Asymmetric Synthesis of β-Amino Acid and Amide Derivatives by Catalytic Conjugate Addition of Aromatic Amines to *N*-Alkenoylcarbamates

Kelin Li,[a] Xiaohui Cheng,[b] and King Kuok (Mimi) Hii*[c]

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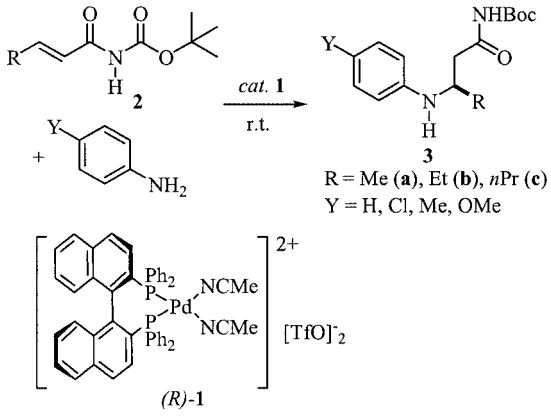
We report a highly active palladium catalyst for the enantioselective conjugate addition of primary aromatic amines to *N*-alkenoylcarbamates, furnishing β-amino *N*-Boc-amides in extremely high yields (>99 %) and unprecedented optical purity (>99 % *ee*) with just 2 mol % catalyst loading.

Introduction

Very few catalysts can facilitate the addition of N−H to double bonds (known as hydroamination, or the aza-Michael addition reaction) with high enantioselectivity.[1] To date, only three late transition metal catalysts are known to result in *ee* values of greater than 90 %. The first example (described by Togni) was a (diphosphane)iridium/fluoride system, which promoted the addition of aniline to norbornene (24 % yield, 91 % *ee*).[2] More recently, the palladium-catalysed addition of primary aromatic amines to 1,3-dienes[3] (up to 95 % *ee*) and the nickel-catalysed addition of secondary aromatic amines to *N*-alkenoyloxazolidinones[4] (up to 90 % *ee*) have been reported by Hartwig and Jørgensen, respectively. In these cases, catalyst loadings of 5 mol % were employed at room temperature, but reaction times between 40 h and 5 days were required to achieve significant yields.

Results and Discussion

Recently, we reported the enantioselective addition of primary and secondary aromatic amines to *N*-alkenoyloxazolidinones, catalysed by the cationic palladium complex $[(R\text{-BINAP})Pd(solvent)_2]^{2+}[TfO]^-_2$ **1**, with enantiomeric excesses up to 93 %.[5] Encouraged by these results, we proceeded to examine other activated α,β-unsaturated compounds as potential substrates. In this paper, we report that the conjugate addition of primary aromatic amines to *N*-alkenoylcarbamates **2**, catalysed by 2−5 mol % of complex **1**, furnishes β-amino *N*-Boc-amides **3**, precursors to β-amino acid and amide derivatives, with some enantiomeric excesses greater than 99 % (Scheme 1, Table 1) − the highest recorded so far in conjugate additions of this kind.



Scheme 1. Conjugate addition of anilines to *tert*-butyl *N*-alkenoylcarbamates

Initially, the addition of aniline to *tert*-butyl *N*-butenoylcarbamate **2a** was examined. Using 5 mol % of complex **1** as the catalyst, reactions proceeded cleanly to furnish product **3a** quantitatively and with high enantiomeric excess (97 % *ee*, Entry 1) after 18 h at room temperature in toluene. The rate of the reaction was retarded (and a slight loss of *ee* observed) when dichloromethane was employed as the solvent (Entry 2), presumably due to competitive coordination of the solvent to the cationic metal centre. More sig-

[a] Department of Chemistry, King's College London, Strand, London WC2R 2LS, United Kingdom
[b] Institute of Polymer Chemistry, Nankai University, Tianjin, 300071, P. R. China
[c] Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, United Kingdom
Fax: (internat.) + 44-20-7594-5804
E-mail: mimi.hii@imperial.ac.uk
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Table 1. Addition of arylamines to *N*-alkenoylcarbamates; unless otherwise indicated, reactions were performed using 1 equiv. of amine and 1.5 equiv. of carbamate ester in toluene at 25 °C

Entry	R	Y	Product	[Pd]/mol %	T/h	Yield/%[a]	*ee*/%[b]
1	Me	H	**3a**	5	18	>99	97
2	Me	H	**3a**	5	40	94	94[c]
3	Me	H	**3a**	2	40	>99	92
4	Me	Cl	**3b**	5	18	>99	>99
5	Me	Cl	**3b**	2	18	>99	>99
6	Me	Me	**3c**	5	18	93	92
7	Me	OMe	**3d**	5	40	99	73
8	Et	H	**3e**	5	72	98	90
9	Et	Cl	**3f**	5	72	92	85
10	Et	Me	**3g**	5	120	94	—[d]
11	Et	OMe	**3h**	5	72	>99	16
12	*n*Pr	H	**3i**	5	120	98	89
13	*n*Pr	Cl	**3j**	5	120	90	89
14	*n*Pr	Me	**3k**	5	120	83	80
15	*n*Pr	OMe	**3l**	5	120	82	17

[a] Isolated yield following column chromatography. [b] Determined by chiral HPLC. [c] In CH_2Cl_2. [d] Unresolved (but sample is optically active).

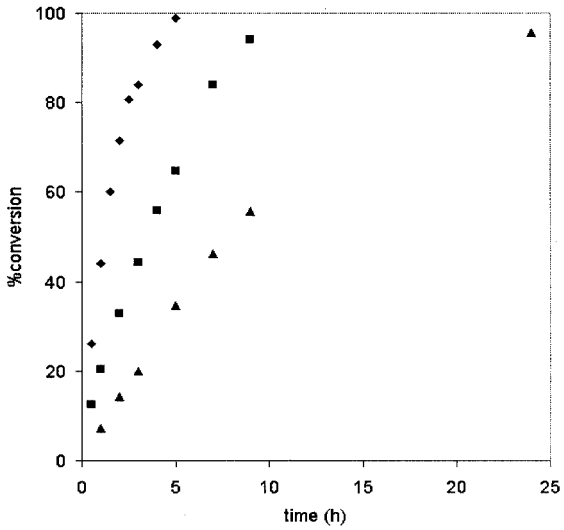


Figure 1. Rate of catalysed addition of *p*-chloroaniline (diamonds), aniline (squares) and *p*-anisidine (triangles) to **2a** (monitored using ^{1}H NMR spectroscopy)

nificantly, quantitative conversions could be obtained within 40 h when the catalytic loading was reduced to 2 mol %, with only a slight erosion in the stereoselectivity (Entry 3).

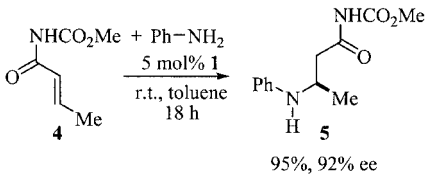
Examining other *para*-substituted anilines, we observed that the rate and enantioselectivity of the reactions are sensitive to the electronic characteristics of the aromatic amine. Remarkably, the reaction of *p*-chloroaniline with **2a** proceeded with perfect enantioselectivity (>99 % *ee*, Entry 4); it also showed the highest turnover. In this case, the catalyst loading could be reduced to 2 mol % without affecting either the yield or selectivity (Entry 5). Conversely, electron-donating substituents on the aromatic ring suppressed the enantioselectivity of the process. Whilst the reaction of *p*-toluidine proceeded with a yield and *ee* value similar to that of aniline (Entry 6), the reaction of electron-rich *p*-anisidine displayed the same number of turnovers, but only after 40 h, with a moderate *ee* of 73 % (Entry 7).

Previously, the addition of nitrogen nucleophiles to activated olefins, such as *N*-alkenoyloxazolidinones, was thought to proceed by a Lewis acidpromoted process,[4,5] in which attack of the weak nucleophile is facilitated by chelation of the oxazolidinone functionality to a cationic metal centre. Therefore, we were rather astonished to find that the relative rates of addition of amines to the *N*-alkenoylcarbamate **2a** increased in the order *p*-anisidine < aniline < *p*-chloroaniline (Figure 1), i.e. the least nucleophilic amine is, in fact, the most reactive. What we have observed in the present system clearly contradicts the earlier hypothesis, thus indicating the operation of either a competitive rate-determining step, or an entirely different reaction mechanism.

With a 5 mol % catalyst loading, the reaction of *p*-chloroaniline was essentially complete within five hours. Corresponding to a turnover rate of 4 h^{-1}, this is not only the most selective, but also, by far, the most active late transition metalcatalysed system. Concurrently, the enantiomeric excess of the product was monitored by chiral HPLC, which showed that enantioselectivity was established at the onset and remained constant throughout the course of the reaction.

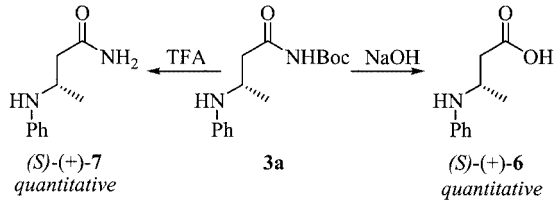
Homologation of the β-substituent to *N*-pentenoyl- and hexenoylcarbamates (**2b** and **2c**) reduced the rate of the conjugate addition (Entries 8−15). The unusually long time required for the reaction of *p*-toluidine to **2b** (Entry 10), compared with other amines (Entries 8, 9 and 11), is also an interesting feature, and suggests the possibility of competitive rate-determining steps. Nevertheless, good to excellent conversions and yields were obtained, and the enantioselectivity was high in most cases, except for the reactions of *p*-anisidine, which proceeded with low selectivity (Entries 11 and 15).

The bulky NHBoc group appeared to play no part in the outcome of the reaction, as shown by the addition of aniline to the methyl carbamate **4** (Scheme 2), which also proceeded in high yield (95 %) and enantioselectivity (92 % *ee*).



Scheme 2. Conjugate addition of aniline to to *N*-butenoyl-methylcarbamate

The NHBoc functionality may be easily transformed under mild basic or acidic conditions to afford valuable optically active β-amino acid or amide derivatives. Hence, **3a** was converted quantitatively into the corresponding β-am-



Scheme 3. Conversions to β-amino acid and amide

ino acid **6** and the β-amino amide **7** (Scheme 3). *N*-Aryl-β-amino acids have been prepared previously by Pd/Cu-catalysed aryl amination of β-amino acids with aryl halides.[6,7] The absolute stereochemistry of **6** (and therefore **7**) was thus established to be (*S*), by comparison of its optical rotation with the literature value.[8]

Conclusion

In summary, we have demonstrated that the cationic palladium(II) complex **1** catalyses the addition of primary aromatic amines to *N*-alkenoylcarbamates under mild conditions with unprecedentedly high turnovers and enantioselectivities. The products can easily be converted into optically active β-amino acid or amide derivatives, providing a novel and facile way to synthesise these valuable compounds.[9,10] The reactivity of the present system precludes an outright Lewis acid mechanism. This will be examined in our future work.

Experimental Section

General Remarks: Manipulations were performed using standard Schlenk techniques under inert atmosphere (N_2 or Ar). Dichloromethane, toluene and acetonitrile were dried over CaH_2, distilled, and stored under a nitrogen atmosphere prior to use. Column chromatography was performed on silica gel (Kieselgel 60, 63−200μm). NMR spectra were recorded on Bruker Avance 360 (^1H and ^{13}C at 360 and 90.6 MHz, respectively) or 400 (^1H and ^{13}C at 400 and 100.6 MHz, respectively) instruments. Chemical shifts are referenced to residual chloroform (for ^1H) and [D]chloroform (for ^{13}C). Optical rotation values were measured on a Perkin-Elmer polarimeter 343 using a 10 cm solution cell and the concentration of the samples is given in g/mL. Melting points (uncorrected) were determined on an Electrothermal Gallenhamp apparatus. The elemental analyses were carried out at London Metropolitan University. Mass spectra (MS) were recorded using Electron Impact (EI, low and high resolution) or Electrospray (ES, high resolution) techniques. HPLC analyses were performed on a Gilson HPLC system using Daicel Chiralpak AD or AS columns (equipped with an autoinjector with a 20 μL loop); detection was effected by UV absorption at 215 nm. Acid chlorides were prepared from the appropriate acid by chlorination (thionyl chloride). Unless otherwise indicated, all chemicals were obtained commercially and used as received. The preparation of complex **1** has been previously reported.[11] Palladium salts were obtained from Johnson Matthey plc. through a precious metals loan agreement.

Typical Procedure for the Synthesis of *tert*-Butyl Alkenoylcarbamates 3a−l and 5: *n*-Butyllithium and 2-butenoyl chloride were added successively to a solution of *tert*-butyl carbamate (1.0 g, 8.54 mmol) in THF (20 mL) at −78 °C in the following quantities: (*n*BuLi, 2-butenoyl chloride) (5.34, 0.41), (2.67, 0.21), (1.34, 0.10), (0.67, 0.05) and (0.34, 0.03) mL. Stirring was continued for 30 min, the reaction mixture poured into an ice-cooled solution of saturated aq. $NaHCO_3$ (50 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents evaporated. The crude product was purified by flash chromatography (Et_2O/pet. ether, 1:3).

***tert*-Butyl (*E*)-But-2-enoylcarbamate (2a):** White solid (1.28 g, 81 %). R_f = 0.4 (Et_2O/pet. ether, 1:3). M.p. 138−139 °C. ^1H NMR: δ = 1.49 (s, 9 H, *t*Bu), 1.92 (dd, 1 H, CH_3CH, $^2J_{H,H}$ = 6.8, $^3J_{H,H}$ = 1.5 Hz), 6.82 (dd, 1 H, COCH, $^2J_{H,H}$ = 15.2, $^3J_{H,H}$ = 1.5 Hz), 7.05−7.15 (m, 1 H, CH_3CH), 7.31 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 15.9 (*C*H_3CH), 27.9 [C(*C*H_3)$_3$], 82.3 [*C*(CH$_3$)$_3$], 121.2 (CO*C*H), 145.5 (CH$_3$*C*H), 150.5 (CO_2), 166.3 (*C*OCH) ppm. *m*/*z* (HR-ESMS): calcd. 185.1052 [M^+]; found 185.1046. $C_9H_{15}NO_3$: calcd. C 58.36, H 8.16, N 7.56; found C 58.08, H 8.05, N 7.63.

***tert*-Butyl (*E*)-Pent-2-enoylcarbamate (2b):** White solid (1.19 g, 70 %). R_f = 0.4 (Et_2O/pet. ether, 1:3). M.p. 78−79 °C. ^1H NMR: δ = 1.09 (t, 3 H, CH_3CH$_2$, $^2J_{H,H}$ = 7.4 Hz), 1.47 (s, 9 H, *t*Bu), 2.23−2.31 (m, 2 H, CH$_3$CH_2), 6.79 (d, 1 H, COCH, $^2J_{H,H}$ = 15.6 Hz), 7.11−7.19 (m, 1 H, CH$_2$CH), 7.31 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 12.1 (*C*H$_3$CH$_2$), 25.7 (CH$_3$*C*H$_2$), 28.0 [C(*C*H$_3$)$_3$], 82.4 [*C*(CH$_3$)$_3$], 120.7 (CO*C*H), 150.5 (CH$_3$*C*H), 152.1 (CO_2), 166.3 (*C*OCH) ppm. *m*/*z* (HR-ESMS): calcd. 199.1208 [M^+]; found 199.1203. $C_{10}H_{17}NO_3$: calcd. C 60.28, H 8.60, N 7.03; found C 60.42, H 8.75, N 6.85.

***tert*-Butyl (*E*)-Hex-2-enoylcarbamate (2c):** White solid (1.46 g, 80 %). R_f = 0.4 (Et_2O/pet. ether, 1:3). M.p. 71−72 °C. ^1H NMR: δ = 0.93 (t, 3 H, CH_3CH$_2$, $^2J_{H,H}$ = 7.3 Hz), 1.45−1.55 (m, 2 H, CH$_3$CH_2), 1.49 (s, 9 H, *t*Bu), 2.20−2.26 (m, 2 H, CH$_3$CH$_2$CH_2), 6.79 (d, 1 H, COCH, $^2J_{H,H}$ = 15.4 Hz), 7.06−7.14 (m, 1 H, CH$_2$CH), 7.36 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.7 (*C*H$_3$CH$_2$), 21.3 (CH$_3$*C*H$_2$), 28.0 [C(*C*H$_3$)$_3$], 34.6 (*C*H$_2$CH), 82.4 121.6 (CO*C*H), 150.5 (CH$_3$*C*H), 150.7 (CO_2), 166.2 (*C*OCH) ppm. *m*/*z* (HR-ESMS): calcd. 213.1365 [M^+]; found 213.1359. $C_{11}H_{19}NO_3$: calcd. C 61.95, H 8.98, N 6.57; found C 62.24, H 8.93, N 6.37.

Typical Catalytic Procedure: Complex **1** (0.022 g, 0.020 mmol) and the appropriate *tert*-butyl alkenoylcarbamate (0.60 mmol) were placed in a thick-walled Young's tube. A solution of the corresponding amine (0.40 mmol) in toluene (2.0 mL) was then added by syringe. The Young's tube was sealed (PTFE tap), and the reaction mixture was stirred at 25 °C. After an appropriate period of time, the resultant homogeneous red solution was absorbed onto silica gel and subjected to column chromatography to furnish the product.

***tert*-Butyl 3-Anilinobutanoylcarbamate (3a):** White solid (111 mg, >99 %). R_f = 0.37 (Et_2O/pentane, 1:3). M.p. 117−118 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.5 mL/min): t_R = 18.4 min (major) and 23.6 min (minor). $[\alpha]_D^{20}$ = −10.4 (*c* = 0.041, $CHCl_3$), 97 % *ee*. ^1H NMR: δ = 1.30 (d, 3 H, CHCH_3, $^2J_{H,H}$ = 6.4 Hz), 1.50 (s, 9 H, *t*Bu), 2.88 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.2, $^2J_{H,H}$ = 15.9 Hz), 3.08 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.8, $^2J_{H,H}$ = 15.9 Hz), 3.85 (br. s, 1 H, PhNH), 4.03−4.07 (m, 1 H, NHCH), 6.62 (d, 2 H, Ph, $^2J_{H,H}$ = 8.6 Hz), 6.70 (t, 1 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 7.17 (t, 2 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 7.51 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 20.8 (*C*H$_3$CH), 27.9 [C(*C*H$_3$)$_3$], 42.1 (CO*C*H$_2$), 45.9 (NHCH), 82.7 [*C*(CH$_3$)$_3$], 113.7 (Ph), 117.7 (Ph), 129.3 (Ph), 146.8 (Ph), 150.5 (CO_2), 172.8 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 278.1630

[M+]; found 278.1625. $C_{15}H_{22}N_2O_3$: calcd. C 64.73, H 7.97, N 10.06; found C 64.80, H 7.77, N 9.93.

***tert*-Butyl 3-[(4-Chlorophenyl)amino]butanoylcarbamate (3b):** White solid (125 mg, >99 %). R_f = 0.26 (Et_2O/pentane, 1:3). M.p. 114−115 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.2 mL/min): t_R = 35.7 min (major) and 41.0 min (minor, located using racemic catalyst). $[\alpha]_D^{20}$ = −18.2 (*c* = 0.036, $CHCl_3$), >99 % *ee*. ^{1}H NMR: δ = 1.28 (d, 3 H, CHC*H*$_3$, $^2J_{H,H}$ = 6.3 Hz), 1.48 (s, 9 H, *t*Bu), 2.86 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.0, $^2J_{H,H}$ = 16.0 Hz), 3.07 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.8, $^2J_{H,H}$ = 16.0 Hz), 3.89 (br. s, 1 H, PhN*H*), 3.92−4.08 (m, 1 H, NHC*H*), 6.53 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 7.10 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 7.33 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 20.7 (*C*H$_3$CH), 27.9 [C(*C*H$_3$)$_3$], 41.9 (CO*C*H$_2$), 46.0 (NHCH), 83.8 [*C*(CH$_3$)$_3$], 115.7 (Ph), 122.1 (Ph), 129.1 (Ph), 145.5 (Ph), 150.6 (CO_2), 172.9 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 312.1241 [M+]; found 312.1237. $C_{15}H_{21}N_2O_3$: calcd. C 57.60, H 6.77, N 8.96; found C 57.58, H 6.66, N 8.67.

***tert*-Butyl 3-[(4-Methylphenyl)amino]butanoylcarbamate (3c):** White solid (109 mg, 93 %). R_f = 0.23 (Et_2O/pentane, 1:3). M.p. 84−85 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.5 mL/min): t_R = 21.4 min (major) and 25.2 min (minor). $[\alpha]_D^{20}$ = −13.6 (*c* = 0.050, $CHCl_3$), 92 % *ee*. ^{1}H NMR: δ = 1.28 (d, 3 H, CHC*H*$_3$, $^2J_{H,H}$ = 6.4 Hz), 1.48 (s, 9 H, *t*Bu), 2.23 (s, 3 H, PhC*H*$_3$), 2.84 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.1, $^2J_{H,H}$ = 15.9 Hz), 3.02 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.9, $^2J_{H,H}$ = 15.9 Hz), 3.68 (br. s, 1 H, PhN*H*), 3.96−3.99 (m, 1 H, NHC*H*), 6.56 (d, 2 H, Ph, $^2J_{H,H}$ = 8.3 Hz), 6.98 (d, 2 H, Ph, $^2J_{H,H}$ = 8.3 Hz), 7.63 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 20.3 (Ph*C*H$_3$), 20.7 (*C*H$_3$CH), 27.9 [C(*C*H$_3$)$_3$], 42.1 (CO*C*H$_2$), 46.3 (NHCH), 82.4 [*C*(CH$_3$)$_3$], 114.1 (Ph), 127.0 (Ph), 129.7 (Ph), 144.5 (Ph), 150.5 (CO_2), 173.0 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 292.1787 [M+]; found 292.1766. $C_{16}H_{24}N_2O_3$: calcd. C 65.73, H 8.27, N 9.58; found C 65.64, H 8.43, N 9.64.

***tert*-Butyl 3-[(4-Methoxyphenyl)amino]butanoylcarbamate (3d):** White solid (122 mg, 99 %). R_f = 0.4 (Et_2O/pentane, 1:1). M.p. 70−71 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 3:97, 1.2 mL/min): t_R = 30.1 min (major) and 37.8 min (minor). $[\alpha]_D^{20}$ = −10.4 (*c* = 0.078, $CHCl_3$), 73 % *ee*. ^{1}H NMR: δ = 1.26 (d, 3 H, CHC*H*$_3$, $^2J_{H,H}$ = 6.4 Hz), 1.47 (s, 9 H, *t*Bu), 2.80 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.8, $^2J_{H,H}$ = 15.9 Hz), 2.98 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.8, $^2J_{H,H}$ = 15.9 Hz), 3.50 (br. s, 1 H, PhN*H*), 3.74 (s, 3 H, OCH$_3$), 3.88−3.93 (m, 1 H, NHC*H*), 6.61 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 6.77 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 7.79 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 20.8 (*C*H$_3$CH), 27.9 [C(*C*H$_3$)$_3$], 42.2 (CO*C*H$_2$), 47.3 (NHCH), 55.7 (OCH$_3$), 82.5 [*C*(CH$_3$)$_3$], 114.9 (Ph), 115.8 (Ph), 140.8 (Ph), 150.4 (CO_2), 152.6 (Ph), 172.8 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 308.1736 [M+]; found 308.1730. $C_{16}H_{24}N_2O_4$: calcd. C 62.32, H 7.84, N 9.08; found C 62.43, H 7.93, N 8.86.

***tert*-Butyl 3-Anilinopentanoylcarbamate (3e):** White solid (115 mg, 98 %). R_f = 0.4 (Et_2O/pentane, 1:3). M.p. 105−106 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.2 mL/min): t_R = 20.4 min (major) and 24.3 min (minor). $[\alpha]_D^{20}$ = −29.0 (*c* = 0.041, $CHCl_3$), 90 % *ee*. ^{1}H NMR: δ = 0.97 (t, 3 H, CH$_2$C*H*$_3$, $^2J_{H,H}$ = 7.4 Hz), 1.48 (s, 9 H, *t*Bu), 1.60−1.72 (m, 2 H, C*H*$_2$CH$_3$), 2.88 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.0, $^2J_{H,H}$ = 15.4 Hz), 3.01 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.9, $^2J_{H,H}$ = 15.4 Hz), 3.84 (br. s, 2 H, NHC*H* and PhN*H*), 6.61 (d, 2 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 6.68 (t, 1 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 7.15 (t, 2 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 7.50 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 10.4 (*C*H$_3$CH$_2$), 27.9 [C(*C*H$_3$)$_3$], 28.0 (CH$_3$*C*H$_2$), 40.0 (CO*C*H$_2$), 51.7 (NHCH), 82.6 [*C*(CH$_3$)$_3$], 113.5 (Ph), 117.5 (Ph), 129.3 (Ph), 147.3 (Ph), 150.5 (CO_2), 173.0 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 292.1787 [M+]; found 292.1781. $C_{16}H_{24}N_2O_3$: calcd. C 65.73, H 8.27, N 9.58; found C 65.95, H 8.12, N 9.49.

***tert*-Butyl 3-[(4-Chlorophenyl)amino]pentanoylcarbamate (3f):** White solid (120 mg, 92 %). R_f = 0.6 (Et_2O/pentane, 1:2). M.p. 93−94 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.0 mL/min): t_R = 32.1 min (major) and 37.3 min (minor). $[\alpha]_D^{20}$ = −34.4 (*c* = 0.052, $CHCl_3$), 85 % *ee*. ^{1}H NMR: δ = 0.96 (t, 3 H, CH$_2$C*H*$_3$, $^2J_{H,H}$ = 7.4 Hz), 1.48 (s, 9 H, *t*Bu), 1.57−1.68 (m, 2 H, C*H*$_2$CH$_3$), 2.88 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.4, $^2J_{H,H}$ = 15.8 Hz), 3.03 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.2, $^2J_{H,H}$ = 15.8 Hz), 3.73−3.85 (m, 1 H, NHC*H*), 3.86 (br. s, 1 H, PhN*H*), 6.53 (d, 2 H, Ph, $^2J_{H,H}$ = 8.9 Hz), 7.08 (d, 2 H, Ph, $^2J_{H,H}$ = 8.9 Hz), 7.33 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 10.4 (*C*H$_3$CH$_2$), 27.9 (CH$_3$*C*H$_2$), 28.0 [C(*C*H$_3$)$_3$], 40.8 (CO*C*H$_2$), 51.9 (NHCH), 82.8 [*C*(CH$_3$)$_3$], 114.5 (Ph), 121.8 (Ph), 129.1 (Ph), 145.9 (Ph), 150.5 (CO_2), 173.0 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 326.1397 [M+]; found 326.1394. $C_{16}H_{23}ClN_2O_3$: calcd. C 58.80, H 7.09, N 8.57; found C 59.12, H 7.04, N 8.29.

***tert*-Butyl 3-[(4-Methylphenyl)amino]pentanoylcarbamate (3g):** White solid (115 mg, 94 %). R_f = 0.3 (Et_2O/pentane, 1:3). M.p. 96−97 °C. The enantiomers could not be resolved by chiral HPLC. $[\alpha]_D^{20}$ = −20.0 (*c* = 0.058, $CHCl_3$). ^{1}H NMR: δ = 0.96 (t, 3 H, CH$_2$C*H*$_3$, $^2J_{H,H}$ = 7.4 Hz), 1.47 (s, 9 H, *t*Bu), 1.57−1.68 (m, 2 H, C*H*$_2$CH$_3$), 2.23 (s, 3 H, PhC*H*$_3$), 2.86 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.3, $^2J_{H,H}$ = 15.5 Hz), 2.97 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.5 Hz), 3.69 (br. s, 1 H, PhN*H*), 3.77−3.83 (m, 1 H, NHC*H*), 6.55 (d, 2 H, Ph, $^2J_{H,H}$ = 8.4 Hz), 6.97 (d, 2 H, Ph, $^2J_{H,H}$ = 8.4 Hz), 7.61 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 10.4 (*C*H$_3$CH$_2$), 20.3 (Ph*C*H$_3$), 27.8 (CH$_3$*C*H$_2$), 27.9 [C(*C*H$_3$)$_3$], 40.0 (CO*C*H$_2$), 52.1 (NHCH), 82.5 [*C*(CH$_3$)$_3$], 113.9 (Ph), 126.8 (Ph), 129.8 (Ph), 144.9 (Ph), 150.4 (CO_2), 173.0 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 306.1943 [M+]; found 306.1938. $C_{17}H_{26}N_2O_3$: calcd. C 66.64, H 8.55, N 9.14; found C 66.83, H 8.68, N 9.27.

***tert*-Butyl 3-[(4-Methoxyphenyl)amino]pentanoylcarbamate (3h):** White solid (128 mg, >99 %). R_f = 0.6 (Et_2O/pentane, 1:1). M.p. 65−66 °C. HPLC (Chiralpak AD, *i*PrOH/hexane, 2:98, 1.2 mL/min): t_R = 43.9 min (major) and 52.7 min (minor). $[\alpha]_D^{20}$ = −5.2 (*c* = 0.067, $CHCl_3$), 16 % *ee*. ^{1}H NMR: δ = 0.96 (t, 3 H, CH$_2$C*H*$_3$, $^2J_{H,H}$ = 7.4 Hz), 1.47 (s, 9 H, *t*Bu), 1.58−1.66 (m, 2 H, C*H*$_2$CH$_3$), 2.88 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.3, $^2J_{H,H}$ = 15.8 Hz), 2.93 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.8 Hz), 3.52 (br. s, 1 H, PhN*H*), 3.69−3.76 (m, 1 H, NHC*H*), 3.73 (s, 3 H, OCH$_3$), 6.60 (d, 2 H, Ph, $^2J_{H,H}$ = 8.6 Hz), 6.76 (d, 2 H, Ph, $^2J_{H,H}$ = 8.6 Hz), 7.61 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 10.4 (*C*H$_3$CH$_2$), 27.7 (CH$_3$*C*H$_2$), 27.9 [C(*C*H$_3$)$_3$], 40.0 (CO*C*H$_2$), 53.0 (NHCH), 55.7 (OCH$_3$), 82.5 [*C*(CH$_3$)$_3$], 114.9 (Ph), 115.4 (Ph), 141.2 (Ph), 150.5 (CO_2), 152.4 (Ph), 172.9 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 322.1893 [M+]; found 322.1887. $C_{17}H_{26}N_2O_4$: calcd. C 63.33, H 8.13, N 8.69; found C 63.47, H 8.00, N 8.66.

***tert*-Butyl 3-Anilinohexanoylcarbamate (3i):** White solid (120 mg, 98 %). R_f = 0.3 (Et_2O/pentane, 1:4). M.p. 103−104 °C. HPLC (Chiralpak AD, EtOH/hexane, 3:97, 1.0 mL/min): t_R = 15.5 min (major) and 17.5 min (minor). $[\alpha]_D^{20}$ = −22.1 (*c* = 0.056, $CHCl_3$), 89 % *ee*. ^{1}H NMR: δ = 0.92 (t, 3 H, CH$_2$C*H*$_3$, $^2J_{H,H}$ = 7.3 Hz), 1.36−1.50 (m, 2 H, C*H*$_2$CH$_3$), 1.47 (s, 9 H, *t*Bu), 1.53−1.62 (m, 2 H, C*H*$_2$CH$_2$CH$_3$), 2.89 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 5.5, $^2J_{H,H}$ = 15.9 Hz), 3.00 (dd, 1 H, COCH$_2$, $^1J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.9 Hz), 3.81 (br. s, 1 H, PhN*H*), 3.88−3.96 (m, 1 H, NHC*H*), 6.61 (d, 2 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 6.68 (t, 1 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 7.15 (t, 2 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 7.41 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 14.0 (*C*H$_3$CH$_2$), 19.3 (CH$_3$*C*H$_2$), 27.9 [C(*C*H$_3$)$_3$], 37.5 (*C*H$_2$CH$_2$CH$_3$), 40.4 (CO*C*H$_2$), 50.0 (NHCH), 82.6 [*C*(CH$_3$)$_3$], 113.4 (Ph), 117.4 (Ph), 129.3 (Ph), 147.3 (Ph), 150.5 (CO_2), 173.0 (*C*OCH$_2$) ppm. *m*/*z* (HR-ESMS): calcd. 306.1943 [M+]; found

306.1938. $C_{17}H_{26}N_2O_3$: calcd. C 66.64, H 8.55, N 9.14; found C 66.72, H 8.49, N 9.02.

***tert*-Butyl 3-[(4-Chlorophenyl)amino]hexanoylcarbamate (3j):** White solid (123 mg, 90 %). R_f = 0.4 (Et_2O/pentane, 1:4). M.p. 76−77 °C. HPLC (Chiralpak AS, *i*PrOH/hexane, 2:98, 1.0 mL/min): t_R = 20.6 min (major) and 26.2 min (minor). $[\alpha]_D^{20}$ = −28.6 (*c* = 0.046, $CHCl_3$), 89 % *ee*. ^{1}H NMR: δ = 0.91 (t, 3 H, CH_2CH_3, $^2J_{H,H}$ = 7.3 Hz), 1.33−1.45 (m, 2 H, CH_2CH_3), 1.48 (s, 9 H, *t*Bu), 1.53−1.59 (m, 2 H, $CH_2CH_2CH_3$), 2.88 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 2.6, $^2J_{H,H}$ = 15.4 Hz), 3.02 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 4.8, $^2J_{H,H}$ = 15.4 Hz), 3.85 (br. s, 2 H, PhN*H*, NHC*H*), 6.52 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 7.08 (d, 2 H, Ph, $^2J_{H,H}$ = 8.8 Hz), 7.38 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 13.9 (CH_3CH_2), 19.3 (CH_3CH_2), 27.9 [$C(CH_3)_3$], 37.4 ($CH_2CH_2CH_3$), 40.3 ($COCH_2$), 50.2 (NHCH), 82.7 [$C(CH_3)_3$], 114.4 (Ph), 121.8 (Ph), 129.1 (Ph), 146.0 (Ph), 150.5 (CO_2), 173.1 ($COCH_2$) ppm. *m*/*z* (HRMS): calcd. 340.1554 [M^+]; found 340.1550. $C_{17}H_{25}ClN_2O_3$: calcd. C 59.90, H 7.39, N 8.22; found C 60.08, H 7.14, N 8.05.

***tert*-Butyl 3-[(4-Methylphenyl)amino]hexanoylcarbamate (3k):** White solid (107 mg, 83 %). R_f = 0.3 (Et_2O/pentane, 1:4). M.p. 63−64 °C. HPLC (Chiralpak AS, *i*PrOH/hexane, 1:99, 1.0 mL/min): t_R = 30.2 min (major) and 27.2 min (minor). $[\alpha]_D^{20}$ = −21.5 (*c* = 0.052, $CHCl_3$), 80 % *ee*. ^{1}H NMR: δ = 0.92 (t, 3 H, CH_2CH_3, $^2J_{H,H}$ = 7.3 Hz), 1.37−1.50 (m, 2 H, CH_2CH_3), 1.48 (s, 9 H, *t*Bu), 1.53−1.61 (m, 2 H, $CH_2CH_2CH_3$), 2.23 (s, 3 H, PhCH_3), 2.87 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.5, $^2J_{H,H}$ = 15.8 Hz), 2.96 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 6.2, $^2J_{H,H}$ = 15.8 Hz), 3.65 (br. s, 1 H, PhN*H*), 3.82−3.90 (m, 1 H, NHC*H*), 6.53 (d, 2 H, Ph, $^2J_{H,H}$ = 8.4 Hz), 6.97 (d, 2 H, Ph, $^2J_{H,H}$ = 8.4 Hz), 7.53 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 14.0 (CH_3CH_2), 19.3 (CH_3CH_2), 20.3 (PhCH_3), 28.0 [$C(CH_3)_3$], 37.4 ($CH_2CH_2CH_3$), 40.5 ($COCH_2$), 50.5 (NHCH), 82.5 [$C(CH_3)_3$], 113.8 (Ph), 126.8 (Ph), 129.8 (Ph), 144.9 (Ph), 150.4 (CO_2), 172.9 ($COCH_2$) ppm. *m*/*z* (HR-ESMS): calcd. 320.2100 [M^+]; found 320.2095. $C_{18}H_{28}N_2O_3$: calcd. C 67.47, H 8.81, N 8.74; found C 67.41, H 8.97, N 8.65.

***tert*-Butyl 3-[(4-Methoxyphenyl)amino]hexanoylcarbamate (3l):** Colourless oil (110 mg, 82 %). R_f = 0.6 (Et_2O/pentane, 1:1). HPLC (Chiralpak AD, *i*PrOH/hexane, 1.6:98.4, 1.2 mL/min): t_R = 56.1 min (major) and 62.9 min (minor). $[\alpha]_D^{20}$ = −4.2 (*c* = 0.043, $CHCl_3$), 17 % *ee*. ^{1}H NMR: δ = 0.90 (t, 3 H, CH_2CH_3, $^2J_{H,H}$ = 7.2 Hz), 1.34−1.44 (m, 2 H, CH_2CH_3), 1.46 (s, 9 H, *t*Bu), 1.49−1.59 (m, 2 H, $CH_2CH_2CH_3$), 2.82 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.4, $^2J_{H,H}$ = 15.6 Hz), 2.92 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 6.2, $^2J_{H,H}$ = 15.6 Hz), 3.51 (br. s, 1 H, PhN*H*), 3.72 (s, 3 H, OCH_3), 3.75−3.81 (m, 1 H, NHC*H*), 6.60 (d, 2 H, Ph, $^2J_{H,H}$ = 8.9 Hz), 6.75 (d, 2 H, Ph, $^2J_{H,H}$ = 8.9 Hz), 7.79 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 14.9 (CH_3CH_2), 19.3 (CH_3CH_2), 27.9 [$C(CH_3)_3$], 37.3 ($CH_2CH_2CH_3$), 40.4 ($COCH_2$), 51.4 (NHCH), 55.7 (OCH_3), 82.4 [$C(CH_3)_3$], 114.9 (Ph), 115.3 (Ph), 141.2 (Ph), 150.4 (CO_2), 152.3 (Ph), 173.0 ($COCH_2$) ppm. *m*/*z* (HR-ESMS): calcd. 336.2049 [M^+]; found 336.2043. $C_{18}H_{28}N_2O_4$: calcd. C 64.26, H 8.39, N 8.33; found C 64.13, H 8.07, N 8.15.

Methyl (*E*)-But-2-enoylcarbamate (4): Styrene (30 mL) and CuCl (0.1 g) were added successively to a mixture of methyl carbamate (1.0 g, 8.54 mmol) and 2-butenoyl chloride (2.4 mL, 25.0 mmol). The reaction mixture was stirred at 114 °C for 16 h. It was then cooled to room temperature and the solvents evaporated to give a white residue, which was dissolved in dichloromethane, washed with water and brine and dried over $MgSO_4$. The solution was concentrated; the addition of pentane to the residue furnished **4** as a white precipitate (0.93 g, 76 %). M.p. 149−150 °C. ^{1}H NMR: δ = 1.94 (dd, 1 H, CH_3CH, $^2J_{H,H}$ = 6.8, $^3J_{H,H}$ = 1.4 Hz), 3.78 (s, 3 H, OCH_3), 6.84 (dd, 1 H, COCH, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 1.3 Hz), 7.10−7.20 (m, 1 H, CH_3CH), 7.89 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 18.4 (CH_3CH), 53.0 (OCH_3), 122.7 ($COCH$), 146.6 (CH_3CH), 152.4 (CO_2), 166.1 ($COCH$) ppm. *m*/*z* (HR-EIMS): calcd. 143.0582 [M^+]; found 143.0577**.** $C_9H_9NO_3$: calcd. C 50.35, H 6.34, N 9.79; found C 50.44, H 6.59, N 9.94.

Methyl 3-Anilinobutanoylcarbamate (5): Colourless oil (90 mg, 95 %). R_f = 0.4 (Et_2O/pentane, 1:1). HPLC (Chiralpak AD, *i*PrOH/hexane, 5:95, 1.0 mL/min): t_R = 26.8 min (major) and 33.8 min (minor). $[\alpha]_D^{20}$ = −6.5 (*c* = 0.037, $CHCl_3$), 92 % *ee*. ^{1}H NMR: δ = 1.30 (d, 3 H, $CHCH_3$, $^2J_{H,H}$ = 6.8 Hz), 2.89 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.9, $^2J_{H,H}$ = 15.9 Hz), 3.05 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.9, $^2J_{H,H}$ = 15.9 Hz), 3.76 (s, 4 H, 1 H, PhN*H*, 3 H, OCH_3), 3.99−4.08 (m, 1 H, NHC*H*), 6.64 (d, 2 H, Ph, $^2J_{H,H}$ = 7.7 Hz), 6.72 (t, 1 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 7.18 (t, 2 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 7.72 (br. s, 1 H, CONH) ppm. ^{13}C NMR: δ = 20.8 (CH_3CH), 42.2 ($COCH_2$), 46.0 (NHCH), 53.0 (OCH_3), 113.9 (Ph), 118.0 (Ph), 129.3 (Ph), 146.7 (Ph), 152.2 (CO_2), 172.5 ($COCH_2$) ppm. *m*/*z* (HR-ESMS): calcd. 236.1161 [M^+]; found 236.1155. $C_{12}H_{16}N_2O_3$: calcd. C 61.00, H 6.83, N 11.86; found C 59.95, H 6.60, N 11.47.

Formation of β-Amino Acid 6 by Deprotection of Compound 3a: Compound (−)-**3a** (0.10 g, 0.36 mmol, 90 % *ee*) was hydrolysed with 1 N KOH in MeOH (2.5 equiv.) at room temperature for 1 h, after which the reaction solvents were evaporated. The residue was then dissolved in water, and washed with portions of Et_2O. The aqueous phase was acidified with 1 N HCl (pH 4), before extracting with EtOAc (4 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents evaporated to afford β-amino acid **6** (64 mg, quantitatively). $[\alpha]_D^{20}$ = +18.1 (*c* = 0.032, $CHCl_3$). ^{1}H NMR: δ = 1.29 (d, 3 H, $CHCH_3$, $^2J_{H,H}$ = 6.4 Hz), 2.51 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.4 Hz), 2.66 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.9, $^2J_{H,H}$ = 15.4 Hz), 3.89−3.98 (m, 1 H, CH_3CH), 6.30 (br. s, 2 H, CHN*H* and COOH), 6.68 (d, 2 H, Ph, $^2J_{H,H}$ = 7.8 Hz), 6.78 (t, 1 H, Ph, $^2J_{H,H}$ = 7.4 Hz), 7.21 (t, 2 H, Ph, $^2J_{H,H}$ = 7.4 Hz) ppm. ^{13}C NMR: δ = 20.6 (CH_3CH), 40.6 ($COCH_2$), 46.5 (NHCH), 114.5 (Ph), 118.7 (Ph), 129.4 (Ph), 146.1 (Ph), 176.6 (CO_2H) ppm. *m*/*z* (HR-EIMS): calcd. 179.0946 [M^+]; found 179.0941.

Formation of β-Amino Amide 7 by Deprotection of Compound 3a: Compound (−)-**3a** (0.10 g, 0.37 mmol, 94 % *ee*) was dissolved in CH_2Cl_2/TFA (1:1, 2 mL). The mixture was stirred at room temperature for 1 h and the solvents evaporated in vacuo. The residue was purified by chromatography (EtOAc/Et_3N, 50:1) to give the pure amide **7** (66 mg, quantitative). $[\alpha]_D^{20}$ = +37.4 (*c* = 0.033, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 1.29 (d, 3 H, $CHCH_3$, $^2J_{H,H}$ = 6.4 Hz), 2.39 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 5.5, $^2J_{H,H}$ = 15.0 Hz), 2.48 (dd, 1 H, $COCH_2$, $^1J_{H,H}$ = 6.4, $^2J_{H,H}$ = 15.0 Hz), 3.73 (br. s, 1 H, PhN*H*), 3.88−3.96 (m, 1 H, CH_3CH), 5.60 (br. s, 1 H, $CONH_2$), 6.03 (br. s, 1 H, $CONH_2$), 6.66 (d, 2 H, Ph, $^2J_{H,H}$ = 7.8 Hz), 6.75 (t, 1 H, Ph, $^2J_{H,H}$ = 7.3 Hz), 7.19 (t, 2 H, Ph, $^2J_{H,H}$ = 7.3 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 20.8 (CH_3CH), 42.1 ($COCH_2$), 46.6 (NHCH), 114.1 (Ph), 118.3 (Ph), 129.4 (Ph), 146.7 (Ph), 173.5 ($CONH_2$) ppm. *m*/*z* (HR-EIMS): calcd. 178.1106 [M^+]; found 178.1101. $C_{10}H_{14}N_2O$: calcd. C 67.39, H 7.92, N 15.72; found C 67.23, H 8.07, N 15.90.

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