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Stereoselective Peptide Modifications via β-C(sp^3)-H Arylations

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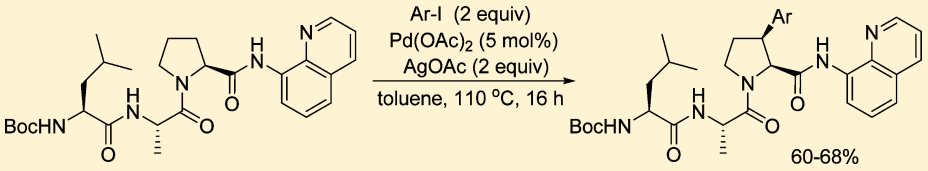
Supporting Information



ABSTRACT: Palladium-catalyzed stereoselective β-arylations of phenylalanine, proline- and pipecolinic acid-containing peptides are a versatile tool for peptide modifications. The reactions proceed without epimerization of stereogenic centers in the peptide chain. If suitable functionalized aryl iodides are introduced, subsequent cross coupling reactions can be used for further modifications. The 8-amino quinoline (AQ) directing group can easily be removed, allowing the prolongation of the peptide chain at the *C*-terminus.

INTRODUCTION

Peptides containing unusual and/or modified amino acids are interesting drug candidates, especially because the incorporation of nonproteinogenic amino acids in general increases the stability of these peptides toward proteases. Peptides containing modified prolines, such as **A** (Figure 1), can act as

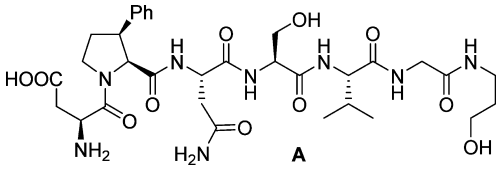


Figure 1. Factor XIa inhibitor containing β-arylated proline.

peptidomimetics[1] showing interesting anti-inflammatory and antitumor activities.[2] The comparable ring-enlarged pipecolinic acid derivatives are found as building blocks, e.g., in factor XIa inhibitors for the treatment of thrombosis.[3]

Therefore, from a synthetic and pharmaceutical point of view, straightforward approaches toward such structures, allowing an easy synthesis of a wide range of derivatives for SAR studies, are highly desired. The classical peptide synthesis approach starts with the asymmetric synthesis of the unusual amino acids,[4] incorporating them subsequently into the desired peptides using standard peptide coupling reagents. A more straightforward approach is based on peptide modifications, either of a functionalized side chain in a given peptide, which can be modified,[5] or by direct introduction of a complete side chain at the desired position of a peptide.[6] This approach, termed backbone modification, is a very flexible approach, because variation of a peptide skeleton can be performed on a relatively late state of the synthesis. The concept of peptide modification via sarcosine enolate alkylation was introduced by Seebach in the early 90s,[7] and the most spectacular application so far was the regioselective modification of cyclosporine.[8]

Our group is also involved in the synthesis of complex peptides via peptide modifications, developing tools for natural product and drug synthesis. Using chelated peptide enolates as nucleophiles in transition metal-catalyzed allylic alkylations,[9] unsaturated side chains can be introduced into peptides in a highly stereoselective fashion.[10] The configuration of the new formed stereogenic center can be controlled by the other stereogenic centers in the peptide chain. Recently we used such a modification approach in the total synthesis of miuraenamides.[11] The protocol of glycine or sarcosine enolate "alkylation" is well suited for the introduction of linear side chains, but cannot be applied to the synthesis of cyclic amino acids such as prolines or pipecolinic acids. But luckily, during the last years, direct C−H bond functionalization emerged as a promising synthetic tool for the synthesis of many key structural units present in drugs and natural products.[12] Currently, transition metal-catalyzed functionalizations of unactivated aliphatic C−H bonds is a hot topic,[13] and especially auxiliary assisted regio- and stereoselective transformations of sp^3 C−H bonds have become an important tools in modern synthetic organic chemistry.[14] Daugulis et al. first demonstrated the concept of auxiliary assisted C(sp^3)-H arylation of aliphatic acids and amines,[15] while Corey et al. reported a similar approach for β-acetoxylation of phthalimide-protected α-amino acids.[16] On the basis of these two pioneering publications, different groups have developed a range of β- and γ-C(sp^3)-H functionalization strategies for carboxylic[17] and amino acids[18,19] using a bidentate directing group. Considering the biological activities and prevalence of cyclic α-amino acids in natural products, efficient methods for the synthesis of substituted prolines[20] and

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pipecolinic acids[21] are required. Although, there are plenty of protocols for the synthesis of functionalized cyclic α-amino acids, atom and step economical direct C−H functionalization strategies are rather limited.[19] While functionalization of α-amino acids are generally carried out with the protected amino acids,[7] direct modification of peptides are scarce.[7,22] Herein, we report Pd-catalyzed β-C(sp^3)-H arylations of small peptides, assisted by easily removable 8-aminoquinoline (AQ) as a directing group.

RESULTS AND DISCUSSION

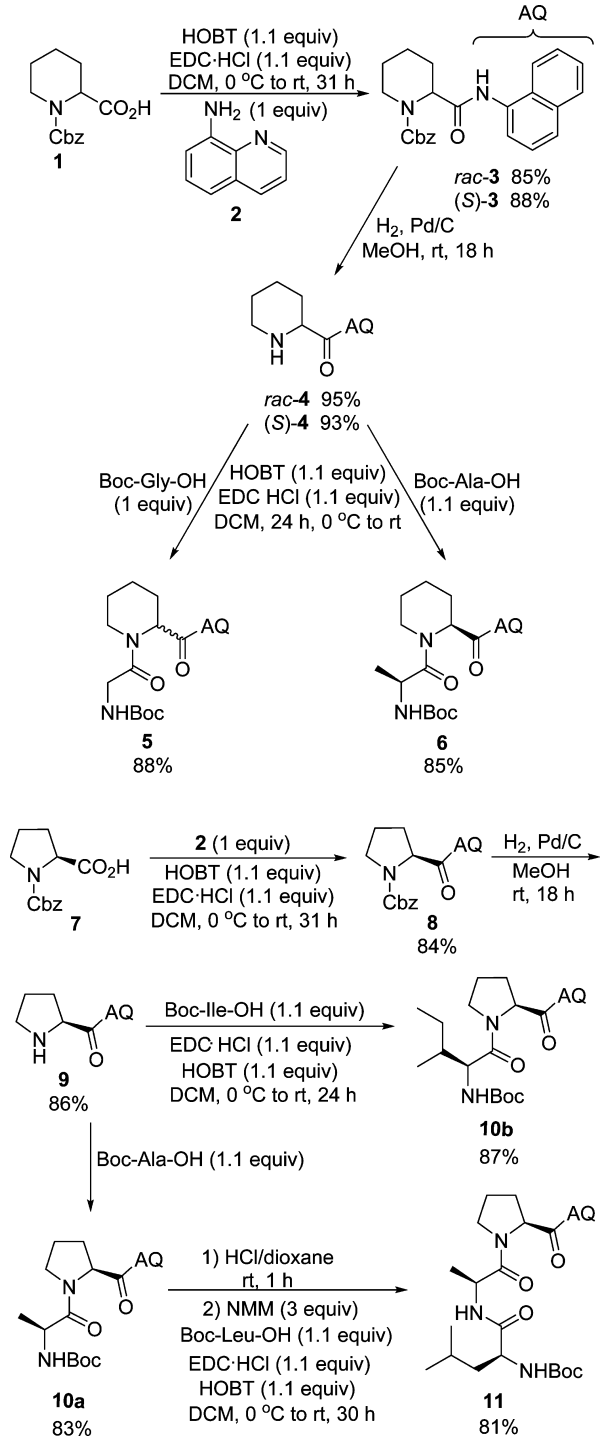
Since 8-aminoquinoline is probably the most popular directing group for transition metal-catalyzed C−H bond activation, we also decided to use this group for our peptide modifications. The synthesis of the required peptides is shown in Scheme 1. For the optimization of the reaction conditions, we decided to start our investigations with the simple racemic dipeptide **5** which was easily obtained by standard peptide synthesis operations. Enantiomerically pure **4**, obtained from (*S*)-**3**[23] was coupled with (*S*)-Ala to give dipeptide **6**. In an analogous way, the corresponding proline peptides **10a** and **10b** were obtained in comparable good yields, and **10a** was also prolonged to tripeptide **11**.

Our initial experiments were carried out with racemic dipeptide **5** and *p*-iodoanisole **12a** and we varied a wide range of reaction conditions (Table 1). According to literature procedures $Pd(OAc)_2$ in toluene was used in combination with several silver salts. While Ag_2O and Ag_2CO_3 did not give satisfying results (entries 1 and 2), a good yield was obtained with AgOAc (entry 3). Replacing toluene by other solvents (entries 4−6) or neat condition (entry 7) did not result higher yields. A slight improvement was observed by increasing the concentration of **5** from 0.2 to 0.4 M (entry 8).

Under optimized conditions a yield of 84% could be obtained, which forced us to use these conditions for the coupling of other aryl and heteroaryl halides (Table 2). In all examples investigated, good yields could be obtained except with 4-iodophenol (**12f**, entry 6) and 6-iodoquinoline (**12g**, entry 7). In these two cases, the reaction was rather sluggish and even after prolonged reaction time (25 h) still some starting material was recovered. The slightly lower yield also obtained with the *p*-diiodobenzene (**12e**, entry 5) can be explained by a double functionalization, but the yield was still in an acceptable range. An excellent yield was obtained with the 1,3-dimethyl-5-iodoracil (**12h**). As expected in all cases the *syn* substitution product was formed exclusively as determined by high temperature NMR and HPLC (**5** and **23b**).

With these results in hand, we next investigated couplings with the enantiomerically pure dipeptides **6** and **10** (Table 3). Comparable yields were obtained, while the electron-rich iodides (**12a**,**b**) in general gave slightly better results compared to electron-poor iodides (**12i**−**k**). Also here only one stereoisomer was formed (*syn*) and no epimerization of the stereogenic centers was observed during the arylation process as determined by NMR and HPLC (**6** and **14b**). In the NMR spectra, in general a few percent of "another isomer" were found, but high temperature NMR (100 °C) clearly indicates that the second signal set is caused by the formation of rotamers and not by epimerization. The formation of the *syn* stereoisomer was confirmed by 2D NMR (NOESY)-analysis of compound **14b** and **15a** (see Supporting Information). Of course, the reaction is not limited to simple glycine or alanine peptides, but can also be

Scheme 1. Synthesis of Peptides with an 8-Aminoquinoline (AQ) Directing Group



applied to other dipeptides such as **10b**, while the yields obtained are comparable (entries 1, 5 and 9).

In principle, also larger peptides, such as tripeptide **11** can be subjected to modifications. In this case, the reactions seem to slow down slightly, because under our standard reaction conditions some starting material could be recovered, but the yields are still in a satisfactory range (Scheme 2).

To illustrate, that this protocol is also not restricted to secondary and cyclic *C*-terminal amino acids such as proline and pipecolinic acids, but can also be applied to other amino acids,

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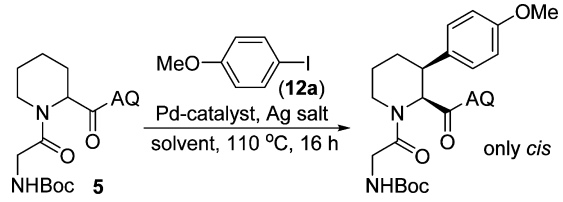
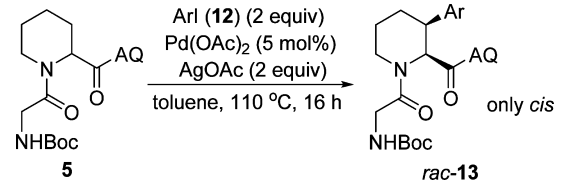
Table 1. Optimization of Reaction Conditions for Chelation-Assisted β-C(sp^3)-H Arylation

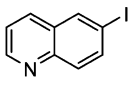
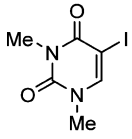


entry	Pd-catalyst	oxidant	solvent	yield (%)[a,b]
1	$Pd(OAc)_2$	Ag_2O	toluene	17
2	$Pd(OAc)_2$	Ag_2CO_3	toluene	39
3	$Pd(OAc)_2$	AgOAc	toluene	78
4	$Pd(OAc)_2$	AgOAc	DCE	69
5	$Pd(OAc)_2$	AgOAc	*t*-AmOH	63
6	$Pd(OAc)_2$	AgOAc	dioxane	64
7	$Pd(OAc)_2$	AgOAc	–	73
8	$Pd(OAc)_2$	AgOAc	toluene (0.4 M)	84

[a]Reaction conditions: **5** (0.2 mmol), **12a** (0.4 mmol), Pd-catalyst (5 mol %), silver salt (0.4 mmol), solvent (1.0 mL). [b]Isolated yield.

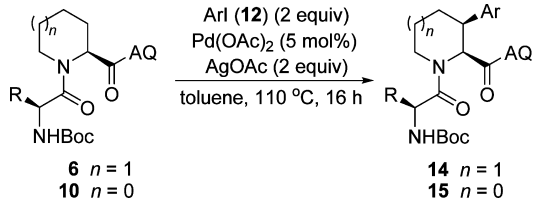
Table 2. Arylation of Dipeptide 5 with Aryl or Heteroaryl Iodides (12)

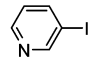
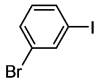


entry	ArI		product	yield(%)
1	MeO–C6H4–I	**12a**	**13a**	84
2	C6H5–I	**12b**	**13b**	77
3	Me–C6H4–I	**12c**	**13c**	87
4	Cl–C6H4–I	**12d**	**13d**	76
5	I–C6H4–I	**12e**	**13e**	71
6	HO–C6H4–I	**12f**	**13f**	41 (54)[a,b]
7		**12g**	**13g**	61 (73)[a]
8		**12h**	**13h**	89

[a]Corrected yield in parentheses. [b]Reaction carried out for 25 h.

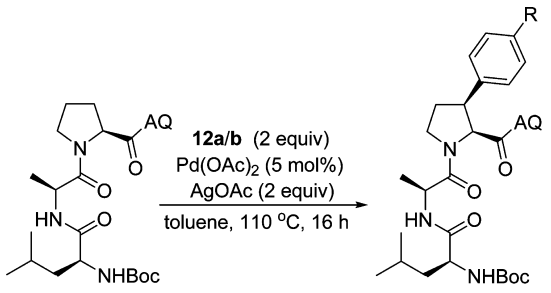
Table 3. Arylation of Dipeptides 6 and 10 with Aryl or Heteroaryl Iodides (12)



entry	peptide	R	ArI		product	yield (%)
1	**6**	Me	MeO–C6H4–I	**12a**	**14a**	83
2	**6**	Me	Me–C6H4–I	**12c**	**14b**	80
3	**6**	Me	O_2N–C6H4–I	**12i**	**14c**	71
4	**6**	Me		**12j**	**14d**	56 (68)[a,b]
5	**10a**	Me	MeO–C6H4–I	**12a**	**15a**	81
6	**10a**	Me	C6H5–I	**12b**	**15b**	82
7	**10a**	Me	O_2N–C6H4–I	**12i**	**15c**	57
8	**10a**	Me		**12k**	**15d**	69
9	**10b**	*s*-Bu	MeO–C6H4–I	**12a**	**15e**	83

[a]Corrected yield in parentheses. [b]Reaction carried out for 25 h.

Scheme 2. Stereoselective Arylations of Dipeptide 10b and Tripeptide 11



we synthesized the corresponding phenylalanine-containing peptide **17** in analogy to the previously used peptides (Scheme 1). The yields obtained in the arylation steps were slightly worse, and interestingly not the expected β-arylated dipeptides were obtained, but the corresponding imidazolidine-2,4-diones **18** (Scheme 3). Obviously, under the reaction conditions used, the internal amide bond attacks the Boc-protecting group, a side

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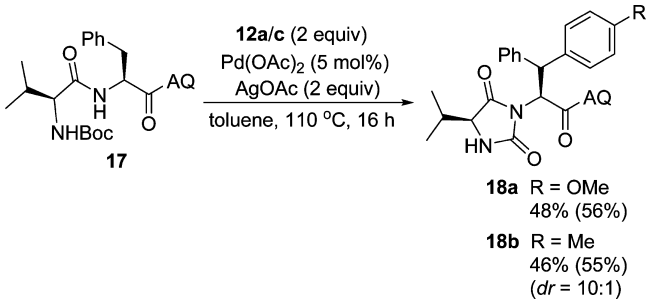
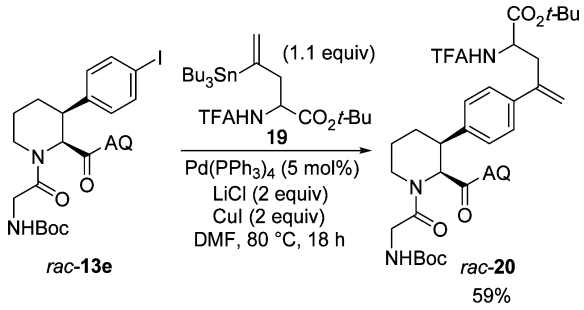
Scheme 3. Stereoselective Arylations of Dipeptide 17



reaction which is not an issue in case of secondary amides. With 4-iodotoluene (**12c**) imidazolidine-2,4-dione **18b** was obtained as a 10:1 diastereomeric mixture, as determined by NMR, while a single set of signals was observed in the spectra of **18a**, indicating a high stereoselectivity in the arylation step.

The introduction of functionalized aryl substituents such as in **13e** allows further modifications via cross coupling reactions, for example Stille couplings (Scheme 4). Coupling with stannylated

Scheme 4. Stille Coupling of Iodoarylated Dipeptide 13e



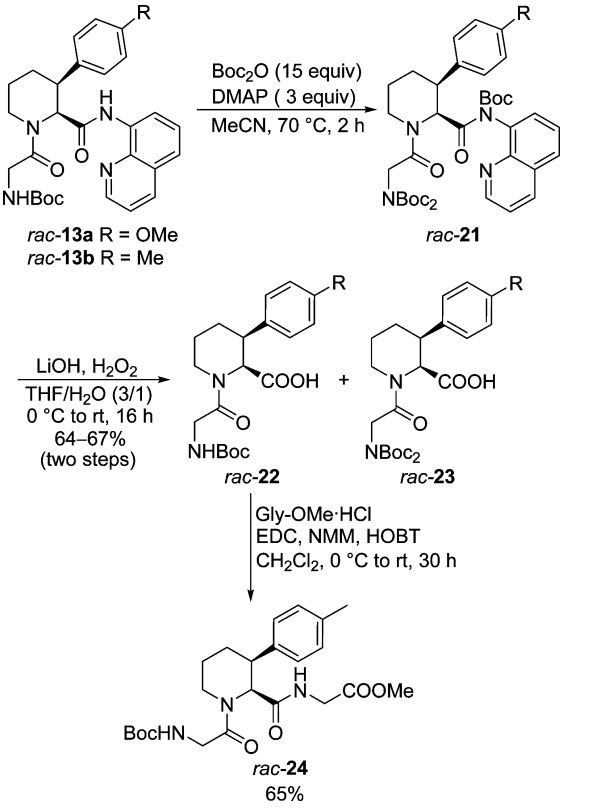
amino acid derivative **19**,[24] easily obtained via Pd-catalyzed glycine enolate allylation[25] using a stannylated allyl acetate,[26] provided access to a dipeptide **20** with an additional amino acid functionality and a reactive double bond for further modifications.

To make this protocol really suitable for natural product or drug syntheses we had to show that the AQ-directing group can be removed without decomposition/destruction of the peptide. Although AQ cannot be removed directly, it is no problem to subject the peptides (e.g., **13**) to complete Boc-protection using DMAP and an excess of Boc_2O (Scheme 5).[27] Saponification of crude **21** using $LiOH/H_2O_2$ gave rise to a mixture of mono- and di-Boc-protected peptide acids **22** and **23**, which is not a major issue, because treatment with acid will cause a cleavage of all Boc-protecting groups. Exemplarily, we subjected **22b** (R = Me) to an additional peptide coupling to illustrate that the peptide chain can be prolonged also at the *C*-terminus.

CONCLUSIONS

In conclusion, we could show that Pd-catalyzed stereoselective *β*-arylations of amino acids via C−H bond activation are not limited to the protected amino acids but can also be performed at the *C*-terminus of peptides. The directing group (AQ) can easily be removed allowing the incorporation of the modified peptides into larger structures. Additional modifications are possible if suitable functionalized aryl substituents are incorporated.

Scheme 5. Removal of the AQ Directing Group and Subsequent Peptide Coupling



EXPERIMENTAL SECTION

General Remarks. Air- or moisture-sensitive reactions were carried out in dried glassware (>100 °C) under an atmosphere of argon. Reactions were monitored by analytical TLC on precoated silica gel plates. Visualization was accomplished with UV-light (254 nm), ninhydrin solution or a iodine chamber. Rotary evaporation was conducted at 40 °C. The products were purified by flash chromatography columns on silica gel (0.063−0.2 mm) or on basic aluminum oxide 90 (0.063−0.2 mm, activation level III). Mixtures of ethyl acetate and petroleum ether (boiling range: 40−60 °C) were used as eluents. These solvents were distilled prior to use. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a 500 MHz (^1H) and a 400 MHz (^1H), 100 MHz (^{13}C), 376 MHz (^{19}F) spectrometer in $CDCl_3$ or DMDS-d_6 unless otherwise specified. Chemical shifts are reported in ppm relative to $Si(CH_3)_4$ and $CHCl_3$ was used as the internal standard [δ (^1H) = 7.27 ppm, δ (^{13}C) = 77.0 ppm]. Mass spectra were recorded with a high resolution quadrupole spectrometer (CI). Optical rotations were measured in a thermostated (20 ± 1 °C) cuvette. The radiation source used was a sodium vapor lamp (λ = 589 nm). The concentrations are given in g/100 mL.

*tert-Butyl 2-oxo-2-[2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]-ethylcarbamate (**5**).* A suspension of Cbz-Pip-AQ (**3**)[18b] (2.00 g, 5.13 mmol) and Pd/C (200 mg, 10%) in MeOH (20 mL) was stirred under an atmosphere of H_2 for 18 h at room temperature. Upon completion (TLC), the reaction mixture was filtered through a pad of Celite, and the solvent was removed in vacuo, giving rise to Pip-AQ (**4**) (1.24g, 95%) which was used in the next step without further purification. Therefore, **4** (1.20 g, 4.72 mmol), Boc-GlyOH (909 mg, 5.19 mmol) and 1-hydroxy benzotriazole hydrate (795 mg, 5.19 mmol) were dissolved in CH_2Cl_2 (30 mL) at 0 °C. EDC HCl (992 mg, 5.19 mmol) was added at 0 °C and the solution was stirred at this temperature for 1 h. Then the reaction mixture was allowed to warm to room temperature and stirred for 24 h. The reaction was diluted with CH_2Cl_2 (150 mL), washed with water (1 × 150 mL), sat. aq. $NaHCO_3$ (2 × 150 mL) and brine solution (1 × 200 mL). The organic layer was

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dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure. Purification by flash column chromatography (petroleum ether/ethyl acetate 7:3) offered dipeptide *tert*-butyl 2-oxo-2-[2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]ethylcarbamate (Boc-Gly-Pip-AQ, **5**) (1.71 g, 4.15 mmol, 88%) as colorless solid; mp 119−120 °C. Mixture of rotamers (87:13). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.79 (dd, J = 4.3, 1.5 Hz, 1H), 8.70 (dd, J = 6.4, 2.4 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.49−7.55 (m, 2H), 7.43 (dd, J = 8.3, 4.3 Hz, 1H), 5.69 (brs, 1H), 5.56−5.57 (m, 1H), 4.16−4.27 (m, 2H), 3.73−3.76 (m, 1H), 3.33−3.40 (m, 1H), 2.48−2.54 (m, 1H), 1.63−1.79 (m, 4H), 1.51−1.57 (m, 1H), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 168.4, 155.8, 148.5, 138.5, 136.2, 133.9, 127.9, 127.2, 121.8, 121.6, 116.3, 79.6, 53.9, 42.8, 42.7, 28.3, 25.6, 25.2, 20.4. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 5.62 (brs, 1H), 4.72−4.75 (m, 1H), 4.63−4.64 (m, 1H), 4.01−4.06 (m, 1H), 2.92−2.99 (m, 1H), 2.59−2.63 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2. HRMS (CI) for $C_{22}H_{29}N_4O_4$ $[M + H]^+$ calcd. 413.2189, found 413.2177.

*tert-Butyl (R)-1-oxo-1-[(S)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]propan-2-ylcarbamate (**6**).* According to **5** *tert*-butyl (*R*)-1-oxo-1-[(*S*)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]propan-2-ylcarbamate (Boc-(*S*)-Ala-(*S*)-Pip-AQ, **6**) was synthesized from (*S*)-Pip-AQ[19e] in a 4 mmol scale (85% yield). Colorless solid; mp 61−62 °C; $[\alpha]_D^{20}$ = −143.8 (c 1, $CHCl_3$). Mixture of rotamers (93:7). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.76 (dd, J = 6.9, 2.1 Hz, 1H), 8.70 (dd, J = 4.3, 1.5 Hz, 1H), 8.16 (dd, J = 8.3, 1.5 Hz, 1H), 7.50−7.57 (m, 2H), 7.44 (dd, J = 8.3, 4.3 Hz, 1H), 5.64−5.69 (m, 2H), 4.80−4.87 (m, 1H), 3.94−3.98 (m, 1H), 3.30−3.37 (m, 1H), 2.54−2.62 (m, 1H), 1.79 (m, 1H), 1.67−1.75 (m, 4H), 1.62 (d, J = 6.8 Hz, 3H), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 168.5, 155.1, 148.0, 138.4, 136.2, 134.0, 127.8, 127.3, 121.7, 121.6, 116.3, 79.5, 53.8, 46.5, 44.1, 28.4, 25.6, 25.4, 20.6, 19.3. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.79−8.81 (m, 1H), 5.59−5.61 (m, 1H), 4.72−4.77 (m, 2H), 2.82−2.89 (m, 1H), 2.68−2.71 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8. HRMS (CI) for $C_{23}H_{31}N_4O_4$ $[M + H]^+$ calcd. 427.2345, found 427.2359.

*tert-Butyl (S)-1-oxo-1-[(S)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]propan-2-ylcarbamate (**10a**).* Compound **10a** was prepared using a procedure similar to that used in the preparation of **5** from Cbz-Pro-AQ (**8**) in a 10 mmol scale in 83% yield. Colorless solid; mp 59−60 °C, $[\alpha]_D^{20}$ = −103.2 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.74−8.77 (m, 2H), 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.50−7.55 (m, 2H), 7.44 (dd, J = 8.3, 4.3 Hz, 1H), 5.45 (d, J = 8.0 Hz, 1H), 4.87−4.89 (m, 1H), 4.59−4.66 (m, 1H), 3.76−3.85 (m, 2H), 2.36−2.44 (m, 1H), 2.14−2.26 (m, 2H), 2.06−2.12 (m, 1H), 1.55 (d, J = 7.0 Hz, 3H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 169.7, 155.2, 148.1, 138.6, 136.2, 134.2, 127.9, 127.3, 121.8, 121.6, 116.6, 79.6, 61.4, 47.8, 47.3, 28.9, 28.4, 25.0, 19.0. HRMS (CI) for $C_{22}H_{29}N_4O_4$ $[M + H]^+$ calcd. 413.2189, found 413.2189.

*tert-Butyl (2S,3R)-3-methyl-1-oxo-1-[(S)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]pentan-2-ylcarbamate (**10b**).* Compound **10b** was prepared using a procedure similar to that used in the preparation of **5** from Cbz-Pro-AQ (**8**) in a 2.76 mmol scale in 87% yield. Colorless solid; mp 49−50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.81 (dd, J = 4.1, 1.6 Hz, 1H), 8.75 (dd, J = 6.0, 2.8 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.49−7.54 (m, 2H), 7.44 (dd, J = 8.3, 4.3 Hz, 1H), 5.23 (d, J = 9.3 Hz, 1H), 4.88 (dd, J = 7.3, 3.5 Hz, 1H), 4.40 (dd, J = 9.0, 7.3 Hz, 1H), 3.88−3.93 (m, 1H), 3.76−3.81 (m, 1H), 2.36−2.40 (m, 1H), 2.15−2.25 (m, 2H), 2.05−2.15 (m, 1H), 1.80−1.87 (m, 1H), 1.59−1.65 (m, 1H), 1.44 (s, 9H), 1.07−1.17 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H), 0.78 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.9, 155.7, 148.2, 138.5, 136.1, 134.4, 127.8, 127.1, 121.7, 121.5, 116.7, 79.5, 61.3, 56.2, 47.6, 37.9, 28.5, 28.3, 25.0, 24.1, 15.6, 11.1. HRMS (CI) for $C_{25}H_{35}N_4O_4$ $[M + H]^+$calcd.455.2658, found 455.2657.

*tert-Butyl (S)-4-methyl-1-oxo-1-{(S)-1-oxo-1-[(S)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]propan-2-ylamino}pentan-2-ylcarbamate (**11**).* Compound **10a** was dissolved in HCl in dioxan under N_2 atmosphere and stirred at room temperature for 1 h, before the solvent was removed in vacuo affording a quantitative amount of (*S*)-Ala-(*S*)-Pro-AQ HCl. This salt (1.40 g, 4.01 mmol) and NMM (1.22 g, 1.32 mL, 12.03 mmol) were dissolved in CH_2Cl_2 (25 mL) at 0 °C and were allowed to stir for 5 min. After that, Boc-(*S*)-LeuOH H_2O (1.10 g, 4.41 mmol), HOBT hydrate (676 mg, 4.41 mmol) and EDC HCl (845 mg, 4.41 mmol) were added to the reaction mixture at the same temperature and stirred for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 30 h. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with water (2 × 100 mL), sat. aq. $NaHCO_3$ (1 × 150 mL) and brine solution (1 × 150 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was removed in vacuo and purification by flash column chromatography (petroleum ether/ethyl acetate 1:1) offered the tripeptide Boc-Leu-Ala-Pro-AQ (**11**) (1.71 g, 3.26 mmol, 81%) as colorless solid; mp 85−86 °C; $[\alpha]_D^{20}$ = −97.4 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 8.72−8.78 (m, 2H), 8.15 (dd, J = 8.3, 1.5 Hz, 1H), 7.49−7.54 (m, 2H), 7.44 (dd, J = 8.3, 4.3 Hz, 1H), 6.97−6.98 (m, 1H), 4.81−4.91 (m, 3H), 4.15 (m, 1H), 3.79 (t, J = 6.6 Hz, 2H), 2.34−2.41 (m, 1H), 2.06−2.27 (m, 3H), 1.59−1.72 (m, 2H), 1.56 (d, J = 7.0 Hz, 3H), 1.47−1.51 (m, 1H), 1.43 (s, 9H), 0.93 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 172.0, 169.6, 155.5, 148.1, 138.4, 136.1, 134.0, 127.8, 127.1, 121.7, 121.5, 116.6, 79.7, 61.4, 53.0, 47.3, 46.7, 41.8, 28.9, 28.2, 24.9, 24.6, 23.0, 21.6, 18.3. HRMS (CI) for $C_{28}H_{40}N_5O_5$ $[M + H]^+$ calcd. 526.3029, found 526.3033.

General Procedure for *β*-C(sp^3)-H Arylation. *tert-Butyl 2-[3-(4-methoxyphenyl)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]-2-oxoethylcarbamate (**13a**).* A round-bottom flask was charged with Boc-Gly-Pip-AQ (**5**) (83 mg, 0.20 mmol, 1.0 equiv), 4-iodoanisole (**12a**) (94 mg, 0.40 mmol, 2.0 equiv), AgOAc (67 mg, 0.40 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.5 mg, 5 mol %), toluene (0.5 mL, 0.4 M) and a magnetic stirring bar. The flask was sealed with a rubber septum and placed in a preheated oil bath (110 °C) and the reaction mixture was stirred at 110 °C for 16 h. Upon completion (TLC) the reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the crude product was purified by flash column chromatography (silica gel, petroleum ether/ethyl acetate 7:3) providing **13a** (88 mg, 0.17 mmol, 84%) as a colorless solid; mp 151−152 °C. Mixture of rotamers (93:7). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.62 (dd, J = 4.1, 1.6 Hz, 1H), 8.54−8.58 (m, 1H), 8.06 (dd, J = 8.3, 1.5 Hz, 1H), 7.42−7.46 (m, 2H), 7.36 (dd, J = 8.3, 4.3 Hz, 1H), 7.25−7.27 (m, 2H), 6.67−6.72 (m, 2H), 5.56 (d, J = 5.3 Hz, 2H), 4.22 (dd, J = 17.1, 5.0 Hz, 1H), 3.98 (dd, J = 17.1, 3.5 Hz, 1H), 3.91 (td, J = 13.0, 3.3 Hz, 1H), 3.68−3.73 (m, 1H), 3.56 (s, 3H), 3.08−3.13 (m, 1H), 2.56 (qd, J = 13.0, 3.3 Hz, 1H), 2.04−2.08 (m, 1H), 1.91−1.95 (m, 1H), 1.68−1.78 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 168.0, 158.5, 155.7, 147.8, 138.1, 135.7, 133.9, 132.3, 128.8, 127.5, 126.9, 121.5, 121.3, 116.2, 113.9, 79.5, 58.6, 54.9, 43.6, 42.8, 41.7, 28.3, 25.6, 24.2. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 5.65−5.66 (m, 1H), 5.38 (d, J = 5.3 Hz, 1H), 4.63−4.69 (m, 2H), 4.37 (dd, J = 16.8, 5.3 Hz, 1H), 3.62−3.66 (m, 1H), 3.52 (s, 3H), 3.18−3.23 (m, 1H), 2.32−2.43 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 128.7, 121.8, 121.4, 116.3, 114.2, 24.3. HRMS (CI) for $C_{29}H_{35}N_4O_5$ $[M + H]^+$ calcd. 519.2607, found 519.2601.

*tert-Butyl 2-oxo-2-(3-phenyl-2-(quinolin-8-ylcarbamoyl)-piperidin-1-yl)ethylcarbamate (**13b**).* According to the general procedure for *β*-C(sp^3)-H arylations **5** (200 mg, 0.48 mmol) was reacted with iodobenzene (**12b**) (198 mg, 0.97 mmol) providing **13b** (182 mg, 0.37 mmol, 77%) as a white solid; mp 142−143 °C. Mixture of rotamers (93:7). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 8.63 (dd, J = 4.3, 1.5 Hz, 1H), 8.53−8.57 (m, 1H), 8.05 (dd, J = 8.3, 1.5 Hz, 1H), 7.41−7.45 (m, 2H), 7.32−7.38 (m, 3H), 7.19 (t, J = 7.6 Hz, 2H), 7.04 (t, J = 7.4 Hz, 1H), 5.62 (d, J = 5.3 Hz, 1H), 5.57 (brs, 1H), 4.23 (dd, J = 17.1, 4.8 Hz, 1H), 3.98 (dd, J = 17.1, 3.8 Hz, 1H), 3.89 (td, J = 13.0, 3.0 Hz, 1H), 3.70−3.73 (m, 1H), 3.12−3.17 (m, 1H), 2.66 (qd, J = 12.8, 3.0 Hz, 1H), 2.06−2.09 (m, 1H), 1.95−1.99 (m, 1H), 1.67−1.79 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.8, 155.7, 147.9, 140.3, 138.1, 135.7, 133.8, 128.5,

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127.8, 127.5, 126.9, 126.8, 121.6, 121.3, 116.3, 79.5, 58.4, 44.3, 42.8, 41.7, 28.3, 25.6, 23.9. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 5.38 (brs, 1H), 4.66−4.71 (m, 2H), 4.39 (dd, J = 16.3, 4.8 Hz, 1H), 3.60−3.64 (m, 1H), 3.22−3.28 (m, 1H), 2.41−2.52 (m, 1H), 1.43 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 128.8, 127.7, 121.9, 121.4, 24.9, 24.0. HRMS (CI) for $C_{28}H_{33}N_4O_4$ $[M + H]^+$ calcd. 489.2502, found 489.2504.

*tert-Butyl 2-oxo-2-(2-(quinolin-8-ylcarbamoyl)-3-p-tolylpiperidin-1-yl)ethylcarbamate (**13c**).* According to the general procedure for β-C(sp^3)-H arylation **5** (200 mg, 0.48 mmol) was reacted with 4-iodotoluene (**12c**) (211 mg, 0.97 mmol) providing **13c** (212 mg, 0.42 mmol, 87%) as a white solid; mp 138−139 °C. Mixture of rotamers (92:8). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.63 (dd, J = 4.1, 1.6 Hz, 1H), 8.54−8.58 (m, 1H), 8.06 (dd, J = 8.3, 1.5 Hz, 1H), 7.41−7.46 (m, 2H), 7.36 (dd, J = 8.3, 4.3 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 5.58−5.59 (m, 2H), 4.23 (dd, J = 17.1, 5.0 Hz, 1H), 3.98 (dd, J = 17.1, 3.5 Hz, 1H), 3.89 (td, J = 13.0, 3.0 Hz, 1H), 3.69−3.72 (m, 1H), 3.08−3.14 (m, 1H), 2.60 (qd, J = 13.0, 3.3 Hz, 1H), 2.05−2.09 (m, 4H), 1.92−1.96 (m, 1H), 1.68−1.78 (m, 1H), 1.46 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 167.9, 155.7, 147.7, 138.1, 137.2, 136.4, 135.7, 133.8, 129.1, 127.6, 127.5, 126.8, 121.4, 121.2, 116.1, 79.4, 58.5, 43.9, 42.7, 41.7, 28.2, 25.5, 24.0, 20.7. Minor rotamer (selected signals): ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.18 (d, J = 7.8 Hz, 2H), 5.66−5.67 (m, 2H), 4.65−4.69 (m, 2H), 4.35−4.40 (m, 1H), 3.61−3.65 (m, 1H), 3.19−3.24 (m, 1H), 2.36−2.47 (m, 1H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 166.9, 147.6, 136.8, 136.7, 133.3, 129.4, 127.4, 121.8, 116.2, 45.2, 39.5, 24.9. HRMS (CI) for $C_{29}H_{35}N_4O_4$ $[M + H]^+$ calcd. 503.2658, found 503.2675.

*tert-Butyl 2-[3-(4-chlorophenyl)-2-(quinolin-8-ylcarbamoyl)-piperidin-1-yl]-2-oxoethylcarbamate (**13d**).* According to the general procedure for β-C(sp^3)-H arylation **5** (200 mg, 0.48 mmol) was reacted with 4-chloro iodobenzene (**12d**) (231 mg, 0.97 mmol) providing **13d** (193 mg, 0.37 mmol, 76%) as a white solid; mp 135−136 °C. Mixture of rotamers (94:6). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.67 (dd, J = 4.3, 1.8 Hz, 1H), 8.51−8.55 (m, 1H), 8.07 (dd, J = 8.3, 1.8 Hz, 1H), 7.44−7.47 (m, 2H), 7.39 (dd, J = 8.3, 4.3 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.13−7.16 (m, 2H), 5.59 (d, J = 5.5 Hz, 1H), 5.55 (brs, 1H), 4.23 (dd, J = 17.3, 5.0 Hz, 1H), 3.99 (dd, J = 17.2, 3.6 Hz, 1H), 3.88 (td, J = 13.0, 3.3 Hz, 1H), 3.70−3.74 (m, 1H), 3.09−3.14 (m, 1H), 2.58 (qd, J = 13.0, 3.5 Hz, 1H), 2.05−2.09 (m, 1H), 1.92−1.96 (m, 1H), 1.66−1.78 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.6, 155.8, 148.2, 138.9, 138.1, 135.9, 133.7, 132.9, 129.3, 128.7, 127.6, 126.8, 121.8, 121.5, 116.3, 79.6, 58.3, 43.8, 42.8, 41.7, 28.33, 25.5, 24.0. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.60 (dd, J = 4.1, 1.6 Hz, 1H), 7.24 (d, J = 8.5 Hz, 2H), 5.65 (brs, 1H), 4.66−4.70 (m, 2H), 4.34−4.39 (m, 1H), 3.94−3.95 (m, 1H), 3.60−3.64 (m, 1H), 3.19−3.24 (m, 1H), 2.33−2.44 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 130.5, 129.1, 129.0, 41.3, 28.28. HRMS (CI) for $C_{28}H_{32}ClN_4O_4$ $[M + H]^+$ calcd. 523.2112, found 523.2121.

*tert-Butyl 2-[3-(4-iodophenyl)-2-(quinolin-8-ylcarbamoyl)-piperidin-1-yl]-2-oxoethylcarbamate (**13e**).* According to the general procedure for β-C(sp^3)-H arylation **5** (400 mg, 0.97 mmol) was reacted with 1,4-diiodobenzene (**12e**) (640 mg, 1.94 mmol) providing **13e** (421 mg, 0.69 mmol, 71%) as a pale yellow solid; mp 73−74 °C. Mixture of rotamers (92:8). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.69 (dd, J = 4.1, 1.6 Hz, 1H), 8.50−8.55 (m, 1H), 8.08 (dd, J = 8.3, 1.8 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.39−7.47 (m, 3H), 7.09 (d, J = 8.3 Hz, 2H), 5.58 (d, J = 5.5 Hz, 1H), 5.55 (brs, 1H), 4.23 (dd, J = 17.1, 5.0 Hz, 1H), 3.98 (dd, J = 17.1, 3.8 Hz, 1H), 3.88 (td, J = 13.0, 3.3 Hz, 1H), 3.69−3.73 (m, 1H), 3.05−3.11 (m, 1H), 2.56 (qd, J = 12.9, 3.4 Hz, 1H), 2.05−2.08 (m, 1H), 1.90−1.94 (m, 1H), 1.65−1.77 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.5, 155.7, 148.3, 140.1, 138.0, 137.6, 135.8, 133.6, 129.9, 127.6, 126.8, 121.8, 121.5, 116.3, 92.7, 79.6, 58.2, 43.9, 42.8, 41.7, 28.3, 25.4, 23.8. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.64 (dd, J = 4.1, 1.6 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 5.66 (brs, 1H), 4.65−4.68 (m, 2H), 4.36 (dd, J = 16.8, 4.8 Hz, 1H), 3.60−3.65 (m, 1H), 3.16−3.21 (m, 1H), 2.32−2.43 (m, 1H), 1.42 (s, 9H).^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 129.7, 28.2. HRMS (CI) for $C_{28}H_{32}IN_4O_4$ $[M + H]^+$ calcd. 615.1468, found 615.1471.

*tert-Butyl 2-(3-(4-hydroxyphenyl)-2-(quinolin-8-ylcarbamoyl)-piperidin-1-yl)-2-oxoethylcarbamate (**13f**).* According to the general procedure for β-C(sp^3)-H arylation **5** (200 mg, 0.48 mmol) was reacted with 4-iodophenol (**12f**) (213 mg, 0.97 mmol) providing **13f** (100 mg, 0.20 mmol, 41%) as a pale yellow solid; mp 71−72 °C. Mixture of rotamers (93:7). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.63 (dd, J = 4.1, 1.6 Hz, 1H), 8.51−8.56 (m, 1H), 8.02 (dd, J = 8.3, 1.8 Hz, 1H), 7.39−7.43 (m, 2H), 7.33 (dd, J = 8.3, 4.3 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 5.56−5.58 (m, 3H), 4.22 (dd, J = 17.1, 5.3 Hz, 1H), 3.96 (dd, J = 17.1, 3.8 Hz, 1H), 3.86 (td, J = 13.0, 3.0 Hz, 1H), 3.66−3.69 (m, 1H), 3.02−3.07 (m, 1H), 2.44−2.56 (m, 1H), 1.97−2.02 (m, 1H), 1.88−1.92 (m, 1H), 1.62−1.70 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.8, 156.0, 155.3, 148.0, 138.1, 135.7, 133.7, 131.6, 128.9, 127.5, 126.8, 121.7, 121.4, 116.3, 115.6, 79.9, 58.8, 43.4, 42.7, 41.8, 28.3, 25.5, 24.1. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 5.66−5.68 (m, 2H), 5.38 (brs, 1H), 4.33−4.38 (m, 1H), 3.54−3.61 (m, 1H), 3.12−3.18 (m, 1H), 2.29−2.39 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8, 115.9, 28.4. HRMS (CI) for $C_{28}H_{33}N_4O_5$ $[M + H]^+$ calcd. 505.2451, found 505.2433.

*tert-Butyl 2-oxo-2-[3-(quinolin-6-yl)-2-(quinolin-8-ylcarbamoyl)-piperidin-1-yl]ethylcarbamate (**13g**).* According to the general procedure for β-C(sp^3)-H arylation **5** (250 mg, 0.61 mmol) was reacted with 6-iodoquinoline (**12g**) (309 mg, 1.21 mmol) providing **13g** (200 mg, 0.37 mmol, 61%) as a pale yellow solid; mp 96−97 °C. Mixture of rotamers (92:8). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.74 (dd, J = 4.3, 1.8 Hz, 1H), 8.49 (dd, J = 7.3, 1.5 Hz, 1H), 8.05 (dd, J = 4.1, 1.6 Hz, 1H), 7.90−7.95 (m, 3H), 7.72−7.74 (m, 2H), 7.33−7.40 (m, 2H), 7.22 (dd, J = 8.3, 4.0 Hz, 1H), 7.15 (dd, J = 8.3, 4.3 Hz, 1H), 5.73 (d, J = 5.5 Hz, 1H), 5.57 (brs, 1H), 4.27 (dd, J = 17.2, 5.1 Hz, 1H), 3.90−4.05 (m, 2H), 3.77 (dd, J = 12.5, 3.0 Hz, 1H), 3.33−3.38 (m, 1H), 2.62−2.72 (m, 1H), 2.05−2.14 (m, 2H), 1.74−1.85 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 167.6, 155.8, 149.9, 147.6, 147.5, 138.7, 137.7, 135.7, 135.5, 133.4, 129.8, 129.6, 128.2, 127.4, 126.7, 126.6, 121.6, 121.2, 120.9, 116.2, 79.6, 58.4, 44.4, 42.8, 41.8, 28.3, 25.5, 24.1. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (s, 1 H), 7.67 (dd, J = 8.8, 1.8 Hz, 1H), 7.10 (dd, J = 8.3, 4.3 Hz, 1H), 5.67−5.69 (m, 1H), 5.41 (brs, 1H), 4.41 (dd, J = 16.6, 5.0 Hz, 1H), 3.70 (dd, J = 13.0, 3.0 Hz, 1H), 3.43−3.48 (m, 1H), 2.46−2.56 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 135.6, 130.2, 129.2, 127.2, 121.9, 121.0, 116.3, 79.7, 28.2, 24.8. HRMS (CI) for $C_{31}H_{34}N_5O_4$ $[M + H]^+$ calcd. 540.2611, found 540.2621.

*tert-Butyl 2-[3-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]-2-oxoethylcarbamate (**13h**).* According to the general procedure for β-C(sp^3)-H arylation **5** (248 mg, 0.60 mmol) was reacted with 1,3-dimethyl-5-iodoracil (**12h**) (322 mg, 1.21 mmol) providing **13h** (295 mg, 0.54 mmol, 89%) as a pale yellow solid; mp 92−93 °C. Mixture of rotamers (82:18). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.76 (dd, J = 4.1, 1.6 Hz, 1H), 8.56 (dd, J = 6.8, 2.0 Hz, 1H), 8.11−8.16 (m, 1H), 7.42−7.54 (m, 3H), 7.01 (s, 1H), 5.75 (d, J = 5.0 Hz, 1H), 5.62 (brs, 1H), 4.13−4.19 (m, 1H), 4.00 (dd, J = 17.1, 3.8 Hz, 1H), 3.70−3.72 (m, 2H), 3.35 (s, 3H), 3.22−3.26 (m, 1H), 3.03(s, 3H), 2.29−2.39 (m, 1H), 1.93−2.03 (m, 1H), 1.68−1.74 (m, 2H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.54, 168.51, 163.1, 155.7, 151.1, 148.5, 141.1, 138.3, 136.1, 133.5, 127.8, 126.8, 122.1, 121.7, 116.6, 112.2, 79.5, 55.3, 42.8, 41.7, 36.7, 35.5, 28.3, 28.0, 25.3, 23.5. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.71−8.72 (m, 1H), 6.93 (s, 1H), 5.58 (brs, 1H), 5.20−5.21 (m, 1H), 4.67−4.71 (m, 1H), 4.39−4.44 (m, 1H), 3.43 (s, 3H), 3.06 (s, 3H), 2.11−2.17 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 167.2, 151.2, 148.6, 140.6, 138.2, 136.2, 133.1, 126.9, 122.3, 121.8, 116.8, 112.1, 57.6, 42.6, 39.5, 37.9, 36.9, 28.1, 24.8, 23.3. HRMS (CI) for $C_{28}H_{35}N_6O_6$ $[M + H]^+$ calcd. 551.2618, found 551.2621.

*tert-Butyl (S)-1-[(2S,3S)-3-(4-methoxyphenyl)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]-1-oxopropan-2-ylcarbamate (**14a**).* Ac-

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cording to the general procedure for β-C(sp^3)-H arylation **6** (170 mg, 0.40 mmol) was reacted with 4-methoxy iodobenzene (**12a**) (186 mg, 0.80 mmol) providing **14a** (176 mg, 0.33 mmol, 83%) as a colorless solid; mp 58−59 °C; $[\alpha]_D^{20}$ = −83.1 (c 1, $CHCl_3$). Mixture of rotamers (97:3). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 8.62 (dd, J = 4.3, 1.5 Hz, 1H), 8.54−8.58 (m, 1H), 8.06 (dd, J = 8.3, 1.5 Hz, 1H), 7.42−7.46 (m, 2H), 7.37 (dd, J = 8.1, 4.1 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 6.72−6.75 (m, 2H), 5.68 (d, J = 5.3 Hz, 1H), 5.64 (d, J = 8.0 Hz, 1H), 4.75−4.82 (m, 1H), 3.80−3.93 (m, 2H), 3.60 (s, 3H), 3.08−3.14 (m, 1H), 2.55 (qd, J = 13.0, 3.5 Hz, 1H), 1.95−2.05 (m, 2H), 1.70−1.82 (m, 1H), 1.48 (s, 9H), 1.34 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.9, 158.4, 155.1, 147.8, 138.2, 135.8, 134.0, 132.6, 128.9, 127.6, 126.9, 121.5, 121.3, 116.2, 113.9, 79.5, 58.3, 54.9, 46.7, 43.5, 42.9, 28.4, 26.0, 24.3, 18.7. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 3.62 (s, 3H). HRMS (CI) for $C_{30}H_{37}N_4O_5$ $[M + H]^+$ calcd. 533.2764, found 533.2761.

*tert-Butyl (S)-1-oxo-1-[(2S,3S)-2-(quinolin-8-ylcarbamoyl)-3-p-tolylpiperidin-1-yl]propan-2-ylcarbamate (**14b**).* According to the general procedure for β-C(sp^3)-H arylation **6** (170 mg, 0.40 mmol) was reacted with 4-iodotoluene (**12c**) (173 mg, 0.80 mmol) providing **14b** (165 mg, 0.32 mmol, 80%) as a colorless solid; mp 61−62 °C; $[\alpha]_D^{20}$ = −88.8 (c 1, $CHCl_3$). Mixture of rotamers (97:3). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.62 (dd, J = 4.1, 1.6 Hz, 1H), 8.53−8.58 (m, 1H), 8.07 (dd, J = 8.3, 1.5 Hz, 1H), 7.43 (d, J = 4.5 Hz, 2H), 7.37 (dd, J = 8.3, 4.3 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.0 Hz, 2H), 5.72 (d, J = 5.5 Hz, 1H), 5.64 (d, J = 7.8 Hz, 1H), 4.75−4.82 (m, 1H), 3.90−3.94 (m, 1H), 3.78−3.85 (m, 1H), 3.09−3.14 (m, 1H), 2.53−2.63 (m, 1H), 2.14 (s, 3H), 1.96−2.05 (m, 2H), 1.71−1.82 (m, 1H), 1.48 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 167.8, 155.1, 147.8, 138.2, 137.6, 136.3, 135.8, 134.0, 129.2, 127.7, 127.6, 126.9, 121.5, 121.3, 116.3, 79.5, 58.3, 46.7, 43.8, 42.9, 28.4, 26.0, 24.1, 20.9, 18.7. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 2.17 (s, 3H). HRMS (CI) for $C_{30}H_{37}N_4O_4$ $[M + H]^+$ calcd. 517.2815, found 517.2812.

*tert-Butyl (S)-1-[(2S,3S)-3-(4-nitrophenyl)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]-1-oxopropan-2-ylcarbamate (**14c**).* According to the general procedure for β-C(sp^3)-H arylation **6** (200 mg, 0.47 mmol) was reacted with 1-iodo-4-nitrobenzene (**12i**) (234 mg, 0.94 mmol) providing **14c** (182 mg, 0.33 mmol, 71%) as a pale brown solid; mp 90−91 °C; $[\alpha]_D^{20}$ = −76.7 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 8.62 (dd, J = 4.3, 1.8 Hz, 1H), 8.50 (dd, J = 6.8, 2.0 Hz, 1H), 8.07−8.11 (m, 3H), 7.57 (d, J = 8.5 Hz, 2H), 7.41−7.48 (m, 2H), 7.38 (dd, J = 8.3, 4.3 Hz, 1H), 5.84 (d, J = 5.0 Hz, 1H), 5.58 (d, J = 8.0 Hz, 1H), 4.78−4.85 (m, 1H), 3.96−3.99 (m, 1H), 3.68−3.75 (m, 1H), 3.20−3.25 (m, 1H), 2.62−2.72 (m, 1H), 2.08 (m, 1H), 2.05 (m, 1H), 1.75−1.86 (m, 1H), 1.49 (s, 9H), 1.40 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 167.0, 155.1, 148.5, 148.1, 146.8, 138.1, 136.1, 133.5, 128.8, 127.7, 126.9, 123.6, 122.0, 121.6, 116.4, 79.7, 57.6, 46.6, 43.9, 42.9, 28.4, 25.7, 23.9, 18.8. HRMS (CI) for $C_{29}H_{34}N_5O_6$ $[M + H]^+$ calcd. 548.2509, found 548.2505.

*tert-Butyl (S)-1-oxo-1-[(2S,3S)-3-(pyridin-3-yl)-2-(quinolin-8-ylcarbamoyl)piperidin-1-yl]propan-2-ylcarbamate (**14d**).* According to the general procedure for β-C(sp^3)-H arylation **6** (200 mg, 0.47 mmol) was reacted with 3-iodopyridine (**12j**) (193 mg, 0.94 mmol) providing **14d** (132 mg, 0.26 mmol, 56%) as a pale yellow solid; mp 72−73 °C; $[\alpha]_D^{20}$ = −73.4 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.67−8.69 (m, 2H), 8.53 (dd, J = 6.1, 2.9 Hz, 1H), 8.37 (dd, J = 4.8, 1.5 Hz, 1H), 8.08 (dd, J = 8.3, 1.8 Hz, 1H), 7.74−7.76 (m, 1H), 7.43−7.46 (m, 2H), 7.38 (dd, J = 8.3, 4.3 Hz, 1H), 7.14 (dd, J = 7.9, 4.9 Hz, 1H), 5.77 (d, J = 5.3 Hz, 1H), 5.62 (d, J = 8.0 Hz, 1H), 4.76−4.83 (m, 1H), 3.93−3.96 (m, 1H), 3.64−3.71 (m, 1H), 3.11−3.17 (m, 1H), 2.69−2.79 (m, 1H), 1.99−2.07 (m, 2H), 1.74−1.85 (m, 1H), 1.48 (s, 9H), 1.35 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 167.2, 155.1, 149.8, 148.19, 148.17, 138.2, 136.2, 135.9, 135.6, 133.7, 127.7, 126.9, 123.2, 121.8, 121.5, 116.4, 79.6, 57.4, 46.6, 42.8, 41.9, 28.4, 25.8, 23.8, 18.7. HRMS (CI) for $C_{28}H_{34}N_5O_4$ $[M + H]^+$ calcd. 504.2611, found 504.2618.

*tert-Butyl (S)-1-[(2S,3S)-3-(4-methoxyphenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]-1-oxopropan-2-ylcarbamate (**15a**).* According to the general procedure for β-C(sp^3)-H arylation **10a** (300 mg, 0.73 mmol) was reacted with 4-methoxy iodobenzene (**12a**) (341 mg, 1.46 mmol) providing **15a** (305 mg, 0.59 mmol, 81%) as a colorless solid; mp 83−84 °C; $[\alpha]_D^{20}$ = −37.8 (c 1, $CHCl_3$). Mixture of rotamers (96:4). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.63 (dd, J = 4.1, 1.4 Hz, 1H), 8.45−8.49 (m, 1H), 8.05 (dd, J = 8.3, 1.0 Hz, 1H), 7.40 (d, J = 4.5 Hz, 2H), 7.36 (dd, J = 8.2, 4.1 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 5.36 (d, J = 8.3 Hz, 1H), 4.94 (d, J = 8.3 Hz, 1H), 4.55−4.63 (m, 1H), 4.04 (t, J = 9.1 Hz, 1H), 3.86−3.92 (m, 1H), 3.65−3.72 (m, 1H), 3.46 (s, 3H), 2.77−2.88 (m, 1H), 2.30 (td, J = 6.1 and 12.4 Hz, 1H), 1.46−1.47 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.8, 158.7, 155.2, 147.8, 138.2, 135.8, 133.8, 128.8, 128.0, 127.5, 127.0, 121.35, 121.28, 116.2, 113.8, 79.5, 65.7, 54.9, 47.4, 46.4, 46.2, 29.0, 28.3, 18.5. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.58 (m, 1H), 8.51−8.52 (m, 1H), 7.44 (d, J = 4.5 Hz, 2H), 6.54 (d, J = 8.5 Hz, 2H), 4.66−4.68 (m, 1H), 3.41 (s, 3H), 1.43 (s, 9H). HRMS (CI) for $C_{29}H_{35}N_4O_5$ $[M + H]^+$ calcd. 519.2607, found 519.2600.

*tert-Butyl (S)-1-oxo-1-[(2S,3S)-3-phenyl-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]propan-2-ylcarbamate (**15b**).* According to the general procedure for β-C(sp^3)-H arylation **10a** (290 mg, 0.70 mmol) was reacted with iodobenzene (**12b**) (287 mg, 1.40 mmol) providing **15b** (282 mg, 0.58 mmol, 82%) as a colorless solid; mp 61−62 °C; $[\alpha]_D^{20}$ = −13.8 (c 1, $CHCl_3$). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H), 8.64 (dd, J = 4.3, 1.5 Hz, 1H), 8.43−8.47 (m, 1H), 8.05 (dd, J = 8.3, 1.8 Hz, 1H), 7.39−7.42 (m, 2H), 7.36 (dd, J = 8.3, 4.3 Hz, 1H), 7.29 (d, J = 7.5 Hz, 2H), 7.09 (t, J = 7.8 Hz, 2H), 6.93 (t, J = 7.4 Hz, 1H), 5.35 (d, J = 8.3 Hz, 1H), 5.00 (d, J = 8.3 Hz, 1H), 4.56−4.63 (m, 1H), 4.07 (t, J = 9.2 Hz, 1H), 3.88−3.95 (m, 1H), 3.71−3.78 (m, 1H), 2.85−2.96 (m, 1H), 2.34 (dt, J = 12.3, 6.3 Hz, 1H), 1.45−1.47 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.7, 155.2, 147.8, 138.1, 136.1, 135.9, 133.7, 128.3, 127.8, 127.5, 127.2, 126.9, 121.4, 121.3, 116.2, 79.5, 65.6, 47.4, 46.8, 46.5, 28.7, 28.3, 18.4. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.58−8.59 (m, 1H), 8.49−8.51 (m, 1H), 7.43−7.44 (m, 1H), 4.72−4.75 (m, 1H), 4.38−4.44 (m, 1H), 1.43 (s, 9H). HRMS (CI) for $C_{28}H_{33}N_4O_4$ $[M + H]^+$ calcd. 489.2502, found 489.2489.

*tert-Butyl (S)-1-[(2S,3S)-3-(4-nitrophenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl)-1-oxopropan-2-ylcarbamate (**15c**).* According to the general procedure for β-C(sp^3)-H arylation **10a** (300 mg, 0.73 mmol) was reacted with 4-nitroiodobenzene (**12i**) (363 mg, 1.46 mmol) providing **15c** (221 mg, 0.41 mmol, 57%) as a pale brown solid; mp 101−102 °C; $[\alpha]_D^{20}$ = −76.0 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.64 (d, J = 4.0 Hz, 1H), 8.41 (d, J = 7.0 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.3 Hz, 2H), 7.41−7.46 (m, 4H), 7.38 (dd, J = 7.9, 3.9 Hz, 1H), 5.31 (d, J = 7.8 Hz, 1H), 5.09 (d, J = 8.3 Hz, 1H), 4.57−4.64 (m, 1H), 4.10 (t, J = 9.2 Hz, 1H), 3.94−4.01 (m, 1H), 3.79−3.86 (m, 1H), 2.86−2.97 (m, 1H), 2.38−2.44 (m, 1H), 1.46−1.48 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 167.0, 155.2, 148.0, 147.0, 144.1, 138.0, 136.1, 133.2, 128.8, 127.6, 126.9, 123.5, 121.9, 121.5, 116.4, 79.7, 65.3, 47.4, 46.39, 46.36, 28.7, 28.3, 18.3. HRMS (CI) for $C_{28}H_{32}N_5O_6$ $[M + H]^+$ calcd. 534.2352, found 534.2353.

*tert-Butyl (S)-1-[(2S,3S)-3-(3-bromophenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]-1-oxopropan-2-ylcarbamate (**15d**).* According to the general procedure for β-C(sp^3)-H arylation **10a** (290 mg, 0.70 mmol) was reacted with 3-bromoiodobenzene (**12k**) (398 mg, 1.41 mmol) providing **15d** (275 mg, 0.49 mmol, 69%) as a pale brown solid; mp 78−79 °C; $[\alpha]_D^{20}$ = −8.5 (c 1, $CHCl_3$). Mixture of rotamers (97:3). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 8.69 (dd, J = 4.1, 1.6 Hz, 1H), 8.43−8.48 (m, 1H), 8.07 (dd, J = 8.3, 1.5 Hz, 1H), 7.42−7.45 (m, 3H), 7.38 (dd, J = 8.3, 4.3 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 7.00−7.02 (m, 1H), 6.89 (t, J = 7.8 Hz, 1H), 5.33 (d, J = 8.5 Hz, 1H), 4.99 (d, J = 8.5 Hz, 1H), 4.55−4.62 (m, 1H), 4.06 (t, J = 9.2 Hz, 1H), 3.88−3.94 (m, 1H), 3.66−3.71 (m, 1H), 2.78−2.89 (m, 1H), 2.33 (dt, J = 12.3, 6.3 Hz, 1H), 1.45−1.47 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 167.4, 155.2, 147.9, 138.6, 138.1, 135.9, 133.4, 131.1, 130.3, 129.8, 127.5, 126.9, 126.3, 122.5, 121.5, 121.3, 116.3, 79.5, 65.4, 47.4, 46.4, 46.3, 28.7, 28.3, 18.4. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30

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J. Org. Chem. 2016, 81, 11646−11655

(s, 1H), 8.64−8.65 (m, 1H), 8.49−8.50 (m, 1H), 7.14 (d, J = 8.3 Hz, 1H), 6.95−6.97 (m, 1H), 6.83 (t, J = 7.8 Hz, 1H), 5.26 (d, J = 8.5 Hz, 1H), 4.73 (d, J = 8.0 Hz, 1H), 4.39−4.44 (m, 1H), 2.53−2.63 (m, 1H), 2.20−2.26 (m, 1H), 1.43 (s, 9H). HRMS (CI) for $C_{28}H_{32}BrN_4O_4$ [M + H]$^+$ calcd. 567.1607, found 567.1589.

*tert-Butyl (2S,3R)-1-[(2S,3S)-3-(4-methoxyphenyl)-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-ylcarbamate (**15e**).* According to the general procedure for β-C(sp^3)-H arylation **10b** (279 mg, 0.61 mmol) was reacted with 4-methoxyiodobenzene (**12a**) (285 mg, 1.22 mmol) providing **15e** (284 mg, 0.51 mmol, 83%) as a colorless solid; mp 68−69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 8.65 (dd, J = 4.3, 1.5 Hz, 1H), 8.45−8.50 (m, 1H), 8.07 (dd, J = 8.3, 1.5 Hz, 1H), 7.40−7.44 (m, 2H), 7.37 (dd, J = 8.3, 4.3 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 5.16 (d, J = 9.8 Hz, 1H), 4.96 (d, J = 8.3 Hz, 1H), 4.39 (t, J = 8.7 Hz, 1H), 4.13 (t, J = 9.2 Hz, 1H), 3.94−4.00 (m, 1H), 3.66−3.73 (m, 1H), 3.45 (s, 3H), 2.79−2.90 (m, 1H), 2.29 (dt, J = 12.4, 6.2 Hz, 1H), 1.80−1.86 (m, 1H), 1.61−1.67 (m, 1H), 1.41−1.55 (m, 10H), 1.08 (d, J = 6.5 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 168.0, 158.6, 155.8, 147.8, 138.2, 135.8, 133.9, 128.9, 128.2, 127.6, 127.0, 121.3, 121.27, 116.3, 113.8, 79.5, 65.8, 55.8, 54.9, 46.8, 46.2, 37.9, 28.9, 28.4, 24.3, 15.5, 11.1. HRMS (CI) for $C_{32}H_{41}N_4O_5$ [M + H]$^+$calcd. 561.3077, found 561.3076.

*tert-Butyl (2S)-1-{(2S)-1-[(2S,3S)-3-(4-methoxyphenyl)-2-(quinolin-8-ylcarbamoyl)pyrroledin-1-yl]-1-oxopropan-2-ylamino}-4-methyl-1-oxopentan-2-ylcarbamate (**16a**).* According to the general procedure for β-C(sp^3)-H arylation tripeptide **11** (335 mg, 0.53 mmol) was reacted with 4-methoxy iodobenzene (**12a**) (248 mg, 1.06 mmol) providing **16a** (224 mg, 0.35 mmol, 68%) as a colorless solid; mp 142−143 °C; $[\alpha]_D^{20}$ = −20.0 (c 1, $CHCl_3$). Mixture of rotamers (96:4). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.50 (s, 1H), 8.65 (dd, J = 4.3, 1.5 Hz, 1H), 8.43−8.47 (m, 1H), 8.07 (dd, J = 8.3, 1.5 Hz, 1H), 7.41−7.43 (m, 2H), 7.37 (dd, J = 8.3, 4.3 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 7.01 (brs, 1H), 6.59 (d, J = 8.5 Hz, 2H), 4.99 (d, J = 8.3 Hz, 1H), 4.93 (d, J = 7.8 Hz, 1H), 4.78−4.85 (m, 1H), 4.22 (brs, 1H), 4.05 (t, J = 9.3 Hz, 1H), 3.82−3.89 (m, 1H), 3.65−3.72 (m, 1H), 3.48 (s, 3H), 2.78−2.90 (m, 1H), 2.31 (td, J = 12.3, 6.3 Hz, 1H), 1.67−1.75 (m, 1H), 1.56−1.63 (m, 1H), 1.48−1.53 (m, 1H), 1.40−1.44 (m, 12H), 0.95 (d, J = 6.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.2, 168.1, 158.5, 155.7, 148.0, 138.5, 135.7, 133.9, 129.0, 128.2, 127.6, 126.8, 121.4, 121.2, 116.8, 113.7, 79.5, 65.2, 54.9, 52.7, 46.4, 46.14, 46.06, 42.8, 28.9, 28.2, 24.6, 23.2, 21.6, 18.0. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.61 (dd, J = 4.0, 1.2 Hz, 1H), 8.49−8.51 (m, 1H), 7.44−7.46 (m, 2H), 7.14 (d, J = 8.5 Hz, 2H), 6.53 (d, J = 8.5 Hz, 2H), 3.41 (s, 3H). HRMS (CI) for $C_{35}H_{46}N_5O_6$ [M + H]$^+$ calcd. 632.3448, found 632.3444.

*tert-Butyl (2S)-4-methyl-1-oxo-1-{(2S)-1-oxo-1-[(2S,3S)-3-phenyl-2-(quinolin-8-ylcarbamoyl)pyrrolidin-1-yl]propan-2-ylamino}-pentan-2-ylcarbamate (**16b**).* According to the general procedure for β-C(sp^3)-H arylation tripeptide **11** (500 mg, 0.95 mmol) was reacted with iodobenzene (**12b**) (388 mg, 1.90 mmol) providing **16b** (343 mg, 0.57 mmol, 60%) as a colorless solid; mp 106−107 °C; $[\alpha]_D^{20}$ = −36.9 (c 1, $CHCl_3$). Mixture of rotamers (97:3). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.66 (dd, J = 4.0, 1.5 Hz, 1H), 8.31−8.32 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.61 (brs, 1H), 7.34−7.37 (m, 5H), 7.10 (t, J = 7.6 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 5.25−5.26 (m, 1H), 5.15 (m, 1H), 4.75−4.82 (m, 1H), 4.48 (brs, 1H), 4.00 (t, J = 8.9 Hz, 1H), 3.79−3.85 (m, 1H), 3.68−3.74 (m, 1H), 2.90−3.01 (m, 1H), 2.32 (dt, J = 12.3, 6.1 Hz, 1H), 1.68−1.78 (m, 1H), 1.48−1.60 (m, 2H), 1.34 (s, 9H), 1.11 (m, 3H), 0.92−0.95 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.3, 168.0, 155.7, 148.1, 138.5, 136.2, 135.7, 133.8, 128.2, 128.0, 127.6, 127.1, 126.8, 121.4, 121.2, 116.8, 79.5, 65.2, 52.7, 46.7, 46.4, 46.2, 42.9, 28.7, 28.2, 24.6, 23.3, 21.6, 18.1. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.60 (dd, J = 4.0, 1.2 Hz, 1H), 8.48−8.50 (m, 1H), 1.38 (s, 9H). HRMS (CI) for $C_{34}H_{44}N_5O_5$ [M + H]$^+$ calcd. 602.3342, found 602.3341.

*tert-Butyl (S)-3-methyl-1-oxo-1-[(S)-1-oxo-3-phenyl-1-(quinolin-8-ylamino)propan-2-ylamino]butan-2-ylcarbamate (**17**).* Compound **17** was prepared according to **10** from Phe-AQ·HCl[28] in a 5.09 mmol (1.995 g) scale in 81% yield (2.026 g, 4.13 mmol) as a colorless solid; mp 118−119 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.68−8.72 (m, 2H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.51−7.55 (m, 2H), 7.43 (dd, J = 8.3, 4.3 Hz, 1H), 7.22−7.28 (m, 4H), 7.16−7.20 (m, 1H), 6.71 d, J = 7.3 Hz, 1H), 5.03−5.08 (m, 2H), 4.03 (t, J = 5.9 Hz, 1H), 3.21−3.32 (m, 2H), 2.20 (dq, J = 13.2, 6.6 Hz, 1H), 1.47 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 168.9, 155.8, 148.2, 138.3, 136.1, 136.0, 133.7, 129.3, 128.6, 127.7, 127.1, 126.9, 121.9, 121.6, 116.6, 79.8, 59.9, 55.3, 38.7, 30.9, 28.3, 19.3, 17.5. HRMS (CI) for $C_{28}H_{35}N_4O_4$ [M + H]$^+$calcd. 491.2658, found 491.2659.

*(2S,3R)-2-[(S)-4-Isopropyl-2,5-dioxoimidazolidin-1-yl]-3-(4-methoxyphenyl)-3-phenyl-N-(quinolin-8-yl)propanamide (**18a**).* According to the general procedure for β-C(sp^3)-H arylation **17** (300 mg, 0.61 mmol) was reacted with 4-methoxyiodobenzene (**12a**) (285 mg, 1.22 mmol) providing **18a** (155 mg, 0.29 mmol, 48%) as a colorless solid; mp 122−123 °C. ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 10.28 (s, 1H), 8.82 (dd, J = 4.0, 1.3 Hz, 1H), 8.42 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 8.5, 1.3 Hz, 1H), 7.92 (brs, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.58 (dd, J = 8.5, 4.4 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 7.34−7.35 (m, 2H), 7.25 (t, J = 7.5 Hz, 2H), 7.14v7.17 (m, 1H), 6.83 (d, J = 8.8 Hz, 2H), 5.63 (d, J = 12.2 Hz, 1H), 5.42 (d, J = 12.2 Hz, 1H), 3.69 (d, J = 3.5 Hz, 1H), 3.66 (s, 3H), 1.81 (dq, J = 11.0, 6.7 Hz, 1H), 0.67 (d, J = 6.9 Hz, 3H), 0.54 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 165.5, 158.7, 157.5, 147.9, 141.2, 138.5, 135.9, 134.1, 132.4, 129.1, 128.7, 127.8, 127.6, 127.1, 126.9, 121.8, 121.4, 116.9, 114.5, 62.1, 58.8, 55.0, 49.1, 30.0, 18.6, 15.6. HRMS (CI) for $C_{31}H_{31}N_4O_4$ [M + H]$^+$calcd. 523.2345, found 523.2338.

*(2S,3R)-2-[(S)-4-Isopropyl-2,5-dioxoimidazolidin-1-yl]-3-phenyl-N-(quinolin-8-yl)-3-p-tolylpropanamide (**18b**).* According to the general procedure for β-C(sp^3)-H arylation **17** (300 mg, 0.61 mmol) was reacted with 4-iodotoluene (**12c**) (266 mg, 1.22 mmol) providing **18b** (143 mg, 0.28 mmol, 46%) as a colorless solid; mp 112−113 °C. Mixture of diastereomers (10:1). ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 10.28 (s, 1H), 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.41 (d, J = 7.5 Hz, 1H), 8.33 (dd, J = 8.3, 1.4 Hz, 1H), 7.94 (brs, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.58 (dd, J = 8.2, 4.1 Hz, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.34−7.36 (m, 2H), 7.25 (t, J = 7.7 Hz, 2H), 7.14−7.17 (m, 1H), 7.07 (d, J = 7.8 Hz, 2H), 5.65 (d, J = 12.2 Hz, 1H), 5.43 (d, J = 12.6 Hz, 1H), 3.70 (d, J = 3.8 Hz, 1H), 2.18 (s, 3H), 1.81 (dq, J = 11.0, 6.8 Hz, 1H), 0.75 (d, J = 6.9 Hz, 3H), 0.54 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 165.5, 157.4, 147.9, 141.1, 138.4, 137.3, 136.8, 135.9, 134.1, 129.8, 128.72, 127.9, 127.8, 127.6, 127.1, 126.9, 121.8, 121.4, 116.9, 62.1, 58.7, 49.5, 29.96, 21.0, 18.6, 15.5. Selected signals of minor diastereomer: ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 10.23 (s, 1H), 8.87 (dd, J = 4.1, 1.6 Hz, 1H), 8.60 (d, J = 7.5 Hz, 1H), 8.38 (dd, J = 8.3, 1.4 Hz, 1H),7.99 (brs, 1H), 7.68 (d, J = 8.2 Hz, 1H),7.28−7.31 (m, 4H), 3.89 (dd, J = 3.9, 1.4 Hz, 1H), 3.60−3.62 (m, 2H), 1.90−1.96 (m, 1H), 0.85 (d, J = 6.9 Hz, 3H), 0.67 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 157.3, 148.2, 136.4, 136.2, 129.1, 128.66, 127.2, 127.0, 122.0, 121.6, 116.8, 29.99. HRMS (CI) for $C_{31}H_{31}N_4O_3$ [M + H]$^+$calcd. 507.2396, found 507.2367.

*tert-Butyl 4-(4-{1-[2-(tert-butoxycarbonylamino)acetyl]-2-(quinolin-8-ylcarbamoyl)piperidin-3-yl}phenyl)-2-(2,2,2-trifluoroacetamido)pent-4-enoate (**20**).* An oven-dried Schlenk tube LiCl (41 mg, 0.98 mmol) was heated with a heat gun under vacuum. After cooling to room temperature CuI (186 mg, 0.98 mmol), **13e** (300 mg, 0.49 mmol) and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol, 5 mol %) were added and the flask was evacuated and flushed with Ar three times. DMF (5 mL) (degassed by bubbling with Ar) and (±) *tert*-butyl 4-(tributylstannyl)-2-(2,2,2-trifluoroacetamido)pent-4-enoate (**19**)[24] (299 mg, 0.54 mmol) were added and the mixture was heated to 80 °C for 18 h. After reaching full conversion (TLC) the mixture was diluted with ethyl acetate and 1 M KF-solution (5 mL). Upon vigorous shaking a colorless precipitate was formed and the mixture was filtered through a pad of Celite. The layers were separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate, 6:4), providing **20** (218 mg, 0.29 mmol, 59%) as a colorless solid; mp 77−78 °C. Mixture of diastereomers

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(1:1) and rotamers (94:6). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.61−8.63 (m, 1H), 8.54−8.57 (m, 1H), 8.04 (dd, J = 8.3, 1.2 Hz, 1H), 7.41−7.46 (m, 2H), 7.31−7.38 (m, 3H), 7.19−7.22 (m, 2H), 6.58 (t, J = 7.4 Hz, 1H), 5.60 (d, J = 4.3 Hz, 1H), 5.57 (brs, 1H), 5.00 (dd, J = 12.3, 0.7 Hz, 1H), 4.945 (m, 1H), 4.29−4.37 (m, 1H), 4.23 (dd, J = 17.1, 4.8 Hz, 1H), 3.98 (dd, J = 17.1, 3.8 Hz, 1H), 3.82−3.89 (m, 1H), 3.70−3.73 (m, 1H), 3.09−3.15 (m, 1H), 2.83−2.98 (m, 2H), 2.64−2.75 (m, 1H), 2.05−2.09 (m, 1H), 1.92−1.95 (m, 1H), 1.69−1.79 (m, 1H), 1.45 (s, 9H), 1.33/1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.5, 167.70/167.68, 155.7, 148.11/148.08, 142.72/142.71, 140.4, 138.5, 138.4, 138.2/138.1, 135.8, 133.9/133.8, 128.25/128.22, 127.60/127.58, 126.9, 126.4/126.3, 121.6, 121.3, 116.4/116.3, 83.33/83.30, 79.6, 58.15/58.11, 52.2/52.1, 44.1/44.0, 42.8, 41.7, 37.2/37.1, 28.3, 27.76/27.73, 25.6, 24.05/24.02. Signals of TFA group could not be observed. ^{19}F NMR (376 MHz, CDCl3) δ −76.13/−76.14. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 8.49−8.51 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 5.64−5.66 (m, 2H), 4.89−4.91 (m, 2H), 4.66−4.71 (m, 1H), 4.53−4.57 (m, 1H), 3.60−3.63 (m, 1H), 3.19−3.25 (m, 1H). HRMS (CI) for $C_{39}H_{47}F_3N_5O_7$ [M + H]$^+$ calcd. 754.3428, found 754.3416.

Removal of 8-Aminoquinoline (AQ) Group.[27] Compound **13a** (280 mg, 0.54 mmol), Boc_2O (1.77 g, 8.10 mmol) and DMAP (198 mg, 1.62 mmol) were dissolved of anhydrous CH_3CN (0.6 mL) and heated to 70 °C for 2 h. The solvent was evaporated in vacuo, and the resulting residue (**21**) was passed quickly through a column (Al_2O_3, activation level III) and was used directly for the next step. Therefore, it was dissolved in THF/H_2O (4:1, 5 mL) at 0 °C before 30% H_2O_2 (1.36 mL, 2.70 mmol) and LiOH·H_2O (45 mg, 1.08 mmol) were added. The suspension was allowed to warm to room temperature and stirred overnight. The reaction mixture was then diluted with water (150 mL), treated with Na_2SO_3 (1.0 g in 10 mL of water), acidified to pH 2 with 1 M HCl, and extracted with ethyl acetate (3 × 150 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated, and purified by flash chromatography (SiO_2), using ethyl acetate/petroleum ether/MeOH (30:70:1) as eluent to give a 1:1 mixture of 1-[2-(*tert*-butoxycarbonylamino)acetyl]-3-(4-methoxyphenyl)piperidine-2-carboxylic acid (**22a**) and 1-(2-[bis(*tert*-butoxycarbonyl)amino)acetyl]-3-(4-methoxyphenyl)piperidine-2-carboxylic acid (**23a**) in an overall yield (two step) of 64% yield.

*1-[2-(tert-Butoxycarbonylamino)acetyl]-3-(4-methoxyphenyl)-piperidine-2-carboxylic acid (**22a**).* Yield: 70 mg (0.18 mmol, 33%), colorless solid; mp 50−51 °C. Mixture of rotamers (80:20). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.21 (m, 2H), 6.83−6.86 (m, 2H), 5.57 (brs, 1H), 5.42 (d, J = 5.8 Hz, 1H), 4.09−4.20 (m, 1H), 3.92 (dd, J = 17.1, 4.0 Hz, 1H) 3.79 (s, 3H), 3.47−3.60 (m, 2H), 2.95−3.00 (m, 1H), 2.17−2.26 (m, 1H), 1.85−1.98 (m, 2H), 1.59−1.66 (m, 1H), 1.45 (s, 9H), signal of the COOH group could not be observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 168.9, 158.5, 156.0, 132.0, 128.7, 113.7, 79.9, 56.9, 55.2, 42.7, 41.3, 28.3, 25.4, 24.1. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (brs, 1H), 4.51−4.54 (m, 1H), 3.97−3.99 (m, 1H), 3.03−3.06 (m, 1H), 2.37−2.48 (m, 1H), 2.33 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 158.6, 131.7, 129.0, 113.8, 80.1. HRMS (CI) for $C_{20}H_{29}N_2O_6$ [M + H]$^+$ calcd. 393.2026, found 393.2033.

*1-{2-[Bis(tert-butoxycarbonyl)amino]acetyl}-3-(4-methoxyphenyl)piperidine-2-carboxylic acid (**23a**).* Yield: 83 mg (0.17 mmol, 31%), colorless gum. Mixture of rotamers (80:20). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 5.44 (d, J = 5.5 Hz, 1H), 4.39−4.59 (m, 2H), 3.79 (s, 3H), 3.65−3.68 (m, 1H), 3.51−3.57 (m, 1H), 2.98−3.02 (m, 1H), 2.20−2.30 (m, 1H), 1.83−1.98 (m, 2H), 1.67−1.73 (m, 1H), 1.49 (s, 18H), signal of the COOH group could not be observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 168.2, 158.5, 152.4, 132.1, 128.78, 113.7, 82.9, 56.9, 55.1, 47.4, 42.5, 41.6, 28.0, 25.5, 24.1. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38−2.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.82, 113.9. HRMS (CI) for $C_{25}H_{37}N_2O_8$ [M + H]$^+$ calcd. 493.2550, found 493.2556.

*1-[2-(tert-Butoxycarbonylamino)acetyl]-3-p-tolylpiperidine-2-carboxylic acid (**22b**).* **22b** was obtained in an analogous manner as **22a** from **13c** (865 mg, 1.72 mmol). Yield: 280 mg (0.74 mmol, 43%), colorless solid; mp 57−58 °C. Mixture of rotamers (80:20). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.18 (m, 4H), 5.56 (brs, 1H), 5.42 (brs, 1H), 4.09−4.15 (m, 1H), 3.87−3.94 (m, 1H), 3.47−3.60 (m, 2H), 2.96−2.99 (m, 1H), 2.32 (s, 3H), 2.21−2.27 (m, 1H), 1.86−1.97 (m, 2H), 1.58−1.67 (m, 1H), 1.46 (s, 9H), signal of the COOH group could not be observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 169.0, 156.0, 137.1, 136.5, 129.0, 127.7, 79.9, 57.1, 43.1, 42.6, 41.4, 28.3, 25.4, 24.0, 21.0. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (brs, 1H), 4.51−4.54 (m, 1H), 3.97−3.99 (m, 1H), 3.03−3.06 (m, 1H), 2.37−2.48 (m, 1H), 2.33 (s, 3H), 1.44 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 129.1, 127.8, 80.0. HRMS (CI) for $C_{20}H_{29}N_2O_5$ [M + H]$^+$ calcd. 377.2076, found 377.2078.

*1-{2-[Bis(tert-butoxycarbonyl)amino)acetyl)-3-p-tolylpiperidine-2-carboxylic acid (**23b**).* **23b** was obtained in an analogous manner as **22b**. Yield: 196 mg (0.41 mmol, 24%), colorless solid; mp 92−93 °C. Mixture of rotamers (80:20). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09−7.17 (m, 4H), 5.47 (d, J = 5.5 Hz, 1H), 4.40−4.59 (m, 2H), 3.66−3.69 (m, 1H), 3.55 (td, J = 13.0.3.0 Hz, 1H), 2.99−3.04 (m, 1H), 2.23−2.30 (m, 4H), 1.91−1.98 (m, 2H), 1.63−1.74 (m, 1H), 1.49 (s, 18H), signal of the COOH group could not be observed. ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 168.0, 152.4, 137.0, 136.5, 129.0, 127.6, 82.89, 56.9, 47.4, 42.9, 41.6, 27.9, 25.5, 23.9, 21.0. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40−2.49 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.7, 129.2, 127.7, 82.93. HRMS (CI) for $C_{25}H_{37}N_2O_7$ [M + H]$^+$ calcd. 477.2601, found 477.2594.

*Methyl 2-{1-[2-(tert-butoxycarbonylamino)acetyl]-3-p-tolylpiperidine-2-carboxamido}acetate (**24**).* Dipeptide **22a** (180 mg, 0.48 mmol), Gly-OMe·HCl (65 mg, 0.53 mmol) and NMM (0.16 mL, 1.43 mmol) were dissolved and stirred in CH_2Cl_2 (5 mL) at 0 °C for 5 min. HOBT (80 mg, 0.53 mmol) and EDC·HCl (101 mg, 0.53 mmol) were added at 0 °C and the solution was stirred at the same temperature for 1 h. The reaction mixture was allowed to warm to room temperature and stirring was continued for 30 h, before it was diluted with CH_2Cl_2 (50 mL) and washed with water (2 × 50 mL) and brine solution (1 × 50 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed in vacuo. Purification by flash column chromatography (petroleum ether/ethyl acetate 3:1) afforded tripeptide **24** (139 mg, 0.31 mmol, 65%) as a colorless solid; mp 44−45 °C. Mixture of rotamers (94:6). Major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.22 (m, 4H), 5.96 (brs, 1H), 5.49 (brs, 1H), 5.26 (d, J = 5.3 Hz, 1H), 4.16 (dd, J = 16.9, 4.9 Hz, 1H), 3.94 (dd, J = 17.1, 3.8 Hz, 1H), 3.87 (dd, J = 18.2, 6.1 Hz, 1H), 3.60−3.65 (m, 4H), 3.52−3.57 (m, 1H), 2.93−2.98 (m, 1H), 2.61 (qd, J = 13.0, 3.5 Hz, 1H), 2.31 (s, 3H), 1.97−2.00 (m, 1H), 1.86−1.89 (m, 1H), 1.78−1.79 (m, 1H), 1.58−1.70 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.2, 168.8, 155.7, 137.4, 136.6, 129.1, 127.8, 79.6, 56.7, 52.1, 43.3, 42.7, 41.6, 40.7, 28.3, 25.5, 23.9, 20.9. Minor rotamer (selected signals): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (brs, 1H), 5.62 (brs, 1H), 4.54−4.58 (m, 1H), 4.42 (d, J = 5.3 Hz, 1H), 3.30−3.38 (m, 1H), 3.02−3.10 (m, 2H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.4, 127.5. ^{1}H NMR (500 MHz, DMSO-d_6, 373 K) δ 7.16 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.27 (s, 1H), 5.19 (brs, 1H), 3.92 (brs, 3H), 3.69 (dd, J = 17.2, 6.1 Hz, 1H), 3.57 (s, 3H), 3.51 (dd, J = 17.1, 5.4 Hz, 1H), 3.45 (brs, 1H), 2.90 (brs, 2H), 2.49−2.42 (m, 1H), 2.28 (s, 3H), 1.91−1.83 (m, 1H), 1.73−1.75 (m, 1H), 1.63−1.53 (m, 1H), 1.43 (s, 9H). HRMS (CI) for $C_{23}H_{34}N_3O_6$ [M + H]$^+$ calcd. 448.2448, found 448.2446.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01963.

Copies of NMR spectra and chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Dr. Rolf Gleiter on the occasion of his 80th birthday.

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