 min to give the product 5d in 87% and 41% isolated yields, respectively. The TMS group was completely cleaved under these reaction conditions.

Friedel-Crafts Acylations of Benzene. Most literature syntheses of chiral arvl α -amino ketones via Friedel–Crafts type reactions involve N-protected α-amino acid chlorides.⁷ However, the preservation of chirality of α -amino acid chlorides was not always successful due

TABLE 1. C-Acylations of Pyrrole and N-Methylpyrrole



	amino ketone (yield. %) ^a		
reactant	from pyrrole	${\it from}N{\rm -}{\it methylpyrrole}$	
Tfa-Phe-Bt (1a)	2a (82)	3a (78)	
Tfa-Ala-Bt (1b)	2b (78)	3b (75)	
Fmoc-Phe-Bt(1c)	2c (72)	3c (56)	
Fmoc-Trp-Bt (1d)	2d (52)	3d (45)	
Fmoc-Met-Bt (1e)	2e (66)	3e (60)	
^a Isolated vield.			





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amino ketone (yield, %) ^{a}	
from indole	from N-methylindole
5a (85)	6a (62)
5b (79)	6b (75)
5c (63)	6c (40)
5d (87) ^{b,c}	6d (45)
5e (83)	6e (90)
d	6f (85)
d	6g (75)
d	6j (64)
	$\begin{array}{c} {\rm amino\ l} \\ \hline \\ \hline {\rm from\ indole} \\ {\bf 5a\ (85)} \\ {\bf 5b\ (79)} \\ {\bf 5c\ (63)} \\ {\bf 5d\ (87)^{b,c}} \\ {\bf 5e\ (83)} \\ d \\ d \\ d \\ \end{array}$

 a Isolated yield. b Reaction condition (N-TMS-indole 1.5 equiv, TiCl₄ 2 equiv, CH₂Cl₂, 10 min, 20 °C). c Reaction with 1H-indole gave no product. d Not attempted.

SCHEME 3. Acylation of Benzene



to the instability of acid chlorides, which can react with an amino protecting group to form oxazolinones.^{7a} To address this issue, we reacted Tfa-Ala-Bt (**1b**) with benzene to give α -aminoalaninyl phenyl ketone **7** in 63%

SCHEME 4. Preparation of Diastereomers 9 and 11

yield. (Scheme 3) The ¹H NMR and melting point of **7** matches the literature report.^{7c} While our yield was comparable to previous reports in the literature, the solid, chirally stable benzotriazole derivatives are clearly more convenient to handle than amino acid chlorides.

Configurational Analysis of Amino Ketones. Because one of the most important features of biologically active amino ketones is associated with the presence of the asymmetric α -carbon in their structures, total control of chirality represents a major goal during the synthesis of these amino ketones. To evaluate the chiral integrity of these reactions, we examined the syntheses of amino ketones 6a (L) and 6j (DL-mixture), prepared from Nmethylindole and Tfa-L-Phe-Bt (1a) and Tfa-DL-Phe-Bt (1j), respectively as models. This study was accomplished by chiral HPLC comparison of the two acvlated products of N-methylindole **6a** and **6j** starting from enantiomerically pure Tfa-L-phenylalanine and Tfa-DL-phenylalanine. Two peaks equal in ratio appeared for 6j at 3.11 min corresponding to L-isomer and at 6.59 min corresponding to the D-isomer, whereas **6a** gave only one peak appearing at 3.11 min (solvent MeOH, flow rate 1.0 mL/min, UV detection at 254 nm). Since all of the acylations were carried out under the same conditions, the HPLC results supported the conclusion that N-(Tfa- and Fmoc- α aminoacyl)benzotriazoles undergo Friedel-Crafts type reactions with nitrogen heterocycles and benzene in the presence of AlCl₃ with full preservation (>99%) of the configuration.

A NMR study utilizing diastereomers also supported the preservation of configuration during the *C*-acylation. Compound **9** was prepared by coupling of **1a** with **8** obtained by the cleavage of the Fmoc group of **6f**, which







was generated from the acylation of Fmoc-L-Ala-Bt (1f) with N-methylindole. A similar process was used to prepare the other diastereomer 11. (Scheme 4) The methyl group of the alanine moiety in a diastereomer 9 (L-Phe-L-Ala) displays a single doublet at 1.51 ppm, whereas 11 (L-Phe-D-Ala) exhibited a single doublet at 1.39 ppm. No trace was found of methyl peaks characteristic of 11 in the ¹H NMR spectrum of 9 and also nothing of 9 in the NMR of 11.

Intramolecular Cyclization of 1a and 1d. The lower yields of α -amino ketones 2d (52%), 3c (41%), and 6d (45%) obtained from aromatic side chains containing aminoacylbenzotriazoles 1c and 1d (as compared to those from aminoacylbenzotriazoles 1a,b,e containing alphatic side chains) suggested a competing intramolecular acylation reaction of the aromatic side chains in 1a and 1d. We reacted the two compounds 1a and 1d under the conditions used for the preparation of 5 and 6 but in the absence of indole and generated the cyclized products 12

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and 13 in 57% and 62% yield, respectively (Scheme 5). The ¹H NMR spectra of **12** and **13** showed the disappearance of Bt signals in aromatic region, indicating the loss of the benzotriazolyl group during the reaction. The ¹³C NMR spectrum of **12** showed a signal at 201.2 ppm corresponding to the carbonyl group of the cyclized ketone and the disappearance of the signal at 168.8 ppm belonging to the carbonyl group at the α position of the benzotriazolyl group in the starting material. Likewise, the ¹³C NMR spectrum of 13 showed a signal for the cyclized ketone at 191.3 ppm and the disappearance of the signal of the α carbonyl group of the benzotriazolyl group at 172.2 ppm. The cyclization also was confirmed in ¹H NMR spectrum by the observation of four protons in the aromatic region of 12 due to the loss of one aromatic proton from the starting material. Furthermore, the splitting patterns of the two protons at the α position to the phenyl ring of 1a and cyclized ketone 12 were different. Regarding 1a, one of the two protons appeared at 3.37 ppm (dd, J = 13.8, 7.2 Hz) and the other one at 3.59 ppm (dd, J = 13.8, 5.1 Hz). In the ¹H NMR spectrum of **12**, one proton was observed at 3.05 ppm (dd, J = 16.8, 5.7 Hz) and the other at 3.89 ppm (dd, J = 16.8, 5.1 Hz). The difference of chemical shifts of the two protons (0.84)ppm) in **12** was much larger than that of the two protons (0.22 ppm) in **1a**, which can be rationalized by the formation of a five-membered ring system.

Configurational Analysis of Intramolecular Cyclization. A NMR study utilizing diastereomers was carried out to examine the preservation of configuration in products **12** and **13** from the intramolecular cyclizations of **1a** and **1d**. Tricyclic amine **14** was obtained by the cleavage of **13** using morpholine. The coupling of amine **14** with Tfa-DL-Ala-Bt (**1i**) gave as expected a mixture of the four stereoisomers **15** (two pairs of diastereomers). The coupling of amine **14** with Tfa-L-Ala-Bt (**1b**) did not give diastereomers **16** exclusively, but

SCHEME 6. Preparation of Diastereomers 15, 16, and 17



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another enantiomer 17 was obtained as a result of racemization (Scheme 6). There were two doublets observed in the NMR spectrum of 15 corresponding to the methyl group of the alanine moiety from Tfa-DL-Ala-Bt (1i), which was the same with the methyl group of the alanine moiety in the mixture of 16 and 17 at 1.49 and 1.51 ppm. This result suggested that racemization occurred during the preparation of the diastereomers. Since compound 13 has OPR value ($[\alpha]^{23}_{D} = -4.3$) and no racemization was observed for the coupling of amine 8 and Tfa-L-Phe-Bt (1a), it is reasonable to conclude that the racemization probably took place in the stage of the cleavage of Fmoc group (from 13 to 14) as a result of the acidic proton at the α position to the carbonyl group of the cyclopentenone, which can be easily deprotonated to form an enol. (Scheme 7)

Conclusion

The syntheses of *N*-Tfa- and *N*-Fmoc- α -amino ketones containing *N*-heterocycles and benzene using *N*-(Tfa- and Fmoc- α -aminoacyl)benzotriazoles under the Friedel– Crafts conditions have been achieved in moderate to high yield. Full preservation (>99%) of chirality has been suggested by HPLC. This new method for the preparation of novel enantiomerically pure α -amino ketones containing heterocyclic moieties offers a facile access to potentially valuable biological and pharmacological compounds.

Experimental Section

General Procedure for the Preparation of N-Protected (Aminoacyl)benzotriazoles (1a–1). Thionyl chloride (10 mmol, 0.73 mL) was added to the 1*H*-benzotriazole (40 mmol, 4.76 g) dissolved in anhydrous THF (30 mL), and the solution was heated at 40 °C for 30 min. After cooling to 0 °C, a solution of N-protected amino acid (10 mmol) in anhydrous THF was added, and the mixture was stirred at 20 °C for 2 h. The white precipitate was filtered off, and the filtrate was concentrated and diluted with dichloromethane followed by washing with saturated sodium carbonate (50 mL×3) and water (50 mL) and drying with anhydrous MgSO₄. Evaporation of the solvent gave products 1a–1 in 63–83% yields, which were recrystallized from CHCl₃/hexanes for CHN analysis. Compounds 1d, 1e, and 1k have been previously reported and fully characterized.^{11b,d}

N-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-benzyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-L-Phe-Bt, 1a): colorless needles; yield, 83%; mp 136–137 °C; $[\alpha]^{23}_{D} = +49.7$ (c 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 3.37 (dd, J = 14.4, 7.2 Hz, 1H), 3.59 (dd, J = 14.1, 5.1 Hz, 1H), 6.31 (dd, J = 12.9, 7.5 Hz, 1H), 7.04–7.09 (m, 3H), 7.26–7.29 (m, 3H), 7.60 (t, J = 8.1Hz, 1H), 7.73 (t, J = 8.1 Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 8.22 (d, J = 7.4 Hz, 2H); ¹³C NMR (CDCl₃) δ 38.5, 54.2, 114.7, 115.5 (q, J = 288.0 Hz), 120.6, 127.0, 127.9, 128.9, 129.1, 130.8, 131.2, 133.8, 146.1, 156.7 (q, J = 38.4 Hz), 168.8 Anal. Calcd for C₁₇H₁₃F₃N₄O₂: C, 56.36; H, 3.62; N, 15.46. Found C, 56.55; H, 3.53; N, 15.34.

N-[(1*S*)-2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-methyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-L-Ala-Bt, 1b): colorless needles; yield, 76%; mp 115–116 °C; [α]²³_D = -106.4 (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 1.82 (d, J = 7.2 Hz, 3H), 6.04 (quintet, J = 7.5 Hz, 1H), 7.29 (d, J = 5.4 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.1, 49.8, 114.4, 115.8 (q, J = 285.7 Hz), 120.8, 127.2, 131.2, 131.4, 146.3, 156.9 (q, J = 38.2 Hz), 170.5. Anal. Calcd for C₁₁H₉F₃N₄O₂: C, 46.16; H, 3.17; N, 19.57. Found: C, 46.33; H, 3.05; N, 19.27.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-benzotriazol-1-yl-2-oxoethyl] carbamate (Fmoc-L-Phe-Bt, 1c): colorless flakes; yield, 83%; mp 136–137 °C; $[\alpha]^{23}_{D} = +35.6$ (c 1.6, DMF); ¹H NMR (DMSO- d_6) δ 3.20 (dd, J = 13.8, 8.1 Hz, 1H), 3.47 (dd, J = 13.8, 4.5 Hz, 1H), 4.15 (t, J = 7.2 Hz, 1H), 4.29–4.42 (m, 2H), 5.86 (d, J = 7.4 Hz, 1H), 6.06–6.11 (m, 1H), 7.12–7.27 (m, 8H), 7.34 (t, J = 7.5 Hz, 2H), 7.44–7.54 (m, 3H), 7.60 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H); ¹³C NMR (DMSO- d_6) δ 25.7, 38.9, 55.8, 68.0, 114.4, 120.0, 120.4, 125.1, 126.6, 127.1, 127.4, 127.8, 128.8, 129.4, 130.9, 131.1, 135.3, 141.3, 143.7, 146.1, 155.8, 171.0. Anal. Calcd for C₃₀H₂₄N₄O₃: C, 73.75; H, 4.95; N, 11.47. Found: C, 73.53; H, 5.07; N, 11.24.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Fmoc-L-Ala-Bt, 1f): colorless microcrystals; yield, 85%; mp 160–161 °C; $[\alpha]^{23}_{\rm D} = -96.8 (c \ 1.6, \rm DMF)$; ¹H NMR (DMSO- d_6) δ 1.59 (d, J = 7.2 Hz, 3H), 4.27 (t, J = 6.6 Hz, 1H), 4.38 (d, J = 6.9 Hz, 2H), 5.45 (quintet, J = 6.9 Hz, 1H), 7.34–7.47 (m, 4H), 7.65 (t, J = 7.8 Hz, 1H), 7.75 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.92 (d, J = 7.2 Hz, 2H), 8.25–8.37 (m, 3H); ¹³C NMR (DMSO- d_6) δ 16.8, 46.6, 50.1, 65.9, 114.0, 120.1, 120.2, 125.2, 126.7, 127.1, 127.7, 130.6, 131.1, 140.8, 143.7, 145.3, 156.1, 172.5. Anal. Calcd for C₂₄H₂₀N₄O₃: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.48; H, 4.94; N, 13.41.

9*H*-Fluoren-9-ylmethyl *N*-[(1*R*)-2-(1*H*-1,2,3-benzotriazol-1-yl)-1-methyl-2-oxoethyl]carbamate (Fmoc-D-Ala-Bt, 1g): colorless microcrystals; yield, 85%; mp 161 °C; $[\alpha]^{23}_{D} =$ +95.6 (*c* 1.6, DMF). ¹H NMR and ¹³C NMR are the same with Fmoc-L-Ala-Bt (1f).

9H-Fluoren-9-ylmethyl *N*-[(1*S*)-4-benzotriazol-1-yl-1-(benzotriazol-1-yl-carbonyl)-4-oxobutyl] carbamate-(**Fmoc-Glu-Di-Bt, 1h**): colorless flakes; yield, 63%; mp 166–167 °C; $[\alpha]^{23}_{D} = -19.7$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 2.40–2.64 (m, 2H), 3.71 (t, *J* = 6.6 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 1H), 4.34 (d, *J* = 6.9 Hz, 2H), 5.67–5.73 (m, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.40 (t, *J* = 7.2 Hz, 2H), 7.58–7.90 (m, 8H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.24–8.28 (m, 3H), 8.46 (d, *J* = 6.6 Hz, 1H); ¹³C NMR (DMSO-*d*₆) δ 24.9, 31.4, 46.6, 53.5, 65.9, 113.9, 114.0, 120.0, 120.1, 120.2, 125.2, 126.4, 126.8, 127.1, 127.6, 130.5, 130.7 (2C), 131.1, 140.7, 143.7, 145.3, 145.4, 156.2, 171.3, 171.5. Anal. Calcd for C₃₀H₂₄N₄O₃: C, 67.24; H, 4.41; N, 17.15. Found: C, 67.09; H, 4.23; N, 17.12.

N-[(1R,S)-2-(1H-1,2,3-Benzotriazol-1-yl)-1-methyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-DL-Ala-Bt, 1i): colorless needles; yield, 80%; mp 110–112 °C. ¹H NMR and ¹³C NMR are the same as for Fmoc-L-Phe-Bt (1b).

N-[(1R,S)-2-(1H-1,2,3-Benzotriazol-1-yl)-1-benzyl-2-oxoethyl]-2,2,2-trifluoroacetamide (Tfa-DL-Phe-Bt, 1j): colorless needles; yield, 89%; mp 132–133 °C. ¹H NMR and ¹³CNMR are the same as for Fmoc-L-Phe-Bt (1a).

General Procedure for the Acylations of Nitrogen Heterocycles. AlCl₃ (0.4 g, 3 mmol) was added to the mixture of nitrogen heterocycle (2.4 mmol) and **1** (2 mmol) dissolved in anhydrous CH₂Cl₂ (20 mL) at 0 °C. After removing the icebath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of CH₂Cl₂ under reduced pressure gave the crude product, which was purified by column chromatography (EtOAc/hexanes = 4:1) to give the desired products **2**, **3**, **5**, **6**, and **7** in 40–90% yields, which were further recrystallized from CHCl₃/hexane for CHN analysis.

N-[(1*S*)-1-Benzyl-2-oxo-2-(1*H*-pyrrol-3-yl)ethyl]-2,2,2trifluoroacetamide (2a): white needles; yield, 82%; mp 171– 172 °C; [α]²³_D = +44.3 (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 3.18 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.35 (dd, *J* = 13.5, 5.1 Hz, 1H), 5.47 (q, *J* = 7.5 Hz, 1H), 6.33–6.36 (m, 1H), 6.97–7.01 (m, 3H), 7.13 (s, 1H), 7.23–7.25 (m, 4H), 9.40 (br s, 1H); ¹³C NMR (CDCl₃) δ 39.8, 55.2, 111.8, 115.7 (q, *J* = 287.8 Hz), 118.4, 126.7, 127.4, 128.5, 128.9, 129.4, 134.7, 156.4 (q, *J* = 37.8 Hz), 184.8. Anal. Calcd for C₁₅H₁₃F₃N₂O₂: C, 58.07; H, 4.22; N, 9.03. Found: C, 57.85; H, 4.16; N, 8.84.

2,2,2-Trifluoro-*N*-**[(1***S***)-1-methyl-2-oxo-2-(1***H***-pyrrol-2yl)ethyl]acetamide (2b): colorless needles; yield, 78%;. mp 142-143 °C; [\alpha]^{23}_{D} = -2.0 (***c* **1.6, CHCl₃); ¹H NMR (CDCl₃) \delta** 1.57 (d, J = 6.9 Hz, 3H), 5.28 (quintet, J = 6.9 Hz, 1H), 6.38 (quintet, J = 1.8 Hz, 1H), 7.07 (s, 1H), 7.16 (s, 1H), 7.58 (br s, 1H), 9.80 (br s, 1H); ¹³C NMR (CDCl₃) δ 20.6, 50.8, 112.0, 115.9 (q, J = 285.2 Hz), 118.5, 127.0, 128.4, 156.7 (q, J = 37.6 Hz), 186.5. Anal. Calcd for C₉H₉F₃N₂O₂: C, 46.16; H, 3.87; N, 11.96. Found: C, 46.39; H, 3.77; N, 11.80.

9H-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-oxo-2-(1*H*-pyrrol-2-yl)ethyl]carbamate (2c): colorless needles; yield, 72%; mp 186–187 °C; $[\alpha]^{23}_{D} = +16.7$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.09 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.26 (dd, *J* = 13.5, 6.0 Hz, 1H), 4.19 (t, *J* = 6.9 Hz, 1H), 4.29 (t, *J* = 6.9 Hz, 1H), 4.44 (dd, *J* = 10.2, 7.2 Hz, 1H), 5.29 (dd, *J* = 14.1, 6.6 Hz, 1H), 5.69 (d, *J* = 8.4 Hz, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 6.99 (s, 1H), 7.05 (d, *J* = 2.4 Hz, 2H), 7.20 (d, *J* = 6.3 Hz, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 4.5 Hz, 2H), 7.76 (d, *J* = 7.5 Hz, 2H), 9.60 (br s, 1H); ¹³C NMR (DMSO-*d*₆) δ 40.4., 47.4, 56.6, 67.1, 111.6, 118.0, 120.2, 125.4, 126.1, 127.1, 127.2, 127.9, 128.6, 129.7, 136.2, 141.5, 144.0, 144.1, 155.8, 187.2. Anal. Calcd for C₂₈H₂₄N₂O₃: C, 77.04; H, 5.54; N, 6.42. Found: C, 76.79; H, 5.70; N, 6.29.

9H-Fluoren-9-ylmethyl-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-oxo-2-(1H-pyrrol-2-yl)ethyl] carbamate (2d): white plates; yield, 52%; mp 196–197 °C; $[\alpha]^{23}_{D} = +32.5$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.04 (dd, J = 14.7, 9.3 Hz, 1H), 3.22 (dd, J = 14.7, 5.1 Hz, 1H), 4.18–4.21 (m, 3H), 4.97–5.04 (m, 1H), 6.21–6.23 (m, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.04–7.09 (m, 2H), 7.13 (s, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.25–7.43 (m, 5H), 7.57 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 6.6 Hz, 2H), 7.87 (d, J = 7.5 Hz, 2H), 7.92 (s, 1H), 10.85 (s, 1H), 11.90 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 27.7, 46.6, 56.4, 65.7, 110.0, 110.2, 111.4, 116.8, 118.1, 118.4, 120.1, 120.9, 123.8, 125.3, 126.1, 127.0, 127.2, 127.6, 129.9, 136.1, 140.7, 143.8, 155.7, 188.2. Anal. Calcd for C₃₀H₂₅N₃O₃: C, 75.77; H, 5.30; N, 8.84. Found: C, 75.55; H, 5.18; N, 8.76.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-3-(methylsulfanyl)-1-(1*H*-pyrrol-2-ylcarbonyl) propyl]carbamate (2e): colorless plates; yield, 66%; mp 163–164 °C; $[\alpha]^{23}_{\rm D} = -5.9$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.92–2.01 (m, 1H), 2.06 (s, 3H), 2.14–2.26 (m, 1H), 2.51–2.60 (m, 2H), 4.21 (t, *J* = 6.9 Hz, 1H), 4.35–4.56 (m, 2H), 5.21 (dd, *J* = 9.3, 8.1 Hz, 1H), 5.83 (d, *J* = 8.4 Hz, 1H), 6.32 (d, *J* = 3.3 Hz, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.28 (t, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 9.80 (br s, 1H); ¹³C NMR (DMSO-*d*₆) δ 15.6, 30.2, 34.2, 47.2, 54.6, 67.0, 111.5, 118.2, 120.0, 125.1, 126.3, 127.1, 127.7, 129.4, 141.3, 143.9, 156.1, 187.7. Anal. Calcd for C₂₄H₂₄N₂O₃S: C, 68.55; H, 5.75; N, 6.66. Found: C, 68.26; H, 5.85; N, 6.74.

N-[(1S)-1-Benzyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (3a): colorless needles; yield, 78%; mp 109–110 °C; $[\alpha]^{23}_{D}$ = +43.6 (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 3.17 (dd, *J* = 13.8, 4.8 Hz, 1H), 3.31 (dd, *J* = 13.8, 6.6 Hz, 1H), 3.68 (s, 3H), 5.32 (dd, *J* = 12.6, 6.0 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 2H), 7.00–7.03 (m, 2H), 7.19–7.26 (m, 4H), 7.36 (br s, 1H); ¹³C NMR (CDCl₃) δ 36.8, 39.3, 56.4, 109.9, 115.9 (q, *J* = 287.3 Hz), 122.3, 124.3, 127.3, 128.3, 128.5, 129.7, 135.4, 156.5 (q, *J* = 37.2 Hz), 190.1. Anal. Calcd for C₁₆H₁₅F₃N₂O₂: C, 59.26; H, 4.66; N, 8.64. Found: C, 59.17; H, 4.62; N, 8.47.

2,2,2-Trifluoro-N-[(1S)-1-methyl-2-(1-methyl-1H-pyrrol-2-yl)-2-oxoethyl]-acetamide (3b): colorless needles; yield, 75%; mp 120–121 °C; $[\alpha]^{23}_{D} = -7.4$ (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 1.53 (d, J = 7.2 Hz, 3H), 3.73 (s, 3H), 5.13 (quintet, J = 6.3 Hz, 1H), 6.61–6.60 (m, 2H), 7.40 (t, J = 1.8 Hz, 1H), 7.73 (br s, 1H); ¹³C NMR (CDCl₃) δ 19.9, 36.7, 51.4, 109.7, 115.7 (q, J = 286.4 Hz), 121.2, 124.1, 127.8, 156.2 (q, J = 37.0 Hz), 191.3. Anal. Calcd for C₁₀H₁₁F₃N₂O₂: C, 48.39; H, 4.47; N, 11.29. Found: C, 48.70; H, 4.38; N, 11.15.

9H-Fluoren-9-ylmethyl *N*-**(**(1*S*)-1-benzyl-2-(1-methyl-1*H*-pyrrol-2-yl)-2-oxoethyl]carbamate (3c): colorless needles; yield, 56%; mp 172–173 °C; $[\alpha]^{23}_{D} = +9.9$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.05 (dd, J = 13.8, 6.3 Hz, 1H), 3.25 (dd, J = 13.8, 5.7 Hz, 1H), 3.89 (s, 3H), 4.20 (t, J = 7.2 Hz, 1H), 4.29 (dd, J = 10.5, 7.5 Hz, 1H), 4.43 (dd, J = 10.2, 7.2 Hz, 1H), 5.31(q, J = 6.3 Hz, 1H), 5.68 (d, J = 8.4 Hz, 1H), 6.15 (q, J = 2.7 Hz, 1H), 6.87 (s, 1H), 7.03–7.05 (m, 3H), 7.21–7.23 (m, 3H), 7.30 (t, J = 7.5 Hz, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.57 (t, J = 6.6 Hz, 2H), 7.76 (d, J = 7.2 Hz, 2H); ¹³C NMR (DMSO- d_6) δ 37.7, 40.5, 47.2, 56.7, 66.9, 108.8, 120.0, 120.5, 125.2, 125.3, 126.9, 127.1, 127.7, 128.3, 129.5, 132.3, 136.3, 141.3, 144.0, 155.6, 187.5. Anal. Calcd for C₂₉H₂₆N₂O₃: C, 77.31; H, 5.82; N, 6.22. Found: C, 76.93; H, 5.76; N, 6.21.

9H-Fluoren-9-ylmethyl-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-oxo-2-(1-methyl-1H-pyrrol-2-yl)ethyl]carbamate (3d): gray microcrystals; yield, 45%; mp 154–155 °C; $[\alpha]^{23}_{D} = +35.6$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.28 (dd, *J* = 14.1, 5.1 Hz, 1H), 3.41 (dd, *J* = 14.7, 6.6 Hz, 1H), 3.56 (s, 3H), 4.20 (t, *J* = 7.2 Hz, 1H), 4.29–4.42 (m, 2H), 5.25 (q, *J* = 6.3 Hz, 1H), 5.84 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 2.1 Hz, 1H), 6.60 (s, 1H), 6.86 (d, *J* = 1.8 Hz, 1H), 7.05–7.10 (m, 2H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.8 Hz, 3H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 3H), 7.75 (d, *J* = 7.5 Hz, 2H), 8.00 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 30.1, 36.8, 47.4, 57.0, 67.1, 109.9, 111.2, 119.1, 119.8, 120.1 (2C), 122.2, 123.1, 123.9, 125.4, 125.5, 127.3, 127.8 (2C), 128.0, 136.2, 141.5, 144.2, 156.1, 193.0; HRMS calcd for C₃₁H₂₇N₃O₃ (M + H)⁺ 490.2125, found 490.2151.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-[(1-methyl-1*H*-pyrrol-2-yl)carbonyl]-3-(methylsulfanyl)propyl]carbamate (3e): light yellow needles; yield, 60%; mp 109–110 °C; $[\alpha]^{23}_{D} = -17.3$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.86–2.00 (m, 1H), 2.06 (s, 3H), 2.14–2.25 (m, 1H), 2.44–2.63 (m, 2H), 3.66 (s, 3H), 4.21 (t, *J* = 6.3 Hz, 1H), 4.37 (d, *J* = 6.9 Hz, 2H), 5.07–5.13 (m, 1H), 5.84 (d, *J* = 8.4 Hz, 1H), 6.59 (t, *J* = 2.4 Hz, 1H), 6.65 (s, 1H), 7.26–7.32 (m, 2H), 7.38 (t, *J* = 6.0 Hz, 3H), 7.60 (d, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.5 Hz, 2H); ¹³C NMR (DMSO*d*₆) δ 15.7, 30.3, 34.2, 36.9, 47.3, 55.6, 67.0, 110.0, 120.1, 122.8, 124.1, 125.3, 127.2, 127.8, 128.0, 141.4, 143.9, 156.2, 192.7. Anal. Calcd for C₂₅H₂₆N₂O₃S: C, 69.10; H, 6.03; N, 6.45. Found: C, 69.11; H, 5.98; N, 6.46.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-4-oxo-4-(1*H*-pyrrol-2yl)-1-(1*H*-pyrrol-2-ylcarbonyl)butyl]carbamate (4): light violet microcrystals; yield, 35%; mp 140–141 °C; $[\alpha]^{23}_{D} = +12.2$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.80–1.92 (m, 1H), 2.09– 2.20 (m, 1H), 2.80–3.03 (m, 2H), 4.22–4.27 (m, 3H), 4.83 (quintet, *J* = 7.5 Hz, 1H), 6.20 (d, *J* = 17.1 Hz, 2H), 6.94 (s, 1H), 7.10 (d, *J* = 16.8 Hz, 2H), 7.29 (s, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.73 (t, *J* = 6.9 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 11.86 (d, *J* = 9.6 Hz, 2H); ¹³C NMR (DMSO-*d*₆) δ 27.2, 33.8, 46.6, 55.4, 65.6, 109.7, 109.9, 116.3, 116.9, 120.1, 125.3, 125.9, 127.1, 127.6, 129.6, 131.5, 140.7, 143.7, 143.9, 156.1, 188.4, 188.8. Anal. Calcd for C₂₈H₂₅N₃O₄: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.11; H, 5.41; N, 8.91.

N-[(1S)-1-Benzyl-2-(1H-indol-3-yl)-2-oxoethyl]-2,2,2-tri-fluoroacetamide (5a): gray needles; yield, 85%; mp 198–199 °C; [α]²³_D = +22.0 (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 3.22 (dd, *J* = 13.5, 5.1 Hz, 1H), 3.31 (dd, *J* = 13.5, 6.3 Hz, 1H), 5.47 (dd, *J* = 12.9, 7.2 Hz, 1H), 7.05 (t, *J* = 3.6 Hz, 2H), 7.20–7.22 (m, 3H), 7.33–7.44 (m, 3H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.64 (d, *J* = 3.0 Hz, 1H), 8.33–8.35 (m, 1H), 8.83 (br s, 1H); ¹³C NMR (CDCl₃) δ 39.8, 56.4, 111.7, 115.2, 115.7 (q, *J* = 285.8 Hz), 122.2, 123.5, 124.5, 125.3, 127.3, 128.5, 129.5, 132.5, 135.2, 136.2, 156.6 (q, *J* = 37.0 Hz), 190.1. Anal. Calcd for C₁₃H₁₁F₃N₂O₂: C, 63.33; H, 4.20; N, 7.77. Found: C, 62.98; H, 4.08; N, 7.75.

2,2.2-Trifluoro-N-[(1S)-2-(1H-indol-3-yl)-1-methyl-2-oxoethyl]acetamide (5b): colorless microcrystals; yield, 79%; mp 189–190 °C; $[\alpha]^{23}_{\rm D} = -7.0$ (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 1.61 (d, J = 6.9 Hz, 3H), 5.31 (quintet, J = 6.9 Hz, 1H), 7.23 (br s, 1H), 7.33–7.45 (m, 2H), 7.44–7.48 (m, 1H), 7.97 (d, J = 3.3 Hz, 1H), 8.35 (t, J = 5.4 Hz, 1H), 8.89 (br s, 1H); ¹³C NMR (CDCl₃) δ 20.4, 51.5, 111.7, 114.2, 115.7 (q, J = 286.4 Hz), 122.3, 123.5, 124.5, 125.5, 132.0, 136.4, 156.5 (q, J = 37.6 Hz), 191.5. Anal. Calcd for C₁₃H₁₁F₃N₂O₂: C, 54.93; H, 3.90; N, 9.86. Found: C, 54.98; H, 3.91; N, 9.85.

9H-Fluoren-9-ylmethyl-N-[(1S)-1-benzyl-2-oxo-2-(1H-indol-3-yl)ethyl]carbamate (5c): yellow flakes; yield, 63%; mp 101–102 °C; $[\alpha]^{23}_{D} = -18.3$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.08 (dd, J = 13.8, 6.0 Hz, 1H), 3.23 (dd, J = 13.8, 6.3 Hz, 1H), 4.11–4.17 (m, 1H), 4.24–4.30 (m, 1H), 4.38–4.44 (m, 1H), 5.25 (dd, J = 14.7, 6.3 Hz 1H), 6.00 (d, J = 7.1 Hz, 1H), 7.06–7.39 (m, 14 H), 7.52 (t, J = 7.2 Hz, 2H), 7.73 (d, J = 7.2 Hz, 1H), 8.34 (d, J = 8.4 Hz, 1H), 9.30 (br s, 1H); ¹³C NMR (DMSO-*d*₆) δ 40.3, 47.3, 57.8, 67.3, 119.3, 115.6, 120.1, 122.3, 123.2, 124.2, 125.3, 125.7, 127.0, 127.3, 127.9, 128.6, 129.7, 132.8, 136.5, 136.6, 141.4, 143.9, 156.2, 192.8. Anal. Calcd for C₃₂H₂₆N₂O₃: C, 78.99; H, 5.39; N, 5.76. Found: C, 78.78; H, 5.65; N, 6.20.

9H-Fluoren-9-ylmethyl-N-[(1S)-2-(1H-indol-3-yl)-1-(1Hindol-3-ylmethyl)-2-oxoethyl]carbamate (5d): To a solution of Fmoc-Trp-Bt (1d) (1.06 g, 2 mmol) and N-TMS-indole¹³ (0.58 g, 3 mmol) in CH₂Cl₂ (30 mL) was added TiCl₄ (1 M CH₂Cl₂ solution) (4 mL, 4 mmol) was added quickly at 0 °C. The reaction mixture was stirred for 15 min at the temperature and quenched with MeOH (2 mL). The solution was directly subjected to column chromatography (EtOAc/hexanes = 1:2) to give the desired product 5d in 0.9 g (87%), which was further recrystallized in CHCl₃/hexanes to provide brown microcrystals: yield, 87%; mp 194–195 °C; $[\alpha]^{23}_{D} = +28.3 (c \ 1.6, DMF);$ ¹H NMR (DMSO- d_6) δ 3.12 (dd, J = 14.6, 8.7 Hz, 1H), 3.29 (dd, J = 14.7, 5.5 Hz, 1H), 4.20 (s, 3H), 5.16 (dd, J = 14.0, 8.2)Hz, 1H), 7.00 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 7.21–7.51 (m, 9H), 7.62–7.68 (m, 3H), 7.86 (d, J = 7.4 Hz, 2H), 7.96 (d, J = 8.3 Hz, 1H), 8.24–8.33 (m, 2H), 10.8 (s, 1H), 12.0 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 21.7, 46.6, 56.9, 65.7, 110.4, 111.3, 112.2, 114.4, 118.3, 120.0, 120.8, 121.4, 121.9, 123.0, 123.7, 125.3, 125.8, 127.0, 127.3, 127.6, 133.8, 136.1, 136.5, 140.6, 143.8, 155.8, 193.7. Anal. Calcd for C34H27N3O3: C, 77.70; H, 5.18; N, 7.99. Found: C, 77.47; H, 5.28; N, 7.90.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-(1*H*-indol-3-ylcarbonyl)-3-(methylsulfanyl)-propyl]carbamate (5e): colorless plates; yield, 83%; mp 128–129 °C; $[\alpha]^{23}_{D} = -51.2$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.90–2.01 (m, 2H), 2.05 (s, 3H), 2.54–2.62 (m, 2H), 4.20–4.30 (m, 3H), 4.96–5.03 (m, 1H), 7.22–7.28 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.40 (td, *J* = 6.9, 2.1 Hz, 2H), 7.50–7.52 (m, 1H), 7.23 (t, *J* = 6.9 Hz, 2H), 7.85 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2H), 8.22 (d, *J* = 6.6 Hz, 1H), 8.42 (d, *J* = 3.0 Hz, 1H), 12.05 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 14.6, 30.1, 31.9, 46.7, 55.7, 65.6, 112.2, 113.9, 120.1, 121.3, 121.9, 123.0, 125.3, 125.7, 127.0, 127.6, 133.8, 136.5, 140.7, 143.8, 156.0, 193.6 Anal. Calcd for C₂₈H₂₆N₂O₃S: C, 71.46; H, 5.57; N, 5.95. Found: C, 71.16; H, 5.89; N, 5.55.

 $\begin{array}{l} \textbf{N-[(1S)-1-Benzyl-2-(1-methyl-1H-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (6a): colorless needles; yield, 62%; mp 176–177 °C; [<math>\alpha$]²³_D = +32.9 (c 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 3.24 (d, J = 2.1 Hz, 1H), 3.26 (d, J = 3.3 Hz, 1H), 3.75 (s, 3H), 5.43 (q, J = 6.3 Hz, 1H), 7.07–7.10 (m, 2H), 7.19–7.22 (m, 3H), 7.34–7.38 (m, 3H), 7.51 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 8.32–8.35 (m, 1H); ¹³C NMR (CDCl₃) δ 33.5, 39.8, 56.4, 109.9, 115.4 (q, J = 285.7 Hz), 113.4, 122.3, 123.3, 124.0, 126.2, 127.1, 128.4, 129.6, 135.6, 136.9, 137.5, 156.5 (q, J = 37.0 Hz), 189.5. Anal. Calcd for C₂₀H₁₇F₃N₂O₂: C, 64.17; H, 4.58; N, 7.48. Found: C, 64.36; H, 4.41; N, 7.46.

2,2,2-Trifluoro-N-[(1S)-1-methyl-2-(1-methyl-1*H***-indol-3-yl)-2-oxoethyl] acetamide (6b):** colorless needles; yield, 75%; mp 161–162 °C; $[\alpha]^{23}_{D} = -84.2$ (*c* 1.6, CHCl₃); ¹H NMR (CDCl₃) δ 1.60 (d, J = 6.9 Hz, 3H), 3.90 (s, 3H), 5.29 (quintet, J = 6.9 Hz, 1H), 7.35–7.40 (m, 3H), 7.77 (d, J = 5.4 Hz, 1H), 7.88 (s, 1H), 8.30–8.34 (m, 1H); ¹³C NMR (CDCl₃) δ 20.7, 34.1, 51.6, 110.3, 112.7, 116.0 (q, J = 287.8 Hz), 122.6, 123.6, 124.3, 126.5, 136.5, 137.9, 156.7 (q, J = 37.8 Hz), 191.1. Anal. Calcd for C₁₄H₁₃F₃N₂O₂: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.44; H, 4.33; N, 9.31.

9H-Fluoren-9-ylmethyl *N*-[(1*S*)-1-benzyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl] carbamate (6c): colorless needles; yield, 40%; mp 153–154 °C; $[\alpha]^{23}_{D} = +13.1$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.16 (dd, *J* = 13.5, 5.7 Hz, 1H), 3.23 (dd, *J* = 13.8, 7.2 Hz, 1H), 3.74 (s, 3H), 4.20 (t, J = 7.2 Hz, 1H), 4.30 (dd, J = 10.2, 7.2 Hz, 1H), 4.42 (dd, J = 10.2, 7.2 Hz, 1H), 5.25 (dd, J = 14.4, 6.9 Hz, 1H), 5.97 (d, J = 8.4 Hz, 1H), 7.11–7.44 (m, 12 H), 7.53 (s, 1H), 7.57 (t, J = 5.1 Hz, 2H), 7.75 (d, J = 7.2 Hz, 1H), 8.37–8.39 (m, 1H); ¹³C NMR (DMSO- d_6) δ 33.6, 40.5, 47.2, 57.7, 67.0, 109.8, 114.2, 120.0, 120.9, 122.6, 123.1, 123.8, 125.2, 125.3, 126.7, 127.1, 127.7, 128.3, 129.7, 136.8, 137.5, 141.3, 143.9, 155.8, 191.9. Anal. Calcd for C₃₃H₂₈N₂O₃: C, 79.18; H, 5.64; N, 5.60. Found: C, 78.98; H, 5.81; N, 5.79.

9H-Fluoren-9-ylmethyl-N-[(1S)-1-(1H-indol-3-ylmethyl)-2-oxo-2-(1-methyl-1H-indol-2-yl)ethyl]carbamate (6d): colorless microcrystals; yield, 45%; mp 191–192 °C; $[\alpha]^{23}_{\rm D}$ = +32.9 (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 3.11 (dd, *J* = 14.7, 9.0 Hz, 1H), 3.27 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.83 (s, 3H), 4.18–4.23 (m, 3H), 5.13 (dd, *J* = 14.1, 8.4 Hz, 1H), 6.99 (t, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.21–7.42 (m, 8H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 6.6 Hz, 3H), 7.86–7.92 (m, 3H), 8.26 (d, *J* = 7.2 Hz, 1H), 8.32 (s, 1H), 10.84 (s, 1H); ¹³C NMR (DMSO-*d*₆) δ 27.8, 33.2, 46.6, 57.0, 65.7, 110.4, 110.6, 111.3, 113.2, 118.3, 120.0, 120.8, 121.5, 122.2, 123.0, 123.6, 125.3 (2C), 126.2, 127.0, 127.3, 127.6, 136.0, 137.2, 137.4, 140.6, 143.8, 155.8, 193.3. Anal. Calcd for C₃₅H₂₉N₃O₃: C, 77.90; H, 5.42; N, 7.79. Found: C, 77.70; H, 5.48; N, 7.61.

9H-Fluoren-9-ylmethyl *N*-[(1S)-1-[(1-methyl-1*H*-indol-**3-yl)carbonyl]-3-(methylsulfanyl)propyl] carbamate (6e):** colorless microcrystals; yield, 90%; mp 140–141 °C; $[\alpha]^{23}_{\rm D} =$ -41.5 (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.95–2.05 (m, 1H), 2.08 (s, 3H), 2.19–2.29 (m, 1H), 2.49–2.69 (m, 2H), 3.85 (s, 3H), 4.22 (t, *J* = 7.2 Hz, 1H), 4.34–4.44 (m, 2H), 5.27 (dd, *J* = 10.2, 8.1 Hz, 1H), 5.94 (d, *J* = 6.9 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.34–7.41 (m, 5H), 7.59 (t, *J* = 7.2 Hz, 2H), 7.75 (d, *J* = 7.2 Hz, 2H), 8.00 (s, 1H), 8.39 (d, *J* = 6.0 Hz, 1H); ¹³C NMR (DMSO-*d*₆) δ 15.8, 30.5, 34.0, 34.3, 47.4, 55.3, 61.2, 110.1, 114.0, 120.2, 122.7, 123.3, 124.1, 125.3, 126.7, 127.2, 127.9, 136.9, 137.8, 141.5, 144.0, 156.4, 192.6. Anal. Calcd for C₂₉H₂₈N₂O₃S: C, 71.87; H, 5.82; N, 5.78. Found: C, 71.48; H, 5.76; N, 6.31.

9*H*-Fluoren-9-ylmethyl *N*-[(1*S*)-1-methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxo-ethyl]carbamate (6f): colorless needles; mp 144–145 °C; yield, 85%; $[\alpha]^{23}_{D} = -60.1$ (*c* 1.6, DMF); ¹H NMR (DMSO-*d*₆) δ 1.52 (d, *J* = 6.9 Hz, 3H), 3.85 (s, 3H), 4.23 (t, *J* = 7.2 Hz, 1H), 4.38 (d, *J* = 7.2 Hz, 2H), 5.10 (quintet, *J* = 7.2 Hz, 1H), 6.00 (d, *J* = 4.8 Hz, 1H), 7.27–7.42 (m, 7H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.86 (s, 1H), 8.34–8.39 (m, 1H); ¹³C NMR (DMSO-*d*₆) δ 21.1, 33.9, 47.4, 52.4, 67.1, 110.0, 113.5, 120.2, 122.7, 123.3, 124.0, 125.4, 126.7, 127.3, 127.9, 136.3, 137.8, 141.5, 144.1, 155.9, 193.5. Anal. Calcd for C₂₇H₂₄N₂O₃: C, 76.40; H, 5.70; N, 6.60. Found: C, 76.52; H, 5.71; N, 6.61.

N-[(1R,S)-1-Benzyl-2-(1-methyl-1H-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (6j): colorless needles; yield, 64%; mp 170–172 °C; ¹H NMR and ¹³C NMR are the same as for N-[(1S)-1-benzyl-2-(1-methyl-1H-indol-3-yl)-2-oxoethyl]-2,2,2-trifluoroacetamide (6a).

Procedure for C-Acylations of Benzene. AlCl₃ (0.4 g, 3 mmol) was added to **1d** (2 mmol) dissolved in benzene (20 mL) at 0 °C. After removing the ice-bath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of solvent under reduced pressure gave the crude product, which was directly purified by column chromatography (EtOAc/hexane = 1:10) to give product **7** in 63% yield.

N-[(1S)-1-Benzyl-2-oxo-2-phenylethyl]-2,2,2-trifluoro-acetamide (7): colorless needles; mp 64–65 °C (lit.^{7c} mp 62–63 °C); yield, 63%; ¹H NMR (CDCl₃) δ 1.57 (d, J = 7.2 Hz, 3H), 5.13 (quintet, J = 7.2 Hz, 1H), 6.70 (br s, 1H), 7.29–7.40 (m, 5H); ¹³C NMR (CDCl₃) δ 21.2, 50.0, 116.0 (q, J = 287.3 Hz), 126.4, 128.3, 129.2, 141.1, 156.6 (q, J = 37.0 Hz), 195.1.

Procedure for Preparation of Amines 8, 10, and 14 by Cleavage of Fmoc Protecting Group. Carbamate **6f or 6g** (0.42 g, 1 mmol) was dissolved in morpholine (10 mL, 10

mmol). After 30 min of stirring, 300 mL of water was added. After the mixture was extracted with hexane until the TLC showed the disappearance of the first spot, indicating the elimination of 9-methylene-9H-fluorene, the water phase was further extracted with EtOAc. Then the EtOAc organic phase was dried with MgSO₄, and the evaporation of solvent gave $crude\ product\ (2S) - 2 - amino - 1 - (1 - methyl - 1H - indol - 3 - yl) - 1 - pro$ panone (8) [or (2R)-2-amino-1-(1-methyl-1H-indol-3-yl)-1-propanone (10) from 6g] in 75% yield (75% from 10 as well), which can be used for the next step without further purification. The cleavage of 9H-fluoren-9-ylmethyl N-[(2S)-3-oxo-1,2,3,4-tetrahydrocyclopenta[b]indol-2-yl]carbamate (13) following the same procedure gave racemic 2-amino-1,2-dihydrocyclopenta-[b]indol-3(4H)-one (14) in 71% yield. We used these three compounds as crude staring materials for the next coupling reaction without purification. Therefore, we do not provide their characterization.

Procedure for the Preparation of Diastereomers 9 and 11. Amine 8 (or 10) 0.21 g (1 mmol) was stirred with Tfa-L-Phe-Bt (1a) (0.36 g, 1 mmol) in CH_2Cl_2 (20 mL) at 20 °C for 1 h. Evaporation of solvent gave crude product, which can be purified by column chromatography (EtOAc/hexane = 1:6).

(2S)-N-[(1S)-1-Methyl-2-(1-methyl-1*H*-indol-3-yl)-2-oxoethyl]-3-phenyl-2-[(2,2,2-trifluoroacetyl) amino]propanamide (9): colorless needles; mp 212–214 °C; yield, 80%; $[\alpha]^{23}_{\rm D}$ = -12.1 (c 1.6, DMF); ¹H NMR (CDCl₃) δ 1.50 (d, J = 6.9 Hz, 3H), 3.14 (d, J = 6.9 Hz, 2H), 3.87 (s, 3H), 5.01 (q, J = 7.2 Hz, 1H), 5.37 (quintet, J = 7.2 Hz, 1H), 7.15 (s, 5H), 7.33–7.40 (m, 3H), 7.49 (d, J = 6.9 Hz, 1H), 8.04 (s, 1H), 8.34–8.37 (m, 1H); ¹³C NMR (CDCl₃) δ 21.0, 33.6, 38.8, 51.0, 54.7, 109.9, 112.9, 115.8 (q, J = 285.7 Hz), 122.5, 123.2, 123.9, 126.5, 127.3, 128.6, 129.2, 135.3, 136.9, 137.7, 156.7 (q, J = 37.6 Hz), 168.8, 192.4. Anal. Calcd for C₂₃H₂₂F₃N₃O₃: C, 62.02; H, 4.98; N, 9.43. Found: C, 61.95; H, 4.91; N, 9.34.

(2S)-N-[(1R)-1-Methyl-2-(1-methyl-1H-indol-3-yl)-2-oxoethyl]-3-phenyl-2-[(2,2,2-trifluoroacetyl) amino]propanamide (11): colorless needles; mp 212–214 °C; yield, 80%; $[\alpha]^{23}_{\rm D}$ = -14.0; ¹H NMR (CDCl₃) δ 1.39 (d, J = 6.6 Hz, 3H), 3.24 (d, J = 7.2 Hz, 2H), 3.75 (s, 3H), 5.24 (q, J = 7.2 Hz, 1H), 5.38 (quintet, J = 7.2 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 7.22–7.34 (m, 8H), 7.86 (d, J = 6.9 Hz, 1H), 7.95 (s, 1H), 8.32–8.34 (m, 1H); ¹³C NMR (CDCl₃) δ 20.7, 33.6, 39.6, 51.5, 54.7, 110.1, 112.9, 115.8 (q, J = 285.7 Hz), 122.5, 123.2, 123.9, 126.7, 127.2, 128.8, 129.3, 136.0, 137.8, 156.7 (q, J = 37.6, Hz), 169.4, 192.9. Anal. Calcd for C₂₃H₂₂F₃N₃O₃: C, 62.02; H, 4.98; N, 9.43. Found: C, 61.95; H, 4.91; N, 9.34.

Procedure for the Intramolecular Acylations of 1a and 1d. $AlCl_3$ (0.4 g, 3 mmol) was added to 1a (or 1d) (2 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) at 0 °C. After removing

the ice-bath, the reaction mixture was stirred at room temperature for 3 h and then quenched by MeOH (1 mL). Removal of solvent under reduced pressure gave the crude product, which was purified by column chromatography (EtOAc/hexanes = 6:1) to give the intramolecular acylated products 12 (13 from 1d). They were further recrystallized from CHCl₃/ hexanes for CHN analysis.

2,2,2-Trifluoro-*N***-[**(**2***S***)-1-oxo-2**,**3-dihydro-1***H***-inden-2·y]acetamide (12):** white flakes; yield, 57%; mp 207–208 °C; $[\alpha]^{23}_{D} = -3.2 (c \ 1.6, DMF)$; ¹H NMR (DMSO-*d*₆) δ 3.05 (dd, *J* = 16.8, 5.4 Hz, 1H), 3.55 (dd, *J* = 16.8, 8.4 Hz, 1H), 4.61–4.68 (m, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.69–7.76 (m, 2H), 9.96 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (DMSO-*d*₆) 32.1, 54.6, 115.8 (q, *J* = 286.9 Hz), 123.5, 126.8, 127.8, 134.6, 135.6, 151.4, 156.3 (q, *J* = 36.5 Hz), 201.2. Anal. Calcd for C₁₁H₈F₃NO₂: C, 54.33; H, 3.32; N, 5.76. Found: C, 54.31; H, 3.24; N, 5.70.

9H-Fluoren-9-ylmethyl *N*-[(2S)-3-oxo-1,2,3,4-tetrahydrocyclopenta[b]indol-2-yl]carbamate (13): white flakes; yield, 62%; 235 °C (dec.); $[\alpha]^{23}{}_D = -39.0$ (c 1.6, DMF); ¹H NMR (DMSO- d_6) δ 2.88 (dd, J = 16.2, 3.0 Hz, 1H), 3.51 (dd, J =16.2, 6.9 Hz, 1H), 4.24–4.38 (m, 3H), 4.53 (quintet, J = 6.9Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.33–7.48 (m, 6H), 7.72 (d, J = 7.5 Hz, 4H), 7.90–8.01 (m, 2H), 11.76 (s, 1H); ¹³C NMR (DMSO- d_6) δ 28.1, 46.7, 59.6, 65.6, 113.6, 120.1, 121.4, 122.8, 127.8, 125.9, 126.9, 127.1, 127.6, 136.6, 140.7, 140.9, 143.4, 143.8, 155.9, 191.3. Anal. Calcd for C₂₆H₂₀N₂O₃: C, 76.45; H, 4.94; N, 6.86. Found: C, 76.24; H, 4.88; N, 6.72.

Procedure for the Preparation of Diastereomers 15 (16 and 17). Amine 14 (0.17 g, 1 mmol) was stirred with Tfa-DL-Ala-Bt (1i) or Tfa-L-Ala-Bt (1b) (0.28 g, 1 mmol) in CH_2Cl_2 (20 mL) at 20 °C for 1 h. Evaporation of solvent gave the corresponding crude product which can be purified by column chromatography (EtOAc/hexanes = 1:3).

N-(1-Oxo-1,2,3,8-tetrahydrocyclopenta[a]inden-2-yl)-2-[(2,2,2-trifluoroacetyl)amino] propanamide (15): white plates; yield, 52%; mp 257−258 °C; ¹H NMR (DMSO-*d*₆) (diastereomeric mixture) δ 1.49 (d, *J* = 7.0 Hz, 3H), 1.50 (d, *J* = 7.0 Hz, 3H), 2.93−3.03 (m, 2H), 3.12 (br s, 2H), 3.57−3.66 (m, 2H), 4.58−4.79 (m, 2H), 4.76−4.92 (m, 2H), 7.16 (t, *J* = 6.9 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.73 (d, *J* = 8.1 Hz, 2H), 8.01−8.08 (m, 2H), 8.58 (br s, 2H), 10.8 (s, 2H); ¹³C NMR (DMSO-*d*₆) (diastereomeric mixture) δ17.4, 17.5, 28.4, 28.5, 49.3 (2C), 59.0, 59.3, 113.6, 116.2 (q, *J* = 285.2 Hz), 120.5, 120.6, 121.5, 123.5, 127.2 (2C), 136.8, 136.9, 143.9(2C), 156.4 (q, *J* = 40.0 Hz), 170.9, 190.0, 190.1; HRMS calcd for C₁₇H₁₅F₃N₂O₃ (M + 2H)+ 354.1191, found 354.1185.

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