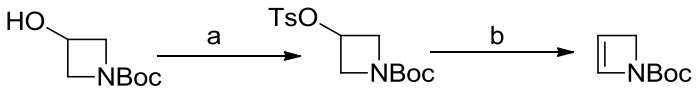
Synthetic procedure for N-tert-butylcarbamate-2-azetine 5-3[1]



Reaction conditions: (a) TsCl, pyridine, 0 ℃, (99%). (b) t-BuOK, tBuOH, 80 ℃, (43%).

Step a: 1-Boc-3-hydroxyazetidine (3.4 g, 19.6 mmol, 1 equiv) was dissolved in pyridine (30 mL) and cooled to 0 ℃. After addition of p-toluenesulfonylchloride (7.47 g, 19.6 mmol, 1 equiv), the reaction flask was capped and placed into the freezer for 24 hours. Et_2O and H_2O were then added, and the product extracted three times with Et_2O. The combine organics were washed with 1N HCl (3 times) and brine to provide the desired product as a colorless oil (99% yield), which was used in the following step without further purification.

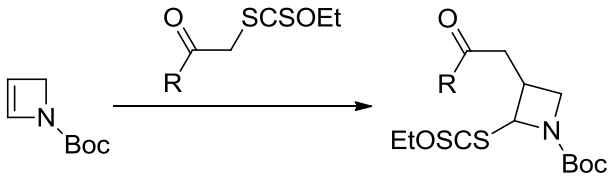
Step b: Under a nitrogen atmosphere, to a solution of tert-butyl 3-(tosyloxy)azetidine -1-carboxylate (3 g, 9.15 mmol, 1 equiv) and t-BuOH (15 mL) was added a solution of t-BuOK (1.029 g, 13.8 mmol, 1.5 equiv) in t-BuOH (30 mL) dropwise via cannulation. The mixture was stirred overnight at 80 ℃. After the reaction was completed, H_2O (60 mL) was added and the mixture was extracted with hexanes (3 times). The hexanes solution was then washed with brine and dried with $MgSO_4$. After removal of the solvent at reduced pressure, the crude oil was purified by silica gel chromatography (elution solvent – pentane:Et_2O = 1:1) to provide 586 mg of a colorless oil (yield: 43%).

^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.57 (s, 1H), 5.52 (s, 1H), 4.39 (s, 2H), 1.46 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 151.9, 138.8, 111.9, 58.4, 28.5, 19.5;

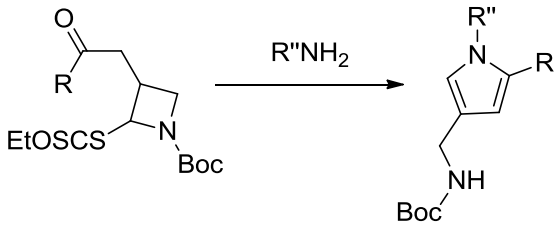
[1] McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R.; *J. Am. Chem. Soc.* **2010**, *132*, 14027.

General procedure A for radical addition



A magnetically stirred solution of xanthate (1 equiv) and olefin (0.8~1.1 equiv) were dissolved in ethyl acetate (1 ml/mmol of xanthate) with several drops of 2,6-lutidine (0.3~0.5 equiv.) was refluxed for 15 min. DLP (5 mol%) was then added and additional DLP (5 mol%) was added every 60 min until total consumption of xanthate. The mixture was then cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired compounds.

General procedure B for pyrrole synthesis[2]

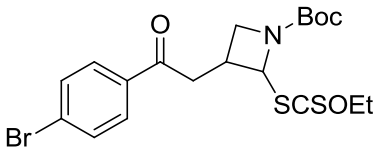


To a solution of xanthate (1 equiv.) in dioxane (5 ml/mmol) were added *p*-toluene sulfonic acid monohydrate (0.5~1 equiv.) and amine (2~4 equiv.). The reaction mixture was refluxed under nitrogen for 0.5~1 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel to give the pyrrole products. In cases of trisubstituted pyrroles synthesis, the residue can be either purified by a column or used in the following step without purification.

[2] Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, *1*, 75.

Adducts 5-6:

Tert-butyl-3-(2-(4-bromophenyl)-2-oxoethyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-6a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5a** (304 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 258 mg **5-6a** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.80 (m, 2H, Ar), 7.60 (m, 2H, Ar), 5.75 (d, 1H, J=4.3Hz, C*H*S), 4.60 (m, 2H, COC*H*$_2$CH$_3$), 4.22 (m, 1H, C*H*HN), 3.70 (m, 1H, CH*H*N), 3.52 (m, 1H,C*H*CHS), 3.37 (m, 1H, COCH*H*), 3.15 (m, 1H, COC*H*H), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 7.80 (m, 2H, Ar), 7.60 (m, 2H, Ar), 6.20 (d, 1H, J=7.5Hz, C*H*S), 4.60 (m, 2H, COC*H*$_2$CH$_3$), 4.22 (m, 1H, C*H*HN), 3.70 (m, 1H, CH*H*N), 3.52 (m, 1H,C*H*CHS), 3.37 (m, 1H, COCH*H*), 3.15 (m, 1H, COC*H*H), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212.4 (*C*=S), 196.7 (*C*O), 154.9 (*C*O), 135.210, 132.110, 129.6, 128.8 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.6 (O*C*H$_2$), 69.9 (CHS), 42.5 (CH$_2$N), 35.8 (CO*C*H$_2$CH), 30.8 (*C*HCH$_2$), 28.3 (OC(CH$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

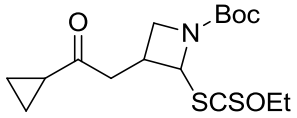
Diastereoisomer 2: δ_C ppm 212.3 (*C*=S), 196.4 (*C*O), 154.8 (*C*O), 135, 132, 129.6, 128.6 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.7 (CHS), 39.8 (CH$_2$N), 35.8 (CO*C*H$_2$CH), 29.7 (*C*HCH$_2$), 28.4 (OC(CH$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1113, 1149, 1230, 1273, 1367, 1391, 1470, 1484, 1541, 1558,

1586, 1691, 1707, 1726, 2927,2960, 2983;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{16}H_{19}BrNO_3$: 352.0543 (352.0546).

Tert-butyl-3-(2-cyclopropyl-2-oxoethyl)-2-((ethoxycarbonothioyl)thio)azetidine-1 - carboxylate (5-6b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5b** (301 mg, 0.84 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (142 mg, 0.7 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 221 mg **5-6b** (yield: 74%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.65 (d, 1H, J=3.7Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.44 (m, 2H, CH*H*N, C*H*CHS), 2.98 (m, 2H, COC*H*$_2$), 1.90 (m, 1H, CH$_2$C*H*), 1.39 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 0.97 (m, 2H, C*H*$_2$CH), 0.86 (m, 2H, C*H*$_2$CH);

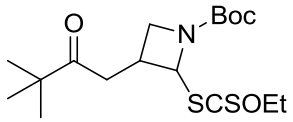
Diastereoisomer 2: δ_H ppm 6.11 (d, 1H, J=7.1Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.44 (m, 2H, CH*H*N, C*H*CHS), 2.98 (m, 2H, COC*H*$_2$), 1.90 (m, 1H, CH$_2$C*H*), 1.39 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 0.97 (m, 2H, C*H*$_2$CH), 0.86 (m, 2H, C*H*$_2$CH);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212.1 (*C*=S), 208.2 (*C*O), 154.8 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.6 (O*C*H$_2$), 69.7 (*C*HS), 46.9 (*C*H$_2$N), 35.5 (CO*C*H$_2$CH), 30.4 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 20.8 (*C*HCH$_2$), 13.8 (OCH$_2$*C*H$_3$), 11.1 (*C*H$_2$CH);

Diastereoisomer 2: δ_C ppm 211.8 (*C*=S), 208 (*C*O), 154.9 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.6 (*C*HS), 44.3 (*C*H$_2$N), 35.5 (CO*C*H$_2$CH), 30.4 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 20.7 (*C*HCH$_2$), 13.8 (OCH$_2$*C*H$_3$), 11 (*C*H$_2$CH);

IR (CCl_4): νmax 1048, 1149, 1226, 1368, 1464, 1539, 1543, 1718, 1786, 2876, 2933;
HRMS (EI+): *m/z* calculated (found) for *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{13}H_{20}NO_3$: 238.1438 (238.1446).

Tert-butyl-3-(3,3-dimethyl-2-oxobutyl)-2-((ethoxycarbonothioyl)thio)azetidine-1-carboxylate (5-6c)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5c** (176 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (103 mg, 0.66 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 203mg **5-6c** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 6.12 (d, 1H, J=7.3Hz C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.39 (m, 1H, C*H*HN), 3.16 (m, 1H, C*H*CHS), 2.89 (m, 2H, COC*H*$_2$), 1.38 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.11 (s, 9H, (C*H*$_3$)$_3$);

Diastereoisomer 2: δ_H ppm 5.62 (d, 1H, J=4.1Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.08 (m, 1H, C*H*HN), 3.39 (m, 1H, C*H*HN), 3.16 (m, 1H, C*H*CHS), 2.89 (m, 2H, COC*H*$_2$), 1.38 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.09 (s, 9H, (C*H*$_3$)$_3$);

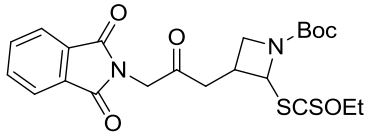
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 213.8 (*C*=S), 212.2 (*C*O), 154.9 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.5 (O*C*H$_2$), 69.8 (CHS), 44.1 (*C*H$_2$N), 40.5 (COCH$_2$CH), 30.6 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 26.5 (C(*C*H$_3$)$_3$), 13.8 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 213.6 (*C*=S), 211.6 (*C*O), 154.7 (*C*O), 80.6 (O*C*(CH$_3$)$_3$), 72.3 (O*C*H$_2$), 69.6 (CHS), 43.9 (*C*H$_2$N), 37.8 (COCH$_2$CH), 30.6 (*C*HCH$_2$), 28.3 (OC(*C*H$_3$)$_3$), 26.4 (C(*C*H$_3$)$_3$), 13.7 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1049, 1114, 1148, 1223, 1367, 1391, 1464, 1501, 1712, 1783, 2872, 2970;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{14}H_{24}NO_3$: 254.1751 (254.1752).

Tert-butyl-3-(3-(1,3-dioxoisoindolin-2-yl)-2-oxopropyl)-2-((ethoxycarbonothioyl) thio)azetidine-1-carboxylate (5-6d)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5d** (310 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 338 mg **5-6d** (yield: 74%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.84 (m, 2H, PhthN), 7.73 (m, 2H, PhthN), 6.12 (d, 1H, J=7.2Hz, C*H*S), 4.61 (m, 2H, J=7.1Hz, COC*H*$_2$CH$_3$), 4.49 (m, 2H, PhthNC*H*$_2$), 4.11 (m, 1H, C*H*HN), 3.51 (m, 2H, CH*H*N, C*H*CHS), 2.99 (m, 2H, COC*H*$_2$), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 7.84 (m, 2H, PhthN), 7.73 (m, 2H, PhthN), 5.67 (d, 1H, J=3.9Hz, C*H*S), 4.61 (m, 2H, J=7.1Hz, COC*H*$_2$CH$_3$), 4.49 (m, 2H, PhthNC*H*$_2$), 4.11 (m, 1H, C*H*HN), 3.51 (m, 1H, CH*H*N), 3.30 (m, 1H, C*H*CHS), 2.99 (m, 2H, COC*H*$_2$), 1.41 (m, 12H, NBoc, COCH$_2$C*H*$_3$);

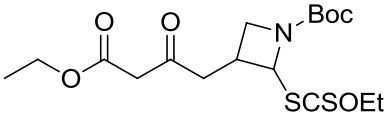
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 211.9 (*C*=S), 200.1 (*C*O), 167.5 (*C*O), 154.7 (*C*O), 134.2, 131.9, 123.6 (Ar), 80.8 (O*C*(CH$_3$)$_3$), 72.3 (*C*HS), 69.8 (O*C*H$_2$), 53.6 (*C*H$_2$N), 46.5 (PhthN*C*H$_2$), 43.5 (C*H*CHS), 40.9 (COC*H*$_2$), 28.2 (OC(*C*H$_3$)$_3$), 13.7 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 211.5 (*C*=S), 199.9 (*C*O), 167.5 (*C*O), 154.6 (*C*O), 134.19, 131.9, 123.5 (Ar), 80.825, 80.79 (O*C*(CH$_3$)$_3$), 72.2 (CHS), 69.7(O*C*H$_2$), 53.2 (*C*H$_2$N), 46.4 (PhthN*C*H$_2$), 43.5 (C*H*CHS), 40.9 (COC*H*$_2$), 30.1 (C*H*CHS), 28.2 (OC(*C*H$_3$)$_3$), 13.69 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1111, 1145, 1219, 1313, 1368, 1390, 1415, 1456, 1547, 1558, 1724, 1779, 2899, 2929, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{19}H_{21}N_2O_5$: 357.1445 (357.1442).

Tert-butyl-3-(4-ethoxy-2,4-dioxobutyl)-2-((ethoxycarbonothioyl)thio)azetidine-1-carboxylate (5-6g)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5g** (240 mg, 0.96 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 264 mg **5-6g** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1, which could be separated.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.64 (d, 1H, J=3.2Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.15 (m, 3H, C*H*HN, COOC*H*$_2$CH$_3$), 3.45 (m, 3H, CH*H*N, COC*H*$_2$CO), 3.27 (m, 1H, C*H*CHS), 3.01 (m, 2H, COC*H*$_2$), 1.40 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.27 (t, 3H, J=7.2Hz, COOCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 5.68 (d, 1H, J=3.2Hz, C*H*S), 4.59 (m, 2H, COC*H*$_2$CH$_3$), 4.15 (m, 3H, C*H*HN, COOC*H*$_2$CH$_3$), 3.45 (m, 3H, CH*H*N, COC*H*$_2$CO), 3.27 (m, 1H, C*H*CHS), 3.01 (m, 2H, COC*H*$_2$), 1.40 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.28 (t, 3H, J=7.2Hz, COOCH$_2$C*H*$_3$);

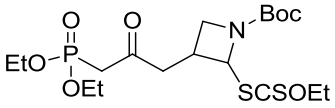
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 212 (*C*=S), 200.3 (*C*O), 166.8 (*C*O), 154.6 (*C*O), 80.7 (O*C*(CH$_3$)$_3$), 72.2 (O*C*H$_2$), 69.6 (*C*HS), 61.5 (COCH$_2$CH$_3$), 49.1 (COCH$_2$CO), 46.4 (*C*H$_2$N), 35.2 (*C*HCH$_2$), 28.2 (OC(*C*H$_3$)$_3$), 14 (COCH$_2$*C*H$_3$), 13.7 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 212.3 (*C*=S), 200.5 (*C*O), 166.9 (*C*O), 154.8 (*C*O), 80.9 (O*C*(CH$_3$)$_3$), 72.4 (O*C*H$_2$), 69.7 (*C*HS), 61.5 (COCH$_2$CH$_3$), 49.2 (COCH$_2$CO), 46.7 (*C*H$_2$N), 35.3 (*C*HCH$_2$), 28.2 (OC(*C*H$_3$)$_3$), 14.1 (COCH$_2$*C*H$_3$), 13.8 (OCH$_2$*C*H$_3$);

IR (CCl_4): νmax 1054, 1111, 1147,1223, 1321, 1367, 1390, 1456, 1477, 1538, 1713, 2856, 2900, 2930, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{14}H_{22}NO_5^+$: 284.1492 (284.1498).

Tert-butyl-3-(3-(diethoxyphosphoryl)-2-oxopropyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-6e)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-5e** (314 mg, 1 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (163 mg, 1.05 mmol) with several drops of 2,6-lutidine, and needed 10 mol% of DLP to go to completion. Flash chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) afforded 318 mg **5-6e** (yield: 68%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 2:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 5.61 (d, 1H, J=4.4Hz, C*H*S), 4.57 (m, 2H, COC*H*$_2$CH$_3$), 4.10 (m, 5H, C*H*HN, 2OC*H*$_2$CH$_3$), 3.42 (m, 1H, CH*H*N), 3.28 (m, 1H, C*H*CHS), 3.03 (m, 4H, COC*H*$_2$CH, POC*H*$_2$CO), 1.37 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.29 (t, 6H, J=7.0 Hz, 2OCH$_2$C*H*$_3$);

Diastereoisomer 2: δ_H ppm 6.07 (d, 1H, J=7.2Hz, C*H*S), 4.57 (m, 2H, COC*H*$_2$CH$_3$), 4.10 (m, 5H, C*H*HN, 2OC*H*$_2$CH$_3$), 3.42 (m, 1H, CH*H*N), 3.28 (m, 1H, C*H*CHS), 3.03 (m, 4H, COC*H*$_2$CH, POC*H*$_2$CO), 1.37 (m, 12H, NBoc, COCH$_2$C*H*$_3$), 1.29 (t, 6H, J=7.0 Hz, 2 OCH$_2$C*H*$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 211.8 (*C*=S), 199.4 (*C*O), 154.6 (*C*O), 80.5 (O*C*(CH$_3$)$_3$), 72.0 (*C*HS), 69.6 (O*C*H$_2$), 62.65, 62.63 (OC*H*$_2$CH$_3$), 52.4 (*C*H$_2$N), 47.2 (*C*HCHS), 44.7 (POC*H*$_2$CO), 41.8 (COCH$_2$CH), 28.1(OC(*C*H$_3$)$_3$), 16.2 (COCH$_2$*C*H$_3$), 13.6 (OCH$_2$*C*H$_3$);

Diastereoisomer 2: δ_C ppm 211.5 (*C*=S), 199.3 (*C*O), 154.5 (*C*O), 80.5 (O*C*(CH$_3$)$_3$), 72.0 (*C*HS), 69.4 (O*C*H$_2$), 62.58, 62.56 (OC*H*$_2$CH$_3$), 47.2 (*C*HCHS), 43.1 (POC*H*$_2$CO), 35.0 (COCH$_2$CH), 30.1 (*C*H$_2$N), 28.1(OC(*C*H$_3$)$_3$), 16.1 (COCH$_2$*C*H$_3$),

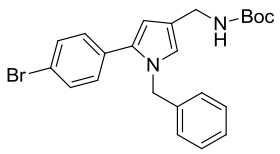
13.5 (OCH_2CH_3);

IR (CCl_4): νmax 1055, 1111, 1147, 1219, 1367, 1391, 1443, 1456, 1478, 1502, 1712, 2931, 2981;

HRMS (EI+): *m/z* calculated (found) for $(M\text{-}SCSOCH_2CH_3)^+$, $C_{15}H_{27}NO_6P$: 348.1571 (348.1576).

Synthesis of pyrroles

Tert-butyl-((1-benzyl-5-(4-bromophenyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7a)



To a solution of **5-6a** (130 mg, 0.28 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (24 mg, 0.14 mmol) and benzylamine (62 mg, 0.56 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 106 mg **5-7a** (yield: 87%) as a pale yellow oil.

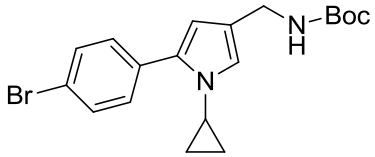
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.44 (d, 2H, J=8.4Hz, C*H*ArBr), 7.29 (m, 3H, Ar), 7.14 (d, 2H, J=8.4Hz, C*H*ArBr), 6.99 (d, 2H, J=7.0Hz, Ar), 6.68 (s, 1H, NC*H*=), 6.20 (s, 1H, C*H*), 5.05 (s, 2H, NCH_2Ph), 4.73 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=4.9Hz, CH_2NHBoc), 1.45 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.7 (*C*O), 138.2 (=*C*-Ph), 133.9, 131.9, 131.7, 130.4, 128.7, 127.4, 127.6, 126.2 (*C*HAr), 121.4 (=*C*-), 121.1 (N*C*H=), 108.9 (*C*H), 79.1 (O*C*$(CH_3)_3$), 50.5 (*C*H_2Ph), 37.6 (*C*H_2NHBoc), 28.3 (OC$(CH_3)_3$);

IR (CCl_4): νmax 1011, 1073, 1170, 1245, 1366, 1391, 1467, 1497, 1544, 1547, 1718, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{25}BrN_2O_2$: 440.1099 (440.1096).

Tert-butyl ((5-(4-bromophenyl)-1-cyclopropyl-1H-pyrrol-3-yl)methyl)carbamate (5-7b)



To a solution of **5-6a** (60 mg, 0.13 mmol) in dioxane (0.65 ml) were added *p*-toluene sulfonic acid monohydrate (10 mg, 0.05 mmol) and cyclopropylamine (14 mg, 0.25 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 47 mg **5-7b** (yield: 93%) as a pale yellow oil.

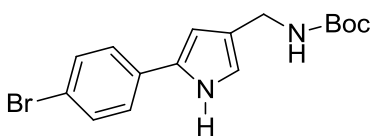
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.54 (d, 2H, J=8.4Hz, Ar), 7.43 (d, 2H, J=8.4Hz, Ar), 6.77 (s, 1H, NC*H*=), 6.20 (s, 1H， C*H*), 4.72 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=5.0Hz, CH_2NHBoc), 3.40 (m, 1H, NC*H*), 1.51 (s, 9H, Boc), 0.92 (m, 2H, CHCH_2), 0.83 (m, 2H, CHCH_2);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 134.4 (=*C*-Ph), 132.2, 131.2, 129.6, 121.4 (Ar), 121.4 (=*C*-), 120.5 (N*C*H=), 108.7 (*C*H), 79.2 (O*C*(CH_3)$_3$), 37.6 (*C*H_2NHBoc), 29.5 (N*C*H), 28.4 (OC(CH_3)$_3$), 8.4 (NCH*C*H_2);

IR (CCl_4): νmax 1012, 1030, 1074, 1171, 1244, 1366, 1391, 1456, 1498, 1716, 2855, 2928, 2979, 3007, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{23}BrN_2O_2$: 390.0943 (390.0956).

Tert-butyl ((5-(4-bromophenyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7c)



To a solution of **5-6a** (90 mg, 0.2 mmol) in dioxane (1.4 ml) were added

ammonium acetate (16 mg, 0.2 mmol) and aqua ammonia (20% NH_3) (32 mg, 0.38 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 66 mg **5-7c** (yield: 95%) as a pale yellow oil.

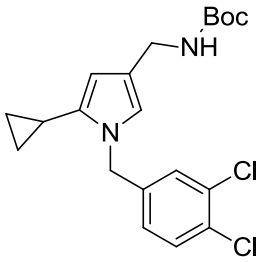
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.61 (br, 1H, N*H*), 7.50 (d, 2H, J=8.4Hz, Ar), 7.36 (d, 2H, J=8.4Hz, Ar), 6.80 (s, 1H, NC*H*=), 6.49 (s, 1H, CH), 4.80 (br, 1H, N*H*Boc), 4.24 (d, 2H, J=4.8Hz, CH_2NHBoc), 1.51 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.9 (*C*O), 131.8 (=*C*-Ph), 131.5, 131.4, 125.2, 122.9, 119.7 (=*C*-), 117.6 (N*C*H=), 106.1 (*C*H), 79.2 (O*C*(CH_3)$_3$), 37.7 (CH_2NHBoc), 28.4 (OC(*C*H_3)$_3$),

IR (CCl_4): νmax 1009, 1075, 1171, 1237, 1366, 1472, 1498, 1548, 1558, 1718, 2360, 2343, 2855, 2927, 3481;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{19}BrN_2O_2$: 350.0630 (350.0623).

Tert-butyl((5-cyclopropyl-1-(3,4-dichlorobenzyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7d)



To a solution of **5-6b** (31 mg, 0.09 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and 3,4-dichloro-benzylamine (32mg, 0.18 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 32 mg **5-7d** (yield: 91%) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (d, 1H, J=8.4Hz, Ar), 7.14 (s, 1H, Ar), 6.84 (d, 1H, J=8.0Hz, Ar), 6.50 (s, 1H, NC*H*=), 5.78 (s, 1H, C*H*), 5.06 (s, 2H,

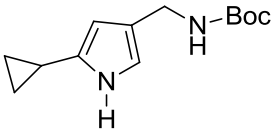
NC*H*$_2$Ar), 4.62 (br, 1H, N*H*Boc), 4.11 (d, 2H, J=4.7Hz, C*H*$_2$NHBoc), 1.45 (s, 9H, Boc), 0.90 (m, 1H, C*H*CH$_2$), 0.73 (m, 2H, CHC*H*$_2$), 0.52 (m, 2H, CHC*H*$_2$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 135.8 (=*C*-), 138.9, 132.9, 131.5, 130.7, 128.6, 125.9 (Ar), 120.3 (=*C*-), 118.9 (N*C*H=), 105.6 (*C*H), 79.2 (O*C*(CH$_3$)$_3$), 49.3 (N*C*H$_2$), 37.9 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 6.8 (*C*HCH$_2$), 6.1 (CH*C*H$_2$);

IR (CCl$_4$): νmax 1032, 1046, 1172, 1391, 1423, 1471, 1495, 1718, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{24}Cl_2N_2O_2$: 394.1215 (394.1219).

Tert-butyl ((5-cyclopropyl-1H-pyrrol-3-yl)methyl)carbamate 5-7e



To a solution of **5-6b** (31 mg, 0.09 mmol) in dioxane (0.5 ml) were added ammonium acetate (7 mg, 0.09 mmol) and aqua ammonia (20% NH$_3$) (23 mg, 0.27 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 19 mg **5-7e** (yield: 91 %) as a pale yellow oil.

^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 7.88 (br, 1H, N*H*), 6.54 (s, 1H, NC*H*=), 5.80 (s, 1H，C*H*), 4.62 (br, 1H, N*H*Boc), 4.12 (d, 2H, J=4.9Hz, C*H*$_2$NHBoc), 1.76 (m, 1H, C*H*CH$_2$), 1.45 (s, 9H, Boc), 0.80 (m, 2H, CHC*H*$_2$), 0.59 (m, 2H, CHC*H*$_2$);

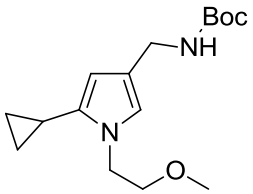
^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 135.1 (=*C*-), 114.3 (=*C*-), 114.2 (N*C*H=), 103.9 (*C*H), 79.1 (O*C*(CH$_3$)$_3$), 37.9 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 8.2 (*C*HCH$_2$), 6.5 (CH*C*H$_2$);

IR (CCl$_4$): νmax 1053, 1170, 1367, 1391, 1499, 1546, 1538, 1717, 2359, 2855, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{13}H_{20}N_2O_2$: 236.1525 (236.1520).

Tert-butyl ((5-cyclopropyl-1-(2-methoxyethyl)-1H-pyrrol-3-yl)methyl) carbamate

(5-7f)



To a solution of **5-6b** (74 mg, 0.2 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (20 mg, 0.1 mmol) and 2-methoxyethylamine (46 mg, 0.62 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 54 mg **5-7f** (yield: 94%) as a pale yellow oil.

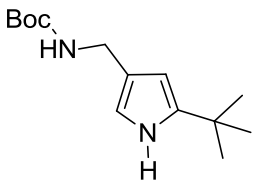
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 6.54 (s, 1H, NC*H*=), 5.71 (s, 1H, =C*H*-), 4.59 (br, 1H, N*H*Boc), 4.09 (m, 4H, NCH_2, CH_2NHBoc), 3.64 (t, 2H, J=5.9Hz, CH_2O), 3.34 (s, 3H, OCH_3), 1.65 (m, 1H, C*H*CH_2), 1.44 (s, 9H, Boc), 0.81 (m, 2H, CHCH_2), 0.57 (m, 2H, CHCH_2);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 135.6 (=*C*-), 119.4 (=*C*-), 118.8 (N*C*H=), 104.6 (*C*H), 78.9 (O*C*(CH_3)$_3$), 72.3 (*C*H_2O), 58.9 (O*C*H_3), 46.1 (N*C*H_2), 37.9 (*C*H_2NHBoc), 28.4 (OC(CH_3)$_3$), 6.7 (*C*HCH_2), 6 (CH*C*H_2);

IR (CCl_4): νmax 1046, 1122, 1172, 1238, 1366, 1390, 1495, 1547, 1717, 2360, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{16}H_{26}N_2O_3$: 294.1943 (294.1947).

Tert-butyl ((5-(tert-butyl)-1H-pyrrol-3-yl)methyl)carbamate **5-7g**



To a solution of **5-6c** (134 mg, 0.36 mmol) in dioxane (2.5 ml) were added ammonium acetate (28 mg, 0.36 mmol) and aqua ammonia (20% NH_3) (88 mg, 1

mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 74 mg **5-7g** (yield: 82%) as a pale yellow oil.

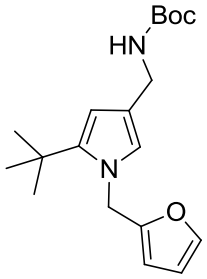
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.0 (br, 1H, N*H*), 6.57 (s, 1H, NC*H*=), 5.88 (s, 1H, C*H*), 4.66 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=4.6Hz, CH_2NHBoc), 1.45 (s, 9H, Boc), 1.27 (s, 9H, (CH_3)$_3$);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.7 (*C*O), 142.5 (=*Cq*NH), 120.4 (=*C*-), 114.2 (N*C*H=), 102.4 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 37.9 (*C*H$_2$NHBoc), 31.3 (*C*H(CH$_3$)$_3$), 30.4 (CH(*C*H$_3$)$_3$), 28.4 (OC(CH$_3$)$_3$);

IR (CCl_4): νmax 1047, 1081, 1172, 1230, 1311, 1366, 1466, 1493, 1581, 1716, 2855, 2928, 2961, 3408, 3461, 3489;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{24}N_2O_2$: 252.1838 (252.1845).

Tert-butyl-((5-(tert-butyl)-1-(furan-2-ylmethyl)-1H-pyrrol-3-yl)methyl) carbamate (5-7h)



To a solution of **5-6c** (82 mg, 0.22 mmol) in dioxane (1.4 ml) were added *p*-toluene sulfonic acid monohydrate (22 mg, 0.12 mmol) and furfurylamine (44 mg, 0.44 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 66 mg **5-7h** (yield: 92%) as a pale red oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.37 (m, 1H, O-C*H*=), 6.47 (s, 1H, NC*H*=), 6.32 (m, 1H, -C*H*=), 6.14 (d, 1H, J=2.5Hz, =C*H*-), 5.86 (s, 1H, C*H*), 5.13 (s, 2H,

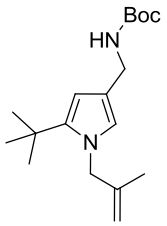
NC*H*$_2$), 4.60 (br, 1H, N*H*Boc), 4.09 (d, 2H, J=4.3Hz, C*H*$_2$NHBoc), 1.45 (s, 9H, Boc), 1.36 (s, 9H, (C*H*$_3$)$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 151.3, 142.4, 110.4, 104.9 (furan), 141.7 (=*C*-), 120.3 (N*C*H=), 120.3 (=*C*-), 108 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 44.9 (N*C*H$_2$), 37.9 (*C*H$_2$NHBoc), 31.9 (*C*H(CH$_3$)$_3$), 30.7 (CH(*C*H$_3$)$_3$), 28.4 (OC(*C*H$_3$)$_3$);

IR (CCl$_4$): νmax 1049, 1102, 1170, 1227, 1367, 1391, 1477, 1710, 2359, 2931, 2974, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{28}N_2O_3$: 332.2100 (332.2107).

Tert-butyl-((5-(tert-butyl)-1-(2-methylallyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7i)



To a solution of **5-6c** (74 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (18 mg, 0.1 mmol) and 2-methylallylamine (34 mg, 0.48 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 53 mg **5-7i** (yield: 88%) as a pale yellow oil.

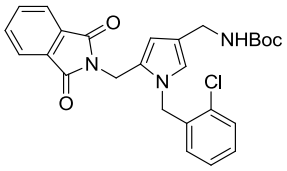
^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 6.43 (s, 1H, NC*H*=), 5.83 (s, 1H, C*H*), 4.89 (s, 1H, H*H*C=), 4.59 (br, 1H, N*H*Boc), 4.46 (m, 3H, *H*HC=, NC*H*$_2$), 4.10 (d, 2H, J=4.1Hz, C*H*$_2$NHBoc), 1.71 (s, 3H, C(C*H*$_3$)), 1.45 (s, 9H, Boc), 1.30 (s, 9H, (C*H*$_3$)$_3$);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.8 (*C*O), 142.5 (=*C*-), 141.9 (*C*=CH$_2$), 120.8 (=*C*-), 118.6 (N*C*H=), 112.3 (C=*C*H$_2$), 104.5 (*C*H), 78.9 (O*C*(CH$_3$)$_3$), 53.9 (N*C*H$_2$), 38 (*C*H$_2$NHBoc), 31.9 (*C*H(CH$_3$)$_3$), 30.7 (CH(*C*H$_3$)$_3$), 28.5 (OC(*C*H$_3$)$_3$), 20 (C(*C*H$_3$));

IR (CCl$_4$: νmax 1024, 1172, 1242, 1366, 1467, 1495, 1545, 1539, 1717, 2855, 2928, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{30}N_2O_2$: 306.2307 (306.2307).

Tert-butyl-((1-(2-chlorobenzyl)-5-((1,3-dioxoisoindolin-2-yl)methyl)-1H-pyrrol -3-yl)methyl)carbamate (5-7j)



To a solution of **5-5d** (47 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and (2-chlorophenyl)methanamine (28.2 mg, 0.2mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 39 mg **5-7j** (yield: 83 %) as a white solid (mp: 124-126 ℃).

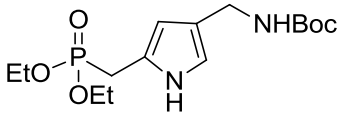
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.68 (m, 4H, PhthN), 7.23 (dd, 1H, J=1.2Hz, J=7.6Hz, Ar), 6.92 (m, 2H, Ar), 6.59 (s, 1H, NC*H*=), 6.39 (s, 1H, =C*H*-), 6.18 (d, 1H, J=6.4Hz, Ar), 5.31 (s, 2H, PhthNCH_2), 4.76 (s, 2H, NHCH_2Ar), 4.71 (br, 1H, N*H*Boc), 4.19 (d, 2H, J=5.0Hz, CH_2NHBoc), 1.49 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): 167.5, 155.8 (*C*O), 133.8, 131.7, 129.1, 128.3, 127.4, 126.5, 123.1, 120.9 (Ar), 136.3 (Cq), 127 (Cq), 121 (=*C*H-), 111.3 (N*C*H=), 79.2 (O*C*(CH_3)$_3$), 48.6 (N*C*H_2Ph), 37.7 (*C*H_2NHBoc), 33.1 (NH*C*H_2Ar), 28.5 (OC(CH_3)$_3$);

IR (CCl_4): νmax 1027, 1050, 1085, 1112, 1171, 1219, 1346, 1366, 1390, 1425, 1415, 1469, 1447, 1718, 1771, 2929, 2979, 3063, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{26}H_{26}ClN_3O_4$: 479.1612 (479.1616).

Tert-butyl-((5-((diethoxyphosphoryl)methyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7k)



To a solution of **5-6e** (93 mg, 0.2 mmol) in dioxane (1 ml) were added ammonium acetate (15 mg, 0.2 mmol) and aqua ammonia (20% NH_3) (67 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 63 mg **5-7k** (yield: 92 %) as a pale yellow oil.

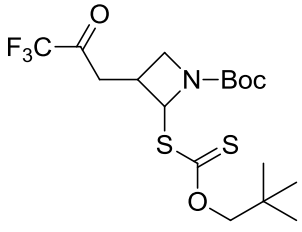
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 8.90 (br, 1H, N*H*), 6.59 (s, 1H, NC*H*=), 5.93 (s, 1H, =C*H*-), 4.66 (br, 1H, N*H*Boc), 4.10 (d, 2H, J=5.2Hz, CH_2NHBoc), 4.00 (m, 4H, 2OC$H_2$$CH_3$), 3.10 (d, 2H, J=20.2Hz, PCH_2), 1.42 (s, 9H, Boc), 1.23 (t, 6H, J=7.1Hz, 2OCH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8(*C*O), 121.3 (=*C*-), 121.3, 121.2 (=*C*-), 116.1 (=*C*-), 108.1, 108 (N*C*H=), 79.1 (O*C*(CH_3)$_3$), 62.5, 62.4 (O*C*$H_2$$CH_3$), 37.8 (*C*$H_2$NHBoc), 28.5 (OC(*C*$H_3$)$_3$), 26.4, 24.9 (P*C*$H_2$), 16.4, 16.3 (O$CH_2$*C*$H_3$);

IR (CCl_4): νmax 1047, 1086, 1154, 1271, 1368, 1445, 1465, 1478, 1541, 1620, 1644, 1736, 1741, 2933, 2983, 3465;

HRMS (EI+): *m/z* calculated (found) for $C_{15}H_{27}N_2O_5$: 346.1658 (346.1646).

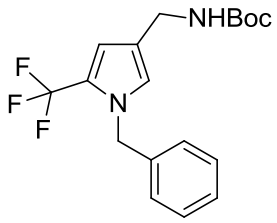
Tert-butyl-2-(((neopentyloxy)carbonothioyl)thio)-3-(3,3,3-trifluoro-2-oxopropyl) azetidine-1-carboxylate (5-6f)



Before doing the radical addition, we should add x mol **5-5f** in 6x ml cyclohexane and remove 4x ml cyclohexane. Then following the general procedure A for radical

addition, the reaction was carried out by adding **5-5f** (197 mg, 0.72 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (101 mg, 0.65 mmol) in cyclohexane (2 ml) and with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. In this case because of the hydrophilic property the mixture of four inseparate isomers were obtained and the solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl ((1-benzyl-5-(trifluoromethyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7l)



To a solution of **5-6f** (42.9 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and benzylamine (21 mg, 0.2 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 29 mg **5-7l** (yield step1+step2: 63 %) as a pale yellow oil.

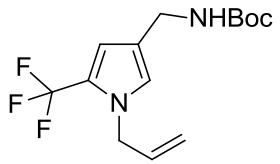
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.34 (m, 3H, Ar), 7.11 (d, 2H, J=7.4Hz, Ar), 6.64 (s, 1H, NC*H*=), 6.54 (s, 1H, =C*H*-), 5.11 (s, 2H, NCH_2), 4.67 (br, 1H, N*H*Boc), 4.11 (d, 2H, J=4.3Hz, CH_2NHBoc), 1.43 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 136.5, 128.7, 127.9, 127.1 (Ar), 123.9 (=*C*H-), 121.19 (q, 1H, J=266.8Hz, *C*F_3), 121.47 (q, 1H, J=37.3Hz, N*Cq*CF_3), 120.9 (*Cq*-CH_2NHBoc), 111.0 (=*C*H-), 79.3 (O*C*$(CH_3)_3$), 51.3 (N*C*H_2), 37.2 (*C*H_2NHBoc), 28.3 (OC$(CH_3)_3$);

IR (CCl_4): νmax 1040, 1110, 1163, 1269, 1367, 1459, 1498, 1547, 1543, 1551, 1720, 2856, 2928, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{21}F_3N_2O_2$: 354.1555 (354.1554).

Tert-butyl ((1-allyl-5-(trifluoromethyl)-1H-pyrrol-3-yl)methyl)carbamate (5-7m)



To a solution of **5-6f** (85 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (19 mg, 0.1 mmol) and allyamine (46 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 55 mg **5-7m** (yield step1+step2: 68%) as a pale yellow oil.

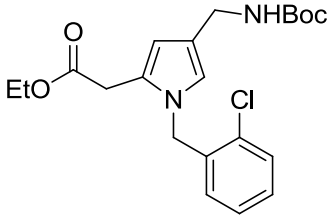
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 6.71 (s, 1H, NC*H*=), 6.49 (s, 1H, =C*H*-), 5.92 (m, 1H, C*H*=CH_2), 5.22 (d, 1H, J=10.2Hz, C*H*=CH*H*), 5.10 (d, 1H, J=16.9Hz, C*H*=C*H*H), 4.70 (br, 1H, N*H*Boc), 4.52 (d, 2H, J=5.7Hz, NCH_2), 4.11 (d, 2H, J=5.3Hz, CH_2NHBoc), 1.44 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 133.0 (*C*H=CH_2), 123.5 (=*C*H-), 121.1 (q, 1H, J=266.7Hz, *C*F_3), 120.9 (q, 1H, J=38.3Hz, N*Cq*CF_3), 120.6 (*Cq*-CH_2NHBoc), 118.1 (C*H*=CH_2), 110.9 (=*C*H-), 79.3 (O*C*(CH_3)$_3$), 50.2 (N*C*H_2), 37.1 (*C*H_2NHBoc), 28.3 (OC(CH_3)$_3$);

IR (CCl_4): νmax 1040, 1111, 1164, 1246, 1272, 1367, 1458, 1499, 1555, 1579, 1720, 2931, 2979, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{14}H_{19}F_3N_2O_2$: 304.1399 (304.1411).

Ethyl 2-(4-(((tert-butoxycarbonyl)amino)methyl)-1-(2-chlorobenzyl)-1H- pyrrol--2-yl) acetate (5-7o)



To a solution of **5-6g** (40 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene

sulfonic acid monohydrate (19 mg, 0.1 mmol) and (2-chlorophenyl)methanamine (28.2 mg, 0.2mmol). The reaction mixture was heated at 80 ℃ under nitrogen for 1 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 25 mg **5-7o** (yield: 64 %) as a yellow oil and 6 mg **5-7p** (yield: 18 %) as a pale yellow oil.

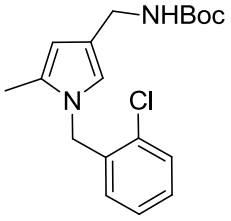
^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.36 (m, 1H, Ar), 7.18 (m, 2H, Ar), 6.56 (s, 1H, NC*H*=), 6.49 (d, 1H, J=7.3Hz, Ar), 6.09 (s, 1H, =C*H*-), 5.11 (s, 2H, NCH_2Ph), 4.67 (br, 1H, N*H*Boc), 4.14 (d, 2H, J=5.0Hz, CH_2NHBoc), 4.02 (q, 2H, J=7.1Hz, OC$H_2$$CH_3$), 3.45 (s, 2H, CH_2COOEt), 1.44 (s, 9H, Boc), 1.19 (t, 3H, J=7.2Hz, OCH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 170.2 (*CO*OEt), 155.7 (*C*O), 135.6, 131.9, 129.2, 128.7, 127.5, 127.2 (Ar), 125.5 (N*Cq*=), 120.6 (N*C*H=), 120.4 (*Cq*CH_2NHBoc), 109.2 (=*C*H-), 79.0 (O*C*(CH_3)$_3$), 61.0 (O*C*$H_2$$CH_3$), 48.2 (N*C*$H_2$), 37.7 (*C*$H_2$NHBoc), 32.5 (*C*$H_2$COOEt), 28.4 (OC(*C*$H_3$)$_3$), 14.0 ($OCH_2$*C*$H_3$);

IR (CCl_4): νmax 1040, 1050, 1170, 1243, 1263, 1367, 1446, 1497, 1547, 1574, 1615, 1655, 1719, 2930, 2980, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{27}ClN_2O_4$: 406.1659 (406.1656).

5-7p tert-butyl ((1-(2-chlorobenzyl)-5-methyl-1H-pyrrol-3-yl)methyl)carbamate



^{1}H NMR (400 MHz; $CDCl_3$): δ_H ppm 7.36 (m, 1H, Ar), 7.19 (m, 2H, Ar), 6.52 (s, 1H, NC*H*=), 6.46 (d, 1H, J=7.2Hz, Ar), 5.92 (s, 1H, =C*H*-), 5.02 (s, 2H, NCH_2Ph), 4.64 (br, 1H, N*H*Boc), 4.14 (d, 2H, J=5.0Hz, CH_2NHBoc), 2.09 (s, 3H, CH_3), 1.45 (s, 9H, Boc);

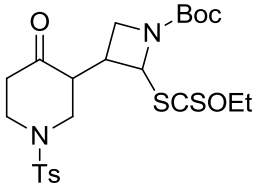
^{13}C NMR (100 MHz, $CDCl_3$): δ_C ppm 155.7 (*C*O), 135.9, 131.8, 129.4, 129.2, 128.5, 127.5 (Ar), 127.3 (N*Cq*=), 120.38 (N*C*H=), 118.995 (*Cq*CH_2NHBoc), 107.1 (=*C*H-),

79.0 (O*C*(CH_3)$_3$), 47.9 (N*C*H_2), 37.8 (*C*H_2NHBoc), 28.4 (OC(*C*H_3)$_3$), 11.7 (*C*H_3);

IR (CCl_4): νmax 1050, 1172, 1239, 1367, 1390, 1446, 1497, 1614, 1718, 2856, 2929, 2979, 3410, 3461;

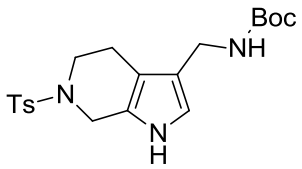
HRMS (EI+): *m/z* calculated (found) for $C_{18}H_{23}ClN_2O_2$: 334.1448 (334.1656).

Tert-butyl-2-((ethoxycarbonothioyl)thio)-3-(4-oxo-1-tosylpiperidin-3-yl)azetidine - -1-carboxylate (5-10a)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9a** (300 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (137 mg, 0.88 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl ((6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridin-3-yl)methyl) carbamate (5-11a)



To a solution of **5-10a** (67 mg, 0.13 mmol) in dioxane (0.7 ml) were added ammonium acetate (10 mg, 0.13 mmol) and aqua ammonia (20% NH_3) (41 mg, 0.51 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 48 mg **5-11a** (yield step1+step2: 67 %) as a pale yellow oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.84 (br, 1H, N*H*) ppm 7.70 (d, 2H, J=8.2Hz,

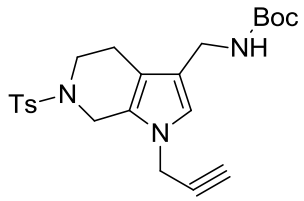
Ar), 7.30 (d, 2H, J=8.0Hz, Ar), 6.52 (s, 1H, NC*H*=), 4.55 (br, 1H, N*H*Boc), 4.11 (m, 4H, CH_2NTs, CH_2NHBoc), 3.38 (t, 2H, J=5.7Hz, CH_2NTs), 2.70 (t, 2H, J=5.4Hz, CH_2CH$_2$NTs), 2.41 (s, 3H, ArCH_3), 1.46 (s, 9H, Boc);

^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.7 (*C*O), 143.4, 129.7, 127.612, 124.6 (Ar), 134.1 (=*C*-Ph), 117.3 (=*C*-), 115.6 (N*C*H=), 111.9 (*C*H), 79.3 (O*C*(CH$_3$)$_3$), 43.6 (*C*H$_2$NTs), 43.2 (*C*H$_2$NTs), 36.2 (*C*H$_2$NHBoc), 28.5 (OC(CH$_3$)$_3$), 23.4 (Ar*C*H$_3$), 21.5 (*C*H$_2$CH$_2$NTs);

IR (CCl$_4$): νmax 1169, 1239, 1359, 1465, 1496, 1624, 1711, 1740, 2855, 2927, 3483;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{27}N_3O_4S$: 405.1722 (405.1723).

Tert-butyl-((1-(prop-2-yn-1-yl)-6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c] pyridin-3-yl)methyl)carbamate (5-11b)



To a solution of **5-10a** (66 mg, 0.13 mmol) in dioxane (0.7 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and mono-propargylamine (21 mg, 0.38 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 50 mg **5-11b** (yield step1+step2: 66 %) as a yellow solid (mp: 102-103 ℃).

^{1}H NMR (400 MHz; CDCl$_3$): δ ppm 7.69 (d, 2H, J=8.1Hz, Ar), 7.29 (d, 2H, J=8.0Hz, Ar), 6.53 (s, 1H, NC*H*=), 4.54 (br, 1H, N*H*Boc), 4.42 (d, 2H, J=2.2Hz, NCH_2), 4.04 (m, 4H, CH_2NTs, CH_2NHBoc), 3.40 (t, 2H, J=5.6Hz, CH_2NTs), 2.70 (t, 2H, J=5.4Hz, CH_2CH$_2$NTs), 2.40 (s, 3H, ArCH_3), 2.34 (s, 1H, CC*H*), 1.45 (s, 9H, Boc);

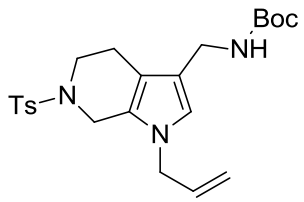
^{13}C NMR (100 MHz, CDCl$_3$): δ ppm 155.6 (*C*O), 143.4, 129.5, 127.5, 125.3 (Ar), 133.9 (=*C*-Ph), 118.5 (=*C*-), 116.9 (N*C*H=), 112.9 (*C*H), 79.2 (O*C*(CH$_3$)$_3$), 77.8 (CH$_2$*C*CH$_2$), 73.4 (C*C*H$_2$), 43.5 (*C*H$_2$NTs), 43.1 (*C*H$_2$NTs), 36 (*C*H$_2$NHBoc), 35.7

(N*C*H_2), 28.4 (OC(CH_3)$_3$), 22.2 (Ar*C*H_3), 21.4 (*C*$H_2$$CH_2$NTs);

IR (CCl_4): νmax 1022, 1100, 1168, 1361, 1458, 1653, 1762, 2361, 2855, 2927, 3675, 3712;

HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{29}N_3O_4S$: 443.1879 (443.1885).

Tert-butyl-((1-allyl-6-tosyl-4,5,6,7-tetrahydro-1H-pyrrolo[2,3-c]pyridin-3-yl) methyl)carbamate (5-11c)



To a solution of **5-10a** (67 mg, 0.13 mmol) in dioxane (0.7 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and allylamine (21mg, 0.37 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 48 mg **5-11c** (yield step1+step2: 63%) as a light yellow solid (mp: 112-113 ℃).

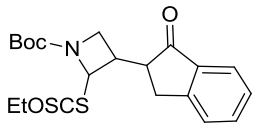
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.69 (d, 2H, J=8.1Hz, Ar), 7.28 (d, 2H, J=8.0Hz, Ar), 6.41 (s, 1H, NC*H*=), 5.79 (m, 1H, -C*H*=), 5.09 (d, 1H, J=10.2Hz, -CH=CH*H*), 4.83 (d, 1H, J=17.1Hz, -CH=C*H*H), 4.52 (br, 1H, N*H*Boc), 4.25 (d, 2H, J=5.0Hz, NC*H*$_2$), 4.08 (s, 2H, C*H*$_2$NTs), 4.04 (d, 2H, J=5.1Hz, C*H*$_2$NHBoc), 3.38 (t, 2H, J=5.7Hz, C*H*$_2$NTs), 2.59 (t, 2H, J=5.4Hz, C*H*$_2$$CH_2$NTs), 2.40 (s, 3H, ArC*H*$_3$), 1.45 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.6 (*C*O), 143.3, 129.5, 127.5, 125.3 (Ar), 134.1 (=*C*-Ph), 133.8 (-*C*H=CH_2), 118.7 (=*C*-), 116.8 (CH=*C*H_2), 116.2 (N*C*H=), 112.1 (*C*H), 79.2 (O*C*(CH_3)$_3$), 48.7 (N*C*H_2), 43.6 (*C*H_2NTs), 43.2 (*C*H_2NTs), 36.1 (*C*H_2NHBoc), 28.4 (OC(CH_3)$_3$), 22.2 (Ar*C*H_3), 21.4 (*C*$H_2$$CH_2$NTs);

IR (CCl_4): νmax 1021, 1100, 1237, 1305, 1357, 1366, 1466, 1497, 1534, 1547, 1716, 2855, 2927, 3459;

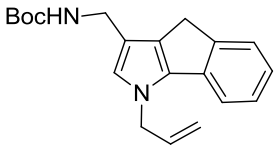
HRMS (EI+): *m/z* calculated (found) for $C_{23}H_{31}N_3O_4S$: 445.2035 (445.2033).

Tert-butyl-2-((ethoxycarbonothioyl)thio)-3-(1-oxo-2,3-dihydro-1H-inden-2-yl) azetidine-1-carboxylate (5-10b)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9b** (200 mg, 0.8 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (137 mg, 0.88 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

Tert-butyl-((1-allyl-1,4-dihydroindeno[1,2-b]pyrrol-3-yl)methyl)carbamate (5-11d)



To a solution of **5-10b** (100 mg, 0.25 mmol) in dioxane (1.2 ml) were added *p*-toluene sulfonic acid monohydrate (23 mg, 0.12 mmol) and allylamine (57 mg, 1 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 74 mg **5-11d** (yield step1+step2: 68%) as a yellow solid (mp: 132-133 ℃).

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.43 (d, 1H, J=7.4Hz, Ar), 7.30 (d, 1H, J=7.5Hz, Ar), 7.24 (m, 1H, Ar), 7.08 (m, 1H, Ar), 6.61 (s, 1H, NC*H*=), 6.05 (m, 1H, C*H*=CH_2), 5.22 (dd, 1H, J=1.3Hz, J=14.1Hz, C*H*H=CH), 5.12 (dd, 1H, J=1.1Hz, J=17.1Hz, CH*H*=CH), 4.72 (br, 1H, N*H*Boc), 4.71 (d, 2H, J=5.2Hz，NCH_2CH=), 4.25 (d, 2H, J=5.4Hz, CH_2NHBoc), 3.48 (s, 2H, CH_2Ar), 1.49 (s, 9H, Boc);

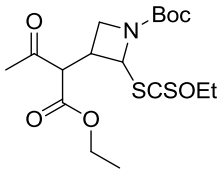
^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 155.8 (*C*O), 146.9 (NCq) 133.9 (*C*H=CH_2),

138.1, 135.3, 126.2, 125.4, 116.4 (Ar), 127.9 (CH_2NHBocC*q*), 122.9 (N*C*H=), 117.1 (CH=*C*H_2), 116.6 (C*q*), 79.1 (O*C*(CH_3)$_3$), 50.5 (N*C*H_2), 37 (*C*H_2NHBoc), 29.9 (*C*H_2Ar), 28.4 (OC(*C*H_3)$_3$);

IR (CCl_4): νmax 1040, 1050, 1086, 1133, 1173, 1227, 1252, 1295, 1365, 1432, 1446, 1494, 1526, 1547, 1712, 2855, 2928, 2979, 3068, 3456;

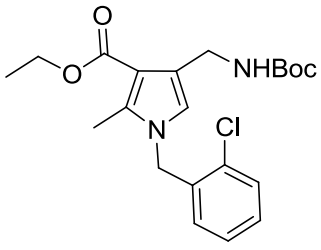
HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{24}N_2O_2$: 324.1838 (324.1836).

Tert-butyl-3-(1-ethoxy-1,3-dioxobutan-2-yl)-2-((ethoxycarbonothioyl)thio)--azetidine-1-carboxylate (5-10c)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9c** (100 mg, 0.4 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (68 mg, 0.45 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was without further purification.

Ethyl-4-(((tert-butoxycarbonyl)amino)methyl)-1-(2-chlorobenzyl)-2-methyl-1H-pyrrole-3-carboxylate (5-11e)



To a solution of **5-10c** (45 mg, 0.11 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9mg, 0.05 mmol) and (2-chlorophenyl) methanamine (31mg, 0.22 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v)

to afforded 39 mg **5-11e** (yield step1+step2: 61 %) as a pale yellow oil.

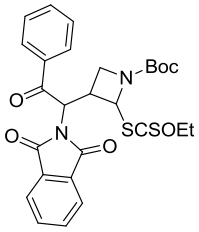
^{1}H NMR (400 MHz; $CDCl_3$): 7.38 (d, 1H, J=7.8Hz, Ar), 7.18 (m, 2H, Ar), 6.54 (s, 1H, NC*H*=), 6.49 (d, 1H, J=6.8Hz, Ar), 5.45 (br, 1H, N*H*Boc), 5.05 (s, 2H, NCH_2Ph), 4.29 (m, 4H, CH_2NHBoc, COOCH_2), 2.37 (s, 3H, CH_3), 1.41 (s, 9H, Boc), 1.36 (t, 3H, J=7.1Hz, $COOCH_2CH_3$);

^{13}C NMR (100 MHz, $CDCl_3$): 165.9, 155.9 (*C*O), 137, 132.1, 129.5, 129, 127.5, 127.4 (Ar), 134.5, 122.7, 110.9 (Cq), 120.6 (N*C*H=), 78.8 (O*C*$(CH_3)_3$), 59.7 ($COOCH_2$), 48.1 (NCH_2Ph), 37.1 (CH_2NHBoc), 28.5 (OC$(CH_3)_3$), 14.5 ($COOCH_2CH_3$), 11.5 (CH_3);

IR (CCl_4): νmax 1012, 1045, 1170, 1245, 1366, 1391, 1449, 1498, 1718, 2928, 2979, 2979, 3459;

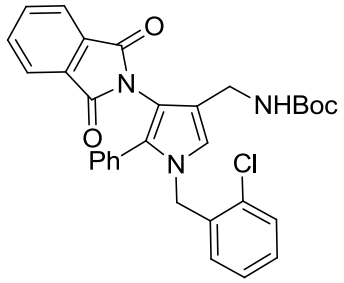
HRMS (EI+): *m/z* calculated (found) for $C_{21}H_{27}ClN_2O_4$: 406.1659 (406.1652).

Tert-butyl-3-(1-(1,3-dioxoisoindolin-2-yl)-2-oxo-2-phenylethyl)-2-((ethoxycarbono thioyl)thio) azetidine-1-carboxylate (5-10d)



Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-9d**(120 mg, 0.32 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (56 mg, 0.34 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do the step without further purification.

Tert-butyl((1-(2-chlorobenzyl)-4-(1,3-dioxoisoindolin-2-yl)-5-phenyl-1H-pyrrol-3-yl) methyl) carbamate (5-11f)



To a solution of **5-10d** (38 mg, 0.1 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (9 mg, 0.05 mmol) and (2-chlorophenyl)methanamine (28 mg, 0.2 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 2:1 v/v) to afforded 43 mg **5-11f** (yield step1+step2: 58%) as a pale yellow oil.

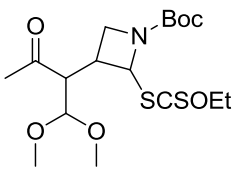
^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 7.83 (m, 2H, PhthN), 7.70 (m, 2H,PhthN), 7.33 (m, 1H, Ar), 7.23 (m, 7H, Ar), 6.83 (m, 1H, Ar), 6.77 (s, 1H, NC*H*=), 5.08 (s, 2H, NCH_2), 4.83 (br, 1H, N*H*Boc), 4.09 (d, 2H, J=5.5Hz, NCH_2), 1.30 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 168.3, 155.5 (*C*O), 135.3, 133.9, 132.9, 132.1, 131.9, 129.7, 129.5, 129.3, 128.9, 128.6, 128.3, 128.3, 123.5 (Ar), 127.4 (*Cq*NthPh),119.9 (N*C*H=), 119.3 (*Cq*CH_2NHBoc), 111.5 (=*C*(Ph)N), 78.9 (O*C*$(CH_3)_3$), 48.7 (N*C*H_2), 35 (*C*H_2NHBoc), 28.2 (OC(*C*$H_3)_3$);

IR (CCl_4): νmax 1041, 1085, 1114, 1171, 1247, 1366, 1391, 1446, 1499, 1725, 2855, 2927, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{31}H_{28}ClN_3O_4$: 541.1768 (541.1773).

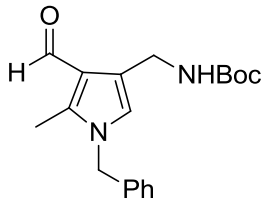
Tert-butyl-3-(1,1-dimethoxy-3-oxobutan-2-yl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-10e)



Following the general procedure A for radical addition, the reaction was carried out

with a solution of **5-9e** (100 mg, 0.4 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (67 mg, 0.44 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do the next step without further purification.

Tert-butyl-((1-benzyl-4-formyl-5-methyl-1H-pyrrol-3-yl)methyl)carbamate (5-11g)



To a solution of **5-10e** (119 mg, 0.29 mmol) in dioxane (1.5 ml) were added *p*-toluene sulfonic acid monohydrate (28 mg, 0.15 mmol) and benzylamine (64 mg, 0.6 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 80 mg **5-11g** (yield step1+step2: 62%) as a pale red oil.

^{1}H NMR (400 MHz; $CDCl_3$): δ ppm 9.87 (s, 1H, C*H*O), 7.31 (m, 3H, Ar), 7.01 (d, 2H, J=6.7Hz, Ar), 6.59 (s, 1H, NC*H*=), 5.79 (br, 1H, N*H*Boc), 4.98 (s, 2H, NCH_2Ph), 4.25 (d, 2H, J=6.3Hz, CH_2NHBoc), 2.37 (s, 3H, CqCH_3), 1.40 (s, 9H, Boc);

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 185.4 (*C*HO), 155.9 (*C*O), 140.6 (*C*qCH_3), 135.9, 128.9, 127.9, 126.4 (Ar), 121.5 (*C*qCHO), 121.5 (NC*H*=), 120.7 (*C*qCH_2NHBoc), 78.7 (O*C*$(CH_3)_3$), 50.2 (N*C*H_2Ph), 36.2 (*C*H_2NHBoc), 28.4 (OC(*C*$H_3)_3$), 9.8 (Cq*C*H_3);

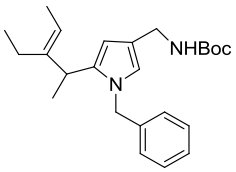
IR (CCl_4): νmax 1017, 1077, 1046, 1118, 1172, 1245, 1284, 1366, 1454, 1466, 1497, 1661, 1712, 2855, 2928, 2979, 3439;

HRMS (EI+): *m/z* calculated (found) for $C_{19}H_{24}N_2O_3$: 328.1787 (328.1788).

Tert-butyl-3-(2,2-diethyl-3-methyl-4-oxocyclobutyl)-2-((ethoxycarbonothioyl)thio) azetidine-1-carboxylate (5-16)

Following the general procedure A for radical addition, the reaction was carried out with a solution of **5-15** (260 mg, 1 mmol) and 2-azetine-1-carboxylic acid tert-butyl ester (170 mg, 1.1 mmol) with several drops of 2,6-lutidine, and needed 5 mol% of DLP to go to completion. The solvent was evaporated under reduced pressure and then the residue was used to do next step without further purification.

(*E*)-Tert-butyl-((1-benzyl-5-(3-ethylpent-3-en-2-yl)-1H-pyrrol-3-yl)methyl) carbamate (5-17a)



To a solution of **5-16** (45 mg, 0.11 mmol) in dioxane (0.5 ml) were added *p*-toluene sulfonic acid monohydrate (12 mg, 0.06 mmol) and benzylamine (24 mg, 0.22 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 28 mg **5-17a** (yield step1+step2: 48 %) as a pink oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 7.28 (m, 3H, Ar), 6.95 (d, 2H, J=7.2Hz, Ar), 6.48 (s, 1H, NC*H*=), 5.96 (s, 1H, =C*H*-), 5.09 (q, 1H, J=6.8Hz, CH_3C*H*=), 4.92 (m, 2H, NCH_2), 4.62 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=3.9Hz, CH_2NHBoc), 3.22 (q, 1H, J=7.1Hz, C*H*CH_3), 1.94 (q, 2H, J=7.5Hz, C$H_2$$CH_3$), 1.54 (d, 3H, J=6.8Hz, CH_3CH=), 1.46 (s, 9H, Boc), 1.27 (d, 3H, J=7.1Hz, CHCH_3), 0.77 (t, 3H, J=7.5Hz, CH_2CH_3);

Diastereoisomer 2: δ_H ppm 7.28 (m, 3H, Ar), 6.95 (d, 2H, J=7.2Hz, Ar), 6.48 (s, 1H, NC*H*=), 5.98 (s, 1H, =C*H*-), 5.20 (q, 1H, J=6.5Hz, CH_3C*H*=),4.92 (m, 2H, NCH_2),

4.62 (br, 1H, N*H*Boc), 4.15 (d, 2H, J=3.9Hz, CH_2NHBoc), 3.76 (q, 1H, J=7.6Hz, C*H*CH_3), 1.94 (q, 2H, J=7.5Hz, CH_2CH_3), 1.57 (d, 3H, J=6.0Hz, CH_3CH=), 1.46 (s, 9H, Boc), 1.27 (d, 3H, J=7.1Hz, CHCH_3), 0.77 (t, 3H, J=7.5Hz, CH_2CH_3);

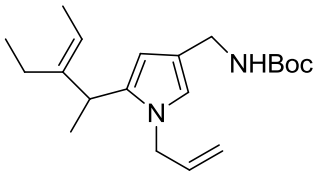
^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 155.8 (*C*O), 144.77 (CH_2*Cq*=CH), 138.5, 128.6, 127.1, 126.44 (Ar), 136.59 (=*Cq*N), 119.34 (=*C*H-) 119.1 (CH_3*C*H=), 116.9 (=*Cq*-CH_2NBoc), 106.2 (=*C*H-), 79 (O*C*$(CH_3)_3$), 49.8 (NCH_2), 38.6 (*C*H_2NHBoc), 38.1 (*C*HCH_3), 29.6 (OC(*C*$H_3)_3$), 21.3 (*C*H_2CH_3), 19.6 (CH*C*H_3), 13.4 (*C*H_3CH=), 13.1 (CH_2*C*H_3);

Diastereoisomer 2: δ_C ppm 155.8 (*C*O), 144.71 (CH_2*Cq*=CH), 138.4, 128.5, 127.1, 126.40 (Ar), 136.54 (=*Cq*N), 119.32 (=*C*H-), 119.1 (CH_3*C*H=), 116.9 (=*Cq*-CH_2NBoc), 106.1 (=*C*H-), 78.9 (O*C*$(CH_3)_3$), 49.7 (NCH_2), 38.0 (*C*H_2NHBoc), 32.1 (*C*HCH_3), 28.4 (OC(*C*$H_3)_3$), 24.2 (*C*H_2CH_3), 18.1 (CH*C*H_3), 12.7 (*C*H_3CH=), 12.6 (CH_2*C*H_3);

IR (CCl_4): νmax 1173, 1246, 1339, 1366, 1392, 1455, 1497, 1539, 1718, 2875, 2932, 2968, 3409, 3460;

HRMS (EI+): *m/z* calculated (found) for $C_{24}H_{34}N_2O_2$: 382.2620 (382.2614).

(*E*)-Tert-butyl-((1-allyl-5-(3-ethylpent-3-en-2-yl)-1H-pyrrol-3-yl)methyl)carbamate (5-17b)



To a solution of **5-16** (82 mg, 0.2 mmol) in dioxane (1 ml) were added *p*-toluene sulfonic acid monohydrate (19 mg, 0.1 mmol) and allyamine (46 mg, 0.8 mmol). The reaction mixture was refluxed under nitrogen for 0.5 h and then the solvent was evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether: ethyl acetate, 4:1 v/v) to afforded 52 mg **5-17b** (yield step1+step2: 56%) as a pale yellow oil and a mixture of two diastereoisomers in a ratio 4:1.

^{1}H NMR (400 MHz; $CDCl_3$): *Diastereoisomer 1*: δ_H ppm 6.46 (s, 1H, NC*H*=), 5.91 (s, 1H, =C*H*-), 5.84 (m, 1H, NCH_2CH), 5.10 (m, 2H, CH=CH_2), 4.95 (m, 1H, CH_3CH=), 4.61 (br, 1H, N*H*Boc), 4.31 (m, 2H, NCH_2), 4.13 (d, 2H, J=4.3Hz, CH_2NHBoc), 3.33 (q, 1H, J=6.9Hz, C*H*CH_3), 1.98 (q, 2H, J=7.5Hz, CH_2CH_3), 1.57 (d, 3H, J=6.8Hz, CH_3CH=), 1.45 (s, 9H, Boc), 1.31 (d, 3H, J=7.1Hz, CHCH_3), 0.80 (t, 3H, J=7.4Hz, CH_2CH_3);

Diastereoisomer 2: δ_H ppm 6.46 (s, 1H, NC*H*=), 5.91 (s, 1H, =C*H*-), 5.84 (m, 1H, NCH_2CH), 5.10 (m, 2H, CH=CH_2), 4.95 (m, 1H, CH_3CH=), 4.61 (br, 1H, N*H*Boc), 4.31 (m, 2H, NCH_2), 4.13 (d, 2H, J=4.3Hz, CH_2NHBoc), 3.87 (q, 1H, J=7.1Hz, C*H*CH_3), 1.98 (q, 2H, J=7.5Hz, CH_2CH_3), 1.70 (d, 3H, J=6.8Hz, CH_3CH=), 1.45 (s, 9H, Boc), 1.31 (d, 3H, J=7.1Hz, CHCH_3), 0.80 (t, 3H, J=7.4Hz, CH_2CH_3);

^{13}C NMR (100 MHz, $CDCl_3$): *Diastereoisomer 1*: δ_C ppm 155.7 (*C*O), 144.8 (CH_2*Cq*=CH), 136.04 (=*Cq*N), 134.5 (NCH_2*C*H), 119.3 (=*Cq*-CH_2NBoc), 119.0 (=*C*H-), 116.5 (CH=*C*H_2), 116.3 (CH_3*C*H=), 105.70 (=*C*H-), 79.0 (O*C*$(CH_3)_3$), 48.6 (N*C*H_2), 38.4 (*C*HCH_3), 38.0 (*C*H_2NHBoc), 28.4 (OC(*C*$H_3)_3$), 21.3 (*C*H_2CH_3), 19.5 (CH*C*H_3), 13.3 (*C*H_3CH=), 13.1 (CH_2*C*H_3);

Diastereoisomer 2: δ_C ppm 155.7 (*C*O), 144.02 (CH_2*Cq*=CH), 136.2 (=*Cq*N), 134.7 (NCH_2*C*H), 119.2 (=*Cq*-CH_2NBoc), 119.0 (=*C*H-), 118.5 (CH_3*C*H=), 116.6 (CH=*C*H_2), 105.77 (=*C*H-), 78.9 (O*C*$(CH_3)_3$), 48.4 (NCH_2), 38.0 (*C*H_2NHBoc), 31.9 (*C*HCH_3), 28.4 (OC(*C*$H_3)_3$), 24.1 (*C*H_2CH_3), 18.0 (CH*C*H_3), 12.7 (*C*H_3CH=), 12.6 (CH_2*C*H_3);

IR (CCl_4): νmax 992, 1025, 1046, 1123, 1171, 1246, 1366, 1390, 1467, 1494, 1539, 1717, 2874, 2858, 2929, 2966, 3461;

HRMS (EI+): *m/z* calculated (found) for $C_{20}H_{32}N_2O_2$: 332.2464 (332.2458).