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Palladium-catalyzed double carbonylation-based diversity-oriented synthesis of 3,4-dihydroisoquinoline-1-carboxamides

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ABSTRACT

A novel palladium-catalyzed double carbonylation approach toward the synthesis of 3,4-dihydroisoquinoline-1-carboxamides is reported. The method developed involves an initial palladium-catalyzed double carbonylation of an *N*-protected alkylamine aryliodide to afford an α-keto carboxamide intermediate, which on subsequent deprotection undergoes intramolecular imine formation to afford the benzo-azacyclic product.

1. Introduction

Benzo-azacycles, compounds harboring a 1,2,3,4-tetrahydroisoquinoline (THIQ)-1-carboxamide structural motif, attract significant attention owing to their biological activities.[1] The THIQ-1-carboxamide (Fig. 1, red color) structural motif can be found in bioactive compounds such as peroxisome proliferator-activated receptor δ (PPAR δ) agonist,[2] opioid antagonist,[3] farnesyl transferase inhibitor,[3a,4] and Rho kinase II (ROCK-II) selective inhibitor.[5] Since the THIQ-1-carboxamides can be construed as conformationally constrained analogues of phenyl alanine (tyrosine) or a surrogate of proline, they are often used as building blocks in the synthesis of modified peptides.

Two routes have been predominantly used for the synthesis of substituted THIQ-1-carboxamides (Scheme 1, methods A and B). Method A is based on the modification of 3,4-dihydroisoquinoline.[1c,d,6] Recently, an Ugi type reaction between 3,4-dihydroisoquinoline *N*-oxides and isocyanides in the presence of TMSCl, has been used to synthesize THIQ-1-carboxamides.[7] In the second method (method B), substituted phenethylamines are coupled with glyoxylate derivatives to yield the corresponding THIQ-1-carboxlic acid; here, the piperidine ring of the THIQ moiety is formed as a result of Pictet–Spengler or Bischler–Napieralski reactions.[8] The intermediate substituted 3,4-dihydroisoquinoline

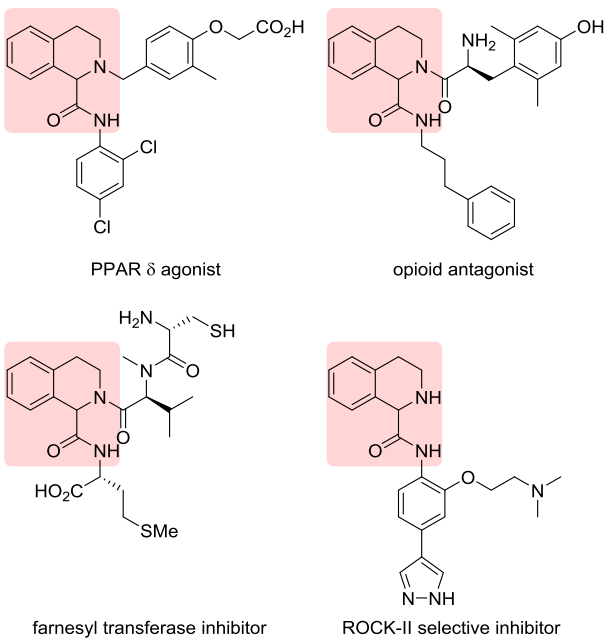

Fig. 1. Bioactive compounds containing the THIQ-1-carboxamide structural motif (red color).

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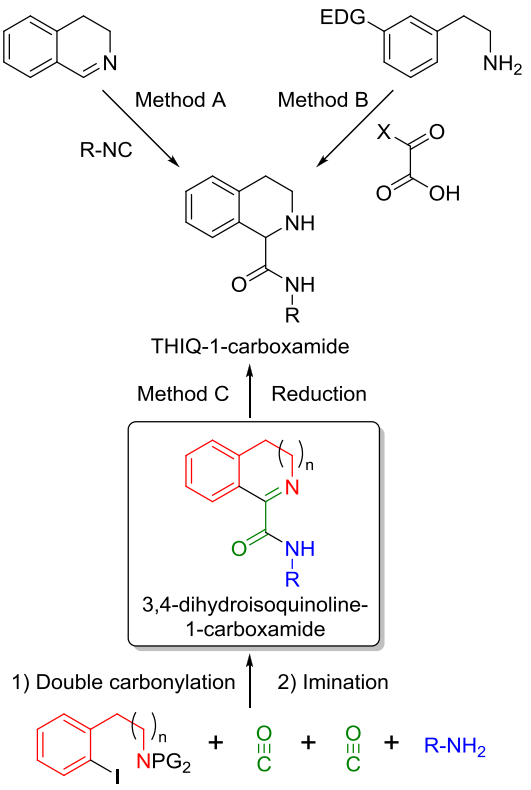


Scheme 1. Methods for the synthesis of THIQ-1-carboxamides.

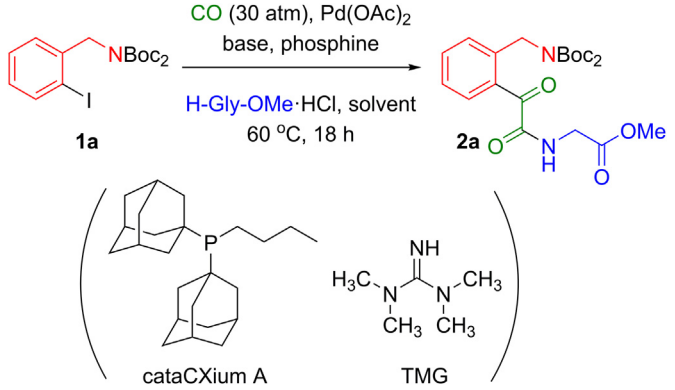
derivative is eventually reduced to afford the THIQ-1-carboxamide derivative.[9]

Development of a divergent route using readily available starting materials remains an important challenge toward the construction of THIQ-1-carboxamides. Herein, we report a novel palladium-catalyzed double carbonylation approach toward the synthesis of 3,4-dihydroisoquinoline-1-carboxamides (Scheme 1, method C). Double carbonylation[10,11] of substituted aryliodide using palladium catalysts followed by subsequent intramolecular cyclization as a result of imine formation are the highlights of this method. Considering that the 3,4-dihydroisoquinones can readily be converted to THIQs,[9] this method then presents a formal synthesis of THIQ-1-carboxamides. Such a synthetic methodology can allow for the rapid synthesis of structurally diverse THIQ-1-carboxamides.

2. Results and discussion

The key double carbonylation of iodobenzene **1a** (details for synthesis of **1a**, see Experimental section) with glycine methyl ester is presented in Table 1. When *tert*-butyl phosphine tetrafluoroborate, tetramethyl guanidine (TMG), and *N*,*N*-dimethylformamide (DMF) are employed as the ligand, base, and solvent, respectively, a good yield of the α-keto carboxamide **2a** is obtained (Table 1, entry 1). Use of other bases, such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]-7-undecene (DBU), significantly reduces the yield (Table 1, entries 2 and 3). The nature of the solvent proves to be critical for the success of the double carbonylation. Reaction conducted in tetrahydrofuran (THF) provides the desired product only in moderate yields (Table 1, entries 4, 6, and 8), while comparable reaction in DMF affords better yields of **2a**. Optimal yield (81%) of **2a** is obtained in the presence of the highly electron-donating phosphine ligand cataCXium A,[12] the base TMG, and the solvent DMF (Table 1, entry 5).

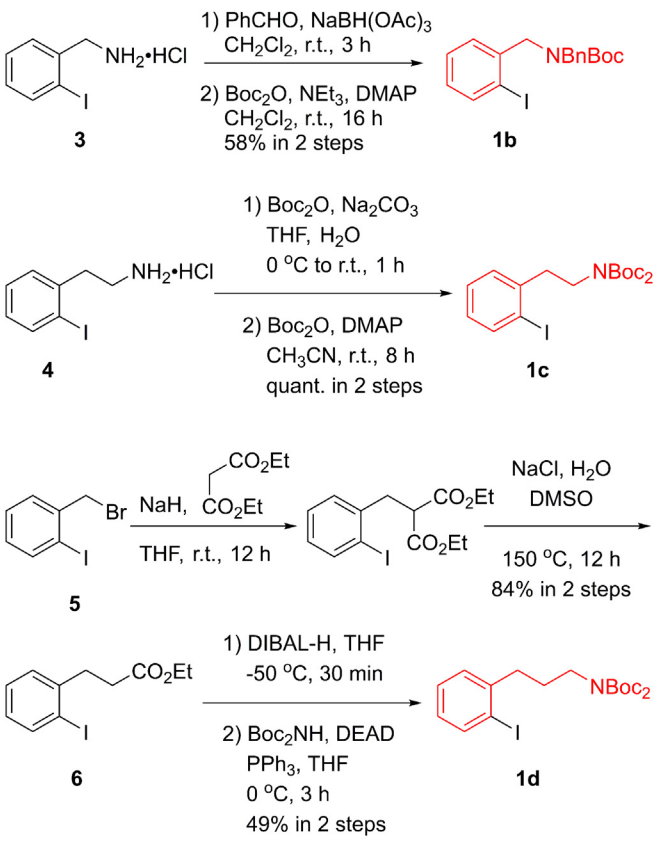
Table 1
Optimization of conditions for the double carbonylation reaction[a]



Entry	Base	Phosphine	Solvent	Yield[b] (%)
1	TMG	*t*-Bu$_3$PHBF$_4$	DMF	72
2	DABCO	*t*-Bu$_3$PHBF$_4$	DMF	43
3	DBU	*t*-Bu$_3$PHBF$_4$	DMF	40
4	TMG	*t*-Bu$_3$PHBF$_4$	THF	46
5	TMG	CataCXium A	DMF	81
6	TMG	CataCXium A	THF	37
7	TMG	PPh$_3$	DMF	37
8	TMG	PPh$_3$	THF	35

[a] Reaction conditions: **1a** (1.00 equiv), Pd(OAc)$_2$ (0.100 equiv), H-Gly-OMe (1.50 equiv), base (3.00 equiv), and phosphine (0.300 equiv) in solvent at room temperature for 18 h under carbon monoxide (30 atm).
[b] Isolated yield.

Schemes for the synthesis of substituted iodobenzenes (**1b**, **1c**, and **1d**) are shown in Scheme 2. An alkyl chain of 1, 2, or 3 carbon(s) connects the protected amine with the phenyl moiety in these structures. The benzyl amine derivative **1b** is prepared from iodobenzylamine **3**[13] in two steps: reductive amination of **3** with



Scheme 2. Synthesis of alkylamine-substituted iodobenzenes **1b**–**1d**.

benzaldehyde followed by *tert*-butyloxycarbonyl (Boc) protection of the resulting secondary amine. Phenethylamine derivative **1c** is synthesized from the amine **4**.[14] Compound **1d** is prepared by transforming 2-iodobenzylbromide (**5**). Alkylation of **5** with ethyl malonate and subsequent decarboxylation affords **6** in a good yield.[15] Reduction of the ethyl ester moiety in **6** to the primary alcohol and its subsequent substitution with the protected amine under Mitsunobu conditions[16] affords the desired compound **1d**.

Double carbonylations of the synthesized iodobenzenes proceed smoothly under the determined optimal conditions. Compounds **1b**, **1c**, and **1d** readily react with carbon monoxide in the presence of primary and secondary amines to afford α-keto carboxamides in excellent yields (Fig. 2, **7**–**11**).

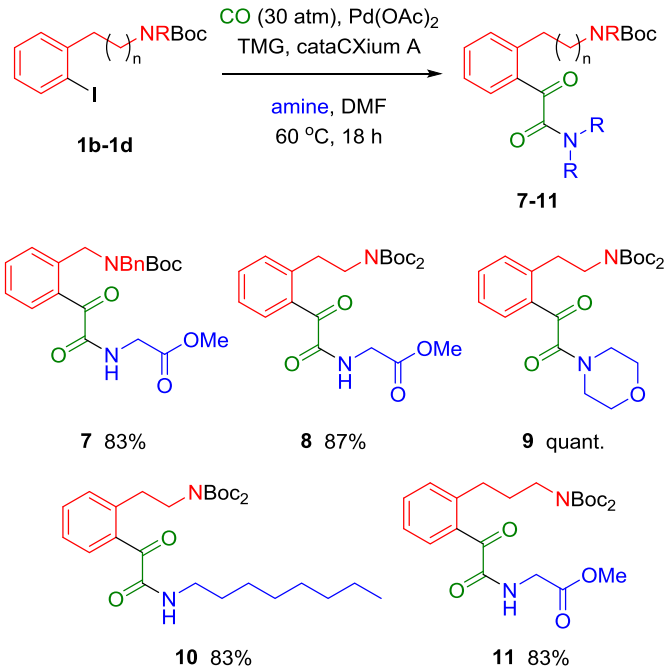


Fig. 2. Double carbonylation of iodobenzene analogues **1b**–**1d**. Reaction conditions: substrate (1.00 equiv), $Pd(OAc)_2$ (0.100 equiv), amine (1.50 equiv), TMG (3.00 equiv), and cataCXium A (0.300 equiv) in DMF at room temperature for 18 h under carbon monoxide (30 atm).

With these α-keto carboxamide in hand, intramolecular imine formation was pursued. On treatment with trifluoroacetic acid (TFA), compounds **7**, **8**, **9**, **10**, and **11** readily yielded the desired products **12**, **13**, **14**, **15**, and **16**, respectively. Although isoindole-1-carboxamide derivative **12** was obtained in low yields (34%; attributed to its instability; Fig. 3, **12**), other products, 3,4-dihydroisoquinoline-1-carboxamide derivatives **13**–**15** and benzoazepine-1-carboxamide derivative **16** were obtained in excellent yields.

3. Conclusion

In summary, we have developed a novel diversity-oriented synthetic methodology for the generation of 3,4-dihydro isoquinoline-1-carboxamides and its analogues. This method involves the initial palladium-catalyzed double carbonylation of an *N*-protected alkylamine aryliodide and an amine partner to afford the intermediate α-keto carboxamide, which on subsequent deprotection undergoes intramolecular imine formation to afford the benzo-azacyclic product. Since 3,4-dihydroisoquinolines can readily be reduced to THIQs, this synthetic methodology allows for the rapid synthesis of structurally diverse THIQ-1-carboxamides.

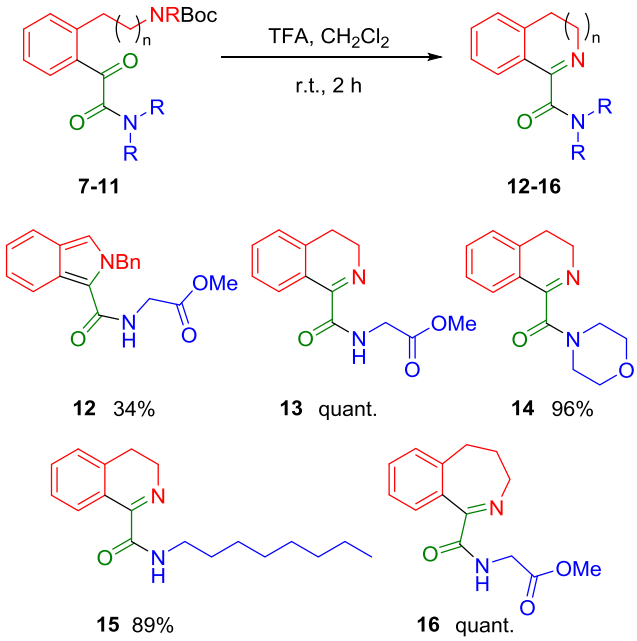


Fig. 3. Intramolecular imination of α-keto carboxamides **7**–**11**.

4. Experimental section

4.1. General

NMR spectra were recorded on a JEOL Model ECA-500 instrument or a JEOL Model ECP-400. Chemical shifts are reported in parts per million (ppm) relative to the signal for the internal standard tetramethylsilane (0.0 ppm) or the solvent $CDCl_3$ (7.26 ppm, ^{1}H NMR; or 77.1 ppm, ^{13}C NMR) peaks. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectrum data are reported as follows: chemical shift (δ ppm), and where applicable, multiplicity and coupling constants. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, multiplet; br, broad; and *J*, coupling constants in hertz. Only the strongest and/or structurally relevant IR peaks are reported (cm^{-1}). All reactions were monitored by thin-layer chromatography performed using 0.2 mm E. Merck silica gel plate (60F-254). The reactants and products were visualized using UV light (254 nm), or by heating after treatment with *p*-anisaldehyde solution, ceric sulfate solution, or 10% ethanolic phosphomolybdic acid. Column chromatography separations were performed using silica gel (Merck). ESI-TOF mass spectra were acquired on a Waters LCT PremierTM XE. HRMS (ESI-TOF) were calibrated using a standard curve obtained using leu-enkephalin. (2-Iodophenyl)methanamine hydrochloride (**3**),[13] 2-(2-iodophenyl)ethanamine hydrochloride (**4**),[14] and ethyl 3-(2-iodophenyl)propanoate (**6**)[15] were prepared according to literature procedures.

4.2. *N*-(Bis-*tert*-butoxycarbonyl)-2-iodobenzylamine (1a)

To a solution of Cs_2CO_3 (3.62 g, 11.1 mmol, 1.10 equiv) in DMF (11.1 mL) were added Boc_2NH (2.41 g, 11.1 mmol, 1.10 equiv) and 2-iodobenzylbromide (3.00 g, 10.1 mmol, 1.00 equiv) at room temperature. After being stirred at the same temperature for 16 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and

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concentrated in vacuo. The residue was purified by column chromatography on silica gel (12% ethyl acetate in hexane) to give *N*-(bis-*tert*-butoxycarbonyl)-2-iodobenzylamine (**1a**) (4.81 g, 11.1 mmol, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J=7.7 Hz, 1H), 7.31 (dd, J=7.7, 7.7 Hz, 1H), 7.08 (d, J=7.7 Hz, 1H), 6.94 (dd, J=7.7, 7.7 Hz, 1H), 4.77 (s, 2H), 1.43 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 140.2, 139.2, 128.4, 128.3, 125.7, 96.9, 82.8, 54.9, 27.9. IR (chloroform solution): 2934, 1790, 1715, 1586, 1566, 1417, 1368, 1228, 1146, 1047, 1013, 961, 933, 894, 855, 747 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{17}H_{25}NO_4I$ $[M+H]^+$ 434.0828, found 434.0807.

4.3. General procedure for the optimization of double carbonylative amidation conditions

N-(Bis-*tert*-butoxycarbonyl)-2-iodobenzylamine (**1a**) (1.00 equiv), $Pd(OAc)_2$ (0.100 equiv), *phosphine* (0.300 equiv), H-Gly-OMe·HCl (1.50 equiv), and *base* (3.00 equiv) in *solvent* (1.16 mL) were added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into 1 M HCl and the aqueous layer was extracted with two portions of Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give methyl 2-(2-((bis-*tert*-butoxycarbonylaminomethyl)phenyl)-2-oxoacetamido)acetate (**2a**) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J=8.2 Hz, 1H), 7.72–7.64 (m, 1H), 7.59–7.46 (m, 1H), 7.48–7.31 (m, 2H), 5.05 (s, 2H), 4.18 (d, J=5.8 Hz, 2H), 3.81 (s, 3H), 1.40 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.7, 169.3, 162.1, 152.4, 141.1, 133.2, 132.3, 131.5, 126.5, 126.3, 82.6, 52.4, 47.6, 41.1, 27.8. IR (chloroform solution): 3320, 2982, 1749, 1681, 1602, 1574, 1529, 1481, 1451, 1369, 1306, 1230, 1112, 1036, 935, 853 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{22}H_{31}N_2O_8$ $[M+H]^+$ 451.2080, found 451.2043.

4.4. *tert*-Butyl benzyl(2-iodobenzyl)carbamate (1b)

To a solution of (2-iodophenyl)methanamine hydrochloride (**3**) (539 mg, 2.00 mmol, 1.00 equiv) in CH_2Cl_2 (6.00 mL) were added benzaldehyde (243 μL, 2.40 mmol, 1.20 equiv) and sodium triacetoxyborohydride (636 mg, 3.00 mmol, 1.50 equiv) at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was quenched with saturated $NaHCO_3$ aq and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the residue (280 mg, 0.866 mmol, 1.00 equiv) in CH_2Cl_2 (2.60 mL) were added DMAP (2.12 mg, 0.0173 mmol, 0.0200 equiv) and Boc_2O (208 mg, 0.953 mmol, 1.10 equiv) at room temperature. After being stirred at the same temperature for 16 h, the reaction mixture was quenched with 1 M HCl and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (10% ethyl acetate in hexane) to give *tert*-butyl benzyl(2-iodobenzyl)carbamate (**1b**) (477 mg, 1.13 mmol, 58% in two steps) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J=8.0 Hz, 1H), 7.37–7.10 (m, 7H), 6.97 (t, J=7.5 Hz, 1H), 4.51 (d, J=10.9 Hz, 1H), 4.39 (d, J=10.9 Hz, 1H), 1.54–1.47 (m, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 139.7, 139.5, 137.8, 137.6, 128.8, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.4, 127.3, 127.1, 98.2, 98.0, 80.3, 80.2, 54.9, 54.4, 50.1, 49.8, 28.4. IR (neat): 2975, 1690, 1585, 1564, 1450, 1406, 1364, 1242, 1157, 1122, 1011, 880, 744, 697 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{19}H_{22}NO_2I$ $[M+H]^+$ 424.0774, found 424.0795.

4.5. *N*-(Bis-*tert*-butoxycarbonyl)-2-(2-iodophenyl)ethanamine (1c)

To a stirred suspension of 2-(2-iodophenyl)ethanamine hydrochloride (**4**) (284 mg, 1.00 mmol, 1.00 equiv) in THF (4.00 mL) and water (2.00 mL) were added Na_2CO_3 (122 mg) and Boc_2O (436 mg, 2.00 mmol, 2.00 equiv) at 0 °C. After being stirred at the room temperature for 1 h, the reaction mixture was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the residue in CH_3CN (3.00 mL) were added DMAP (122 mg, 1.00 mmol, 1.00 equiv) and Boc_2O (655 mg, 3.00 mmol, 3.00 equiv) at room temperature. After being stirred at the same temperature for 8 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give *N*-(bis-*tert*-butoxycarbonyl)2-(2-iodophenyl)ethanamine (**1c**) (643 mg, 1.44 mmol, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J=1.0, 7.7 Hz, 1H), 7.26 (ddd, J=1.0, 7.7, 7.7 Hz, 1H), 7.20 (dd, J=1.0, 7.7 Hz, 1H), 7.04 (ddd, J=1.0, 7.7, 7.7 Hz, 1H), 3.84 (t, J=7.2 Hz, 2H), 3.03 (t, J=7.2 Hz, 2H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 141.9, 139.4, 130.3, 128.4, 128.2, 100.7, 82.2, 46.0, 40.0, 28.0, 27.9. IR (chloroform solution): 3319, 2979, 1790, 1733, 1589, 1563, 1468, 1367, 1255, 1142, 1013, 857, 750 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{18}H_{27}NO_4I$ $[M+H]^+$ 448.0985, found 448.0962.

4.6. *N*-(Bis-*tert*-butoxycarbonyl)-3-(2-iodophenyl)propan-1-amine (1d)

To a solution of ethyl 3-(2-iodophenyl)propanoate (**6**) (1.80 g, 5.92 mmol, 1.00 equiv) in THF (17.8 mL) was added DIBAL-H (1.0 M solution in hexane, 14.8 mL, 14.8 mmol, 2.50 equiv) at −50 °C. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with MeOH and 10% aqueous Rochelle salt and the aqueous layer was extracted with two portions of ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was used for the next reaction without further purification.

To a solution of the residue in THF (17.8 mL) were added Boc_2NH (1.54 g, 7.10 mmol, 1.20 equiv), triphenylphosphine (1.86 g, 7.10 mmol, 1.20 equiv), and DEAD (2.2 M solution in toluene, 3.23 mL, 7.10 mmol, 1.20 equiv) at 0 °C. After being stirred at the same temperature for 3 h, the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexane) to give *N*-(bis-*tert*-butoxycarbonyl)-3-(2-iodophenyl)propan-1-amine (**1d**) (1.61 g, 3.49 mmol, 49%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, J=8.0 Hz, 1H), 7.26 (dd, J=7.4, 7.4 Hz, 1H), 7.20 (d, J=6.3 Hz, 1H), 6.87 (dd, J=7.4 Hz, 1H), 3.66 (t, J=7.4 Hz, 2H), 2.71 (t, J=8.0 Hz, 2H), 1.90–1.85 (m, 2H), 1.49 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5, 144.2, 139.5, 129.3, 128.4, 127.9, 100.6, 82.2, 46.0, 38.2, 29.6, 28.1. IR (neat): 2977, 1740, 1692, 1456, 1436, 1392, 1365, 1290, 1244, 1173, 1137, 1117, 1040, 1009, 855, 748, 647 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{19}H_{29}NO_4I$ $[M+H]^+$ 462.1141, found 462.1188.

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4.7. Methyl (2-(2-((benzyl(*tert*-butoxycarbonyl)amino) methyl)phenyl)-2-oxoacetyl)glycinate (7)

tert-Butyl benzyl(2-iodobenzyl)carbamate (**1b**) (216 mg, 0.500 mmol, 1.00 equiv), $Pd(OAc)_2$ (11.2 mg, 0.0500 mmol, 0.100 equiv), cataCXium A (53.8 mg, 0.150 mmol, 0.300 equiv), H-Gly-OMe·HCl (94.2 mg, 0.750 mmol, 1.50 equiv), and tetramethyl guanidine (188 μL, 1.50 mmol, 3.00 equiv) in DMF (2.50 mL) were added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into 1 M HCl and the aqueous layer was extracted with two portions of Et_2O. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give methyl (2-(2-((benzyl(*tert*-butoxycarbonyl) amino)methyl)phenyl)-2-oxoacetyl)glycinate (**7**) (182 mg, 0.413 mmol, 83%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.54 (dd, J=7.5, 7.5 Hz, 2H), 7.38–7.12 (m, 7H), 4.64 (br s, 2H), 4.38 (br s, 2H), 4.13 (d, J=5.8 Hz, 2H), 3.78 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.9, 169.3, 161.8, 156.1, 137.7, 133.2, 132.2, 128.5, 127.6, 127.3, 126.6, 80.3, 52.6, 50.1, 47.9, 41.2, 28.3. IR (neat): 2977, 1752, 1669, 1600, 1573, 1524, 1451, 1408, 1365, 1246, 1204, 1160, 1030, 933, 883, 749, 699, 666 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{29}N_2O_6$ $[M+H]^+$ 441.2026, found 441.2027.

4.8. Methyl 2-(2-(2-(2-((bis-*tert*-butoxycarbonyl)amino)ethyl) phenyl)-2-oxoacetamido)acetate (8)

A solution of *N*-(bis-*tert*-butoxycarbonyl)2-(2-iodophenyl) ethanamine (**1c**) (100 mg, 0.224 mmol, 1.00 equiv), $Pd(OAc)_2$ (5.03 mg, 0.0224 mmol, 0.100 equiv), cataCXium A (24.0 mg, 0.0671 mmol, 0.300 equiv), H-Gly-OMe·HCl (42.2 mg, 0.336 mmol, 1.50 equiv), and tetramethyl guanidine (84.2 μL, 0.671 mmol, 3.00 equiv) in DMF (1.16 mL) was added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by TLC (33% ethyl acetate in hexane) to give methyl 2-(2-(2-(2-((bis-*tert*-butoxycarbonyl)amino)ethyl)phenyl)-2-oxoacetamido) acetate (90.4 mg, 0.195 mmol, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J=7.7 Hz, 1H), 7.60 (t, J=5.8 Hz, 1H), 7.47 (t, J=7.7 Hz, 1H), 7.33 (d, J=7.7 Hz, 1H), 7.29 (t, J=7.7 Hz, 1H), 4.18 (d, J=5.8 Hz, 2H), 3.90 (t, J=6.8 Hz, 2H), 3.80 (s, 3H), 3.11 (t, J=6.8 Hz, 2H), 1.44 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 169.3, 162.5, 152.5, 140.9, 132.9, 132.2, 132.0, 126.1, 82.2, 52.5, 47.1, 41.2, 33.2, 28.0. IR (chloroform solution): 3328, 2981, 1747, 1600, 1524, 1479, 1440, 1368, 1123, 1036, 934, 854, 769 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{23}H_{33}N_2O_8$ $[M+H]^+$ 465.2237, found 465.2236.

4.9. 1-(2-(2-(Bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-2-morpholinoethane-1,2-dione (9)

A solution of *N*-(bis-*tert*-butoxycarbonyl)2-(2-iodophenyl) ethanamine (**1c**) (800 mg, 1.79 mmol, 1.00 equiv), $Pd(OAc)_2$ (40.1 mg, 0.179 mmol, 0.100 equiv), cataCXium A (193 mg, 0.537 mmol, 0.300 equiv), morpholine (234 μL, 2.69 mmol, 1.50 equiv), and tetramethyl guanidine (672 μL, 5.37 mmol, 3.00 equiv) in DMF (8.95 mL) was added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give 1-(2-(2-(bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-2-morpholinoethane-1,2-dione (**9**) (835 mg, 1.81 mmol, quant.) as a white solid. Mp 46–49 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J=8.0 Hz, 1H), 7.49 (dd, J=7.4, 7.4 Hz, 1H), 7.35 (dd, J=7.4, 7.4 Hz, 1H), 7.26 (d, J=7.4 Hz, 1H), 3.95 (t, J=7.4 Hz, 2H), 3.79–3.76 (m, 4H), 3.65 (t, J=5.1 Hz, 2H), 3.47 (t, J=5.1 Hz, 2H), 3.33 (t, J=6.3 Hz, 2H), 1.40 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 166.0, 152.6, 142.4, 133.9, 133.4, 133.3, 131.6, 127.0, 82.2, 67.0, 66.8, 46.3, 46.2, 41.7, 33.9, 28.1. IR (neat): 2975, 1743, 1702, 1675, 1645, 1570, 1451, 1365, 1353, 1300, 1268, 1231, 1147, 1112, 977, 924, 837, 747, 712, 650 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{35}N_2O_7$ $[M+H]^+$ 463.2444, found 463.2477.

4.10. 2-(2-(2-(Bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-*N*-octyl-2-oxoacetamide (10)

A solution of *N*-(bis-*tert*-butoxycarbonyl)2-(2-iodophenyl) ethanamine (**1c**) (400 mg, 0.894 mmol, 1.00 equiv), $Pd(OAc)_2$ (20.1 mg, 0.0894 mmol, 0.100 equiv), cataCXium A (96.2 mg, 0.268 mmol, 0.300 equiv), *n*-octylamine (133 μL, 1.34 mmol, 1.50 equiv), and tetramethyl guanidine (336 μL, 2.68 mmol, 3.00 equiv) in DMF (4.47 mL) was added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (40% ethyl acetate in hexane) to give 2-(2-(2-(bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-*N*-octyl-2-oxoacetamide (**10**) (373 mg, 0.739 mmol, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J=8.0 Hz, 1H), 7.46 (dd, J=7.4, 7.4 Hz, 1H), 7.31 (dd, J=7.4, 7.4 Hz, 1H), 7.28 (d, J=7.4 Hz, 1H), 7.16 (br s, 1H), 3.88 (t, J=7.4 Hz, 2H), 3.38 (t, J=6.9 Hz, 2H), 3.10 (t, J=7.4 Hz, 2H), 1.66–1.48 (m, 2H), 1.44 (s, 18H), 1.42–1.27 (m, 10H), 0.87 (t, J=7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 162.5, 152.5, 140.7, 133.4, 132.7, 132.1, 132.0, 126.1, 82.3, 47.2, 39.7, 33.3, 31.8, 29.3, 29.2, 28.1, 27.0, 22.7, 14.2. IR (neat): 2927, 1780, 1745, 1668, 1520, 1455, 1366, 1271, 1256, 1235, 1172, 1143, 1118, 855, 752, 663 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{28}H_{45}N_2O_6$ $[M+H]^+$ 505.3278, found 505.3292.

4.11. Methyl (2-(2-(3-(bis-*tert*-butoxycarbonyl)aminopropyl) phenyl)-2-oxoacetyl)glycinate (11)

A solution of *N*-(bis-*tert*-butoxycarbonyl)-3-(2-iodophenyl) propan-1-amine (**1d**) (103 mg, 0.224 mmol, 1.00 equiv), $Pd(OAc)_2$ (5.03 mg, 0.0224 mmol, 0.100 equiv), cataCXium A (24.0 mg, 0.0671 mmol, 0.300 equiv), H-Gly-OMe·HCl (42.2 mg, 0.336 mmol, 1.50 equiv), and tetramethyl guanidine (84.2 μL, 0.671 mmol, 3.00 equiv) in DMF (1.16 mL) was added to a glass vessel at room temperature under Ar atmosphere. The vessel was placed in autoclave, which was purged with CO three times before applying a pressure (30 atm). After being stirred at 60 °C for 18 h, the reaction mixture was filtered through a pad of Celite®. The filtrate

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was poured into 1 M HCl and the aqueous layer was extracted with two portions of diethyl ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by TLC (33% ethyl acetate in hexane) to give methyl (2-(2-(3-(bis-*tert*-butoxycarbonyl)aminopropyl)phenyl)-2-oxoacetyl)glycinate (**11**) (89.0 mg, 0.186 mmol, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J=8.0 Hz, 1H), 7.58 (t, J=5.8 Hz, 1H), 7.45 (dd, J=7.7, 7.7 Hz, 1H), 7.29–7.25 (m, 2H), 4.16 (d, J=5.8 Hz, 2H), 3.78 (s, 3H), 3.61 (t, J=7.4 Hz, 2H), 2.78 (t, J=7.7 Hz, 2H), 1.90–1.83 (m, 2H), 1.46 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 169.4, 162.2, 152.5, 143.9, 132.9, 132.3, 132.1, 130.7, 125.7, 82.1, 52.6, 46.2, 41.2, 31.0, 30.9, 28.0. IR (neat): 2979, 1742, 1675, 1599, 1523, 1479, 1438, 1392, 1366, 1295, 1248, 1203, 1177, 1139, 987, 934, 851, 754, 734, 703, 664 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{24}H_{35}N_2O_8$ $[M+H]^+$ 479.2393, found 479.2423.

4.12. Methyl (2-benzyl-2*H*-isoindole-1-carbonyl)glycinate (12)

To a solution of methyl (2-(2-((benzyl(*tert*-butoxycarbonyl)amino)methyl)phenyl)-2-oxoacetyl)glycinate (**7**) (20.0 mg, 0.0454 mmol, 1.00 equiv) in CH_2Cl_2 (720 μL) was added trifluoroacetic acid (180 μL) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by TLC (33% ethyl acetate in hexane) to give methyl (2-benzyl-2*H*-isoindole-1-carbonyl)glycinate (**12**) (5.00 mg, 0.0155 mmol, 34%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, J=9.2 Hz, 1H), 7.60 (d, J=8.6 Hz, 1H), 7.36–7.21 (m, 5H), 7.17 (d, J=6.8 Hz, 2H), 7.05 (t, J=8.0 Hz, 1H), 6.53 (br s, 1H), 5.89 (s, 2H), 4.29 (d, J=5.2 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 162.1, 137.7, 128.8, 127.8, 127.5, 126.0, 125.0, 123.9, 121.7, 120.9, 119.5, 118.4, 53.4, 52.5, 41.5. IR (neat): 2925, 1747, 1697, 1639, 1517, 1496, 1455, 1434, 1395, 1358, 1290, 1206, 1178, 1075, 1030, 724, 702, 627 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{19}H_{19}N_2O_3$ $[M+H]^+$ 323.1396, found 323.1393.

4.13. Methyl (3,4-dihydroisoquinoline-1-carbonyl)glycinate (13)

To a solution of methyl 2-(2-(2-(2-((bis-*tert*-butoxycarbonyl)amino)ethyl)phenyl)-2-oxoacetamido)acetate (**8**) (20.0 mg, 0.0431 mmol, 1.00 equiv) in CH_2Cl_2 (860 μL) was added trifluoroacetic acid (860 μL) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by TLC (33% ethyl acetate in hexane) to give methyl (3,4-dihydroisoquinoline-1-carbonyl)glycinate (**13**) (13.7 mg, 0.0556 mmol, quant.) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J=7.7 Hz, 1H), 7.92 (br s, 1H), 7.38 (ddd, J=1.5, 7.7, 7.7 Hz, 1H), 7.31 (dd, J=7.7, 7.7 Hz, 1H), 7.19 (d, J=7.7 Hz, 1H), 4.18 (d, J=5.8 Hz, 2H), 3.81 (t, J=7.7 Hz, 2H), 3.79 (s, 3H), 2.74 (t, J=7.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 164.4, 159.2, 137.9, 131.4, 128.4, 127.2, 127.0, 126.1, 52.4, 47.2, 41.1, 25.7. IR (chloroform solution): 3379, 2953, 1751, 1675, 1611, 1520, 1436, 1371, 1204, 970, 755 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{15}N_2O_3$ $[M+H]^+$ 247.1083, found 247.1085.

4.14. (3,4-Dihydroisoquinolin-1-yl)(morpholino)methanone (14)

To a solution of 1-(2-(2-(bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-2-morpholinoethane-1,2-dione (**9**) (165 mg, 0.357 mmol, 1.00 equiv) in CH_2Cl_2 (1.43 mL) was added trifluoroacetic acid (357 μL) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by TLC (ethyl acetate) to give (3,4-dihydroisoquinolin-1-yl)(morpholino)methanone (**14**) (83.7 mg, 0.343 mmol, 96%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J=7.4, 7.4 Hz, 1H), 7.36 (d, J=7.4 Hz, 1H), 7.31 (dd, J=7.4, 7.4 Hz, 1H), 7.22 (d, J=7.4 Hz, 1H), 3.90–3.73 (m, 6H), 3.66–3.55 (m, 2H), 3.49–3.41 (m, 2H), 2.83 (t, J=8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 163.0, 136.9, 132.0, 128.0, 127.5, 126.0, 66.9, 66.8, 46.9, 46.8, 41.8, 25.2. IR (neat): 2853, 1639, 1616, 1572, 1464, 1440, 1388, 1362, 1303, 1269, 1214, 1197, 1111, 1066, 1018, 995, 931, 895, 848, 794, 739, 718, 699, 670, 583 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1290, found 245.1295.

4.15. *N*-Octyl-3,4-dihydroisoquinoline-1-carboxamide (15)

To a solution of 2-(2-(2-(bis-*tert*-butoxycarbonyl)aminoethyl)phenyl)-*N*-octyl-2-oxoacetamide (**10**) (83.7 mg, 0.166 mmol, 1.00 equiv) in CH_2Cl_2 (571 μL) was added trifluoroacetic acid (143 μL) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by TLC (50% ethyl acetate in hexane) to give *N*-octyl-3,4-dihydroisoquinoline-1-carboxamide (**15**) (42.2 mg, 0.147 mmol, 89%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J=6.3 Hz, 1H), 7.68 (br s, 1H), 7.40 (dd, J=7.4, 7.4 Hz, 1H), 7.33 (dd, J=6.3, 6.3 Hz, 1H), 7.20 (d, J=7.4 Hz, 1H), 3.81 (s, 2H), 3.39 (s, 2H), 2.78 (s, 2H), 1.59 (s, 2H), 1.36–1.10 (m, 10H), 0.87 (t, J=6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 161.2, 138.2, 132.2, 129.1, 127.3, 127.2, 126.0, 39.7, 31.8, 29.5, 29.3, 29.2, 27.0, 26.9, 25.8, 22.7, 14.1. IR (neat): 2924, 2853, 1668, 1609, 1570, 1519, 1454, 1376, 1236, 1199, 1134, 1023, 937, 890, 799, 750, 720, 692, 608 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{18}H_{27}N_2O$ $[M+H]^+$ 287.2123, found 287.2128.

4.16. Methyl (4,5-dihydro-3*H*-benzo[*c*]azepine-1-carbonyl) glycinate (16)

To a solution of methyl (2-(2-(3-(bis-*tert*-butoxycarbonyl)aminopropyl)phenyl)-2-oxoacetyl)glycinate (**11**) (47.9 mg, 0.100 mmol, 1.00 equiv) in CH_2Cl_2 (400 μL) was added trifluoroacetic acid (100 μL) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was purified by TLC (33% ethyl acetate in hexane) to give methyl (4,5-dihydro-3*H*-benzo[*c*]azepine-1-carbonyl) glycinate (**16**) (26.3 mg, 0.101 mmol, quant.) as a pale yellow solid. Mp 86–89 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.47 (d, J=7.4 Hz, 1H), 7.34 (dd, J=7.4, 7.4 Hz, 1H), 7.31 (dd, J=7.4, 7.4 Hz, 1H), 7.21 (d, J=7.4 Hz, 1H), 4.17 (d, J=5.8 Hz, 1H), 3.78 (s, 3H), 3.40 (t, J=6.3 Hz, 1H), 2.51 (t, J=7.4 Hz, 1H), 2.37–2.29 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 164.0, 163.8, 140.6, 131.8, 130.3, 129.5, 128.4, 126.0, 52.4, 49.9, 41.3, 34.1, 30.3. IR (neat): 2940, 1752, 1665, 1610, 1510, 1471, 1453, 1435, 1365, 1303, 1256, 1211, 1193, 1178, 1039, 982, 955, 882, 749 cm^{-1}. HRMS (ESI-TOF) calcd for $C_{14}H_{17}N_2O_3$ $[M+H]^+$ 261.1239, found 261.1244.

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