JOC The Journal of Organic Chemistry

Article

Nickel-Catalyzed ortho-C-H Thiolation of N-Benzoyl alpha-Amino Acid Derivatives

Feng Gao, Wei Zhu, Dengyou Zhang, Shuangjie Li, Jiang Wang, and Hong Liu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b01702 • Publication Date (Web): 14 Sep 2016

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Nickel-Catalyzed *ortho*-C-H Thiolation of *N*-Benzoyl α-Amino Acid Derivatives

Feng Gao, Wei Zhu, Dengyou Zhang, Shuangjie Li, Jiang Wang, and Hong Liu*

CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, China

hliu@simm.ac.cn (Hong Liu)

Graphic Abstract

Abstract

We developed the first nickel-catalyzed direct *ortho*-thiolation of *N*-benzoyl α-amino acid derivatives. This novel strategy showed wide generality, functional tolerance and high regioselectivity. In addition, dipeptide derivatives were also compatible with this transformation system, providing a potential protocol for the direct modification of peptide derivatives.

Introduction

Functionalized amino acid derivatives have been employed widely as useful substrates in medicinal chemistry and the pharmaceutical industry for their broad biological activities[1] and facile membrane permeability.[2] Among them, *ortho*-thio substituted *N*-benzoyl α-amino acid derivatives are found frequently as building blocks in bioactive compounds (Figure 1).[3] Traditionally, the construction of such scaffolds is achieved by the cross coupling reactions between aryl-halides and thiol/disulfides, suffering from harsh reaction conditions, low substrate scopes and pre-functionalization of the substrates.[4] Thus, there remains the need to develop efficient and environmentally friendly synthetic methods to elaborate amino acid derivatives.

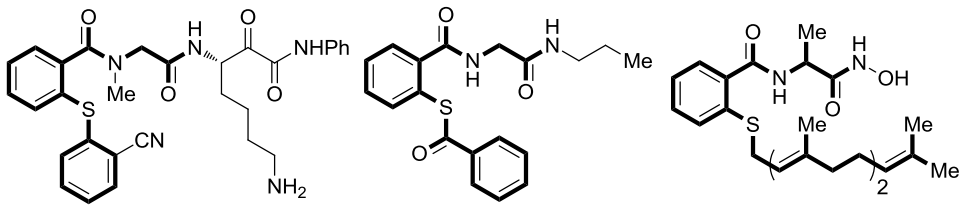
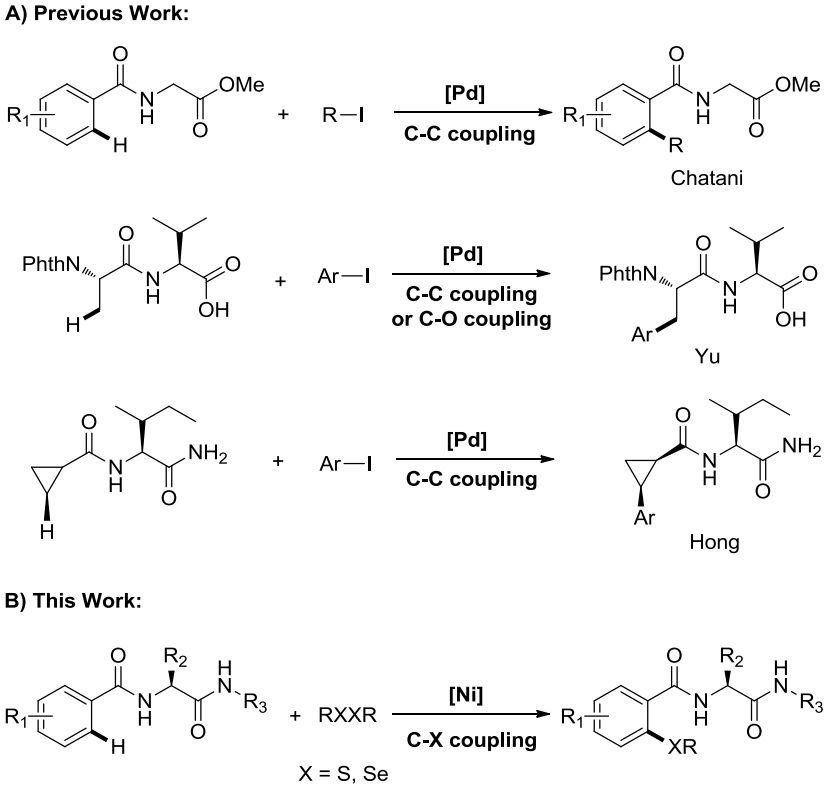


Figure 1. Bioactive *ortho*-thio substituted *N*-benzoyl α-amino acid derivatives.

In recent decades, transition-metal-catalyzed direct C-H functionalization has made great progress, in which diverse transformations and good regioselectivity have been realized with the assistance of

various directing groups.[5] Very recently, environmentally friendly and inexpensive amino acid moieties have been employed as novel directing groups in C-H activation for the direct modification of amino acid derivatives. Chatani reported an elegant work of *ortho*-C(sp^2)–H arylation/alkylation using α-amino ester moieties as bidentate directing groups (Scheme 1A).[6] By the employment of similar strategy, direct C(sp^3)–H functionalization of the amino acid derivatives has been accomplished by Yu's,[7] and Hong's group.[8] Mostly, these protocols demonstrated the formation of C-C bonds via C-H cleavage using palladium as the catalyst. Recently, nickel catalysts in C-H activation reactions have attracted increasing attention owing to their abundance, low cost and relatively less toxicity.[9,10] Given the importance of *ortho*-thio substituted *N*-benzoyl α-amino acid derivatives, we proposed the construction of such privilege frameworks via nickel-catalyzed direct C-H activation. Herein, we report the first example of nickel-catalyzed C-H thiolation of *N*-benzoyl α-amino acid as well as dipeptide derivatives (Scheme 1B).

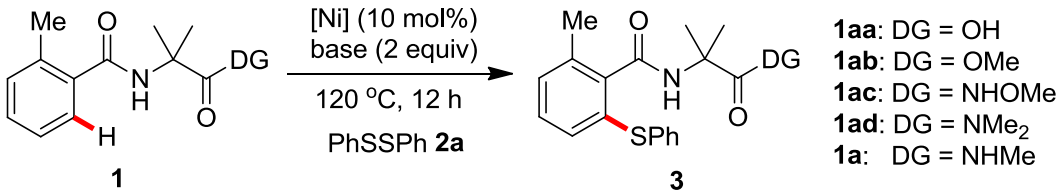
Scheme 1. Nickel-Catalyzed C(sp^2)–H Thiolation.



Results and Discussion

To verify the hypothesis, we initiated our studies by investigating the reaction with a series of *N*-benzoyl α-amino acid derivatives. The treatment of **1a** with disulfide **2a** in the presence of nickel catalyst and base afforded the desired thiolated product **3a** in 76% yield (Table 1, entries 1-5), while other substrates were not effective. This result suggested that bis-NH of amides were essential for the nickel-catalyzed C-H activation. The optimization of nickel salts revealed that $Ni(OTf)_2$ was the most effective catalyst to provide product **3a**, giving a yield of 93% (entries 6-10). Further screening of bases determined that ^{t}BuOLi was the best (entries 11-13). The efficiency of the reaction was also significantly affected by different solvents (entries 14-18), with DMF being identified as the optimal solvent. No desired product was obtained in non-polar or protonic solvents, while the use of DMSO resulted in a dramatic decrease yield.

Table 1. Optimization of Reaction Conditions[a]



Entry	DG	[Ni]	Base	Solvent	Yield (%)
1	**1aa**	$NiCl_2$	^{t}BuOLi	DMF	trace
2	**1ab**	$NiCl_2$	^{t}BuOLi	DMF	trace
3	**1ac**	$NiCl_2$	^{t}BuOLi	DMF	trace
4	**1ad**	$NiCl_2$	^{t}BuOLi	DMF	trace
5	**1a**	$NiCl_2$	^{t}BuOLi	DMF	76
6	**1a**	$NiBr_2$	^{t}BuOLi	DMF	80
7	**1a**	NiI_2	^{t}BuOLi	DMF	88
8	**1a**	$Ni(acac)_2$	^{t}BuOLi	DMF	81
9	**1a**	$Ni(OAc)_2$	^{t}BuOLi	DMF	82

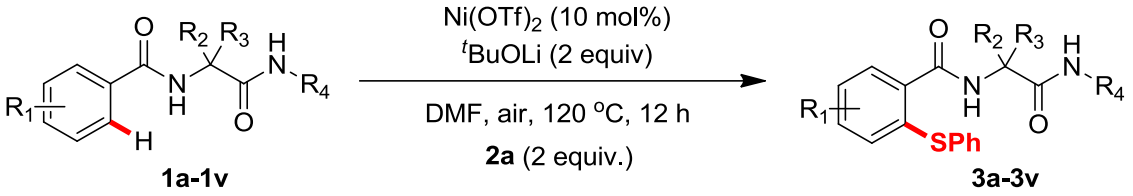
10	**1a**	$Ni(OTf)_2$	^tBuOLi	DMF	93
11	**1a**	$Ni(OTf)_2$	^tBuONa	DMF	88
12	**1a**	$Ni(OTf)_2$	^tBuOK	DMF	84
13	**1a**	$Ni(OTf)_2$	Na_2CO_3	DMF	trace
14	**1a**	$Ni(OTf)_2$	^tBuOLi	DMSO	18
15	**1a**	$Ni(OTf)_2$	^tBuOLi	Toluene	trace
16	**1a**	$Ni(OTf)_2$	^tBuOLi	DCE	trace
17	**1a**	$Ni(OTf)_2$	^tBuOLi	Dioxane	trace
18	**1a**	$Ni(OTf)_2$	^tBuOLi	^{t}AmylOH	trace

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), [Ni] (10 mol%), base (2 equiv), solvent (1 mL) in air at 120 °C.

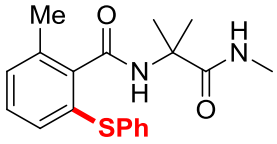
With the optimized reaction conditions in hand, we investigated the scope of *N*-benzoyl α-amino acid derivatives. Generally, this thiolation reaction tolerated various substituents both on the aromatic ring and α-amino acid moieties, and generated the desired products in moderate to high yields (Table 2). Benzamides bearing a large group in the *ortho*-position, such as trifluoromethyl and phenyl groups, gave moderate yields, probably due to the steric hindrance while halogen could be tolerated well under standard conditions (**3b**-**3d**). When *meta*-substituted benzamides were employed, the C-H bond thiolation took place at the less sterically hindered position irrespective of the electronic nature of the substituents (**3e**-**3g**). The unsubstituted and *para*-substituted benzamides afforded a mixture of mono- and di-thiolated products, while exclusive di-thiolated products were obtained in good yields by increasing the amounts of disulfide, nickel catalyst and base (**3h**-**3j**). Multisubstituted benzamide derivative and naphthamide provided the desired products in high yields (**3k** and **3l**). Furthermore, heterocycles were also compatible with the optimal conditions (**3m** and **3n**). Next, the reaction efficiency of different α-amino acid moieties were evaluated. Cyclic amino acid derivatives proceeded

smoothly and produced the corresponding products in high yields (**3o** and **3p**). Substrates bearing natural α-amino acid moieties, such as alanine, valine, leucine and phenylalanine, worked well under the standard conditions (**3q**-**3t**). Notably, the chirality at the α-position of valine was not influenced after the transformation (97% *ee*). In addition, dipeptide derivatives (**1u** and **1v**) were also effective substrates, indicating that the reaction system could be a potential strategy for direct modification of peptides. Importantly, the C(sp^2)-H thiolation was carried out on a gram scale without any additives to afford **3a** in 90% yield (Scheme 2).

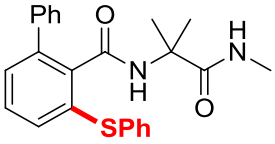
Table 2. Scope of N-Benzoyl α-Amino Acid Derivatives[a]



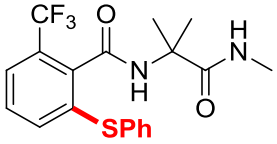
1a-1v **3a-3v**



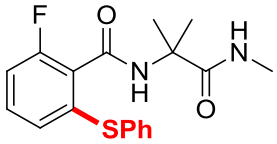
3a, 93%



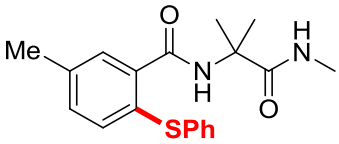
3b, 64%[c]



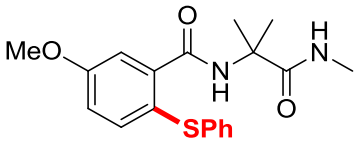
3c, 41%



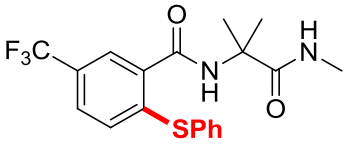
3d, 58%[b]



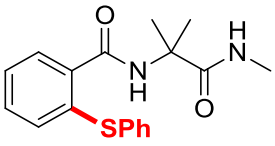
3e, 71%



3f, 74%

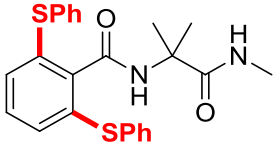


3g, 75%

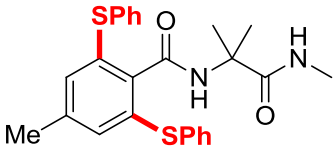


3h, 80%

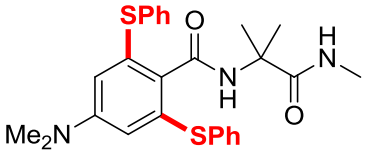
(mono:di = 1:1.4)



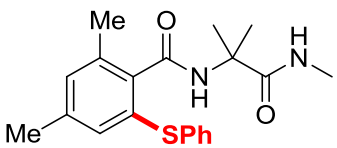
3h', 76%[c]



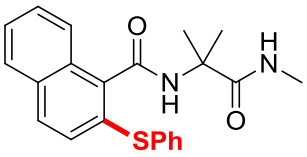
3i, 76%[c]



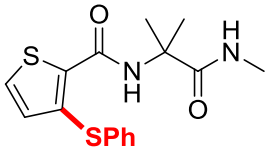
3j, 77%[c]



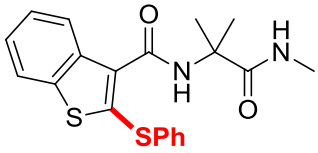
3k, 85%



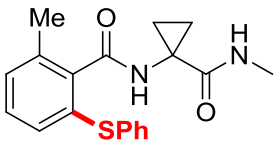
3l, 87%



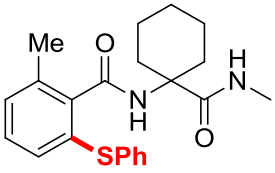
3m, 35%[b]



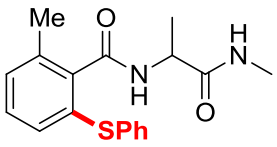
3n, 79%



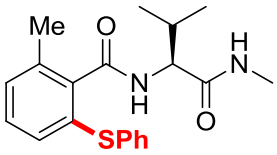
3o, 90%



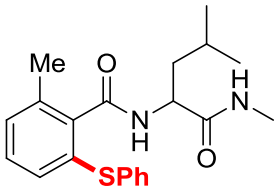
3p, 80%



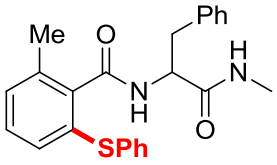
3q, 73%



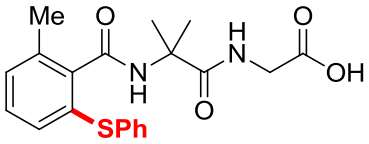
3r, 81% (97% *ee*)[d]



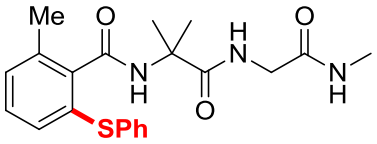
3s, 76%



3t, 54%



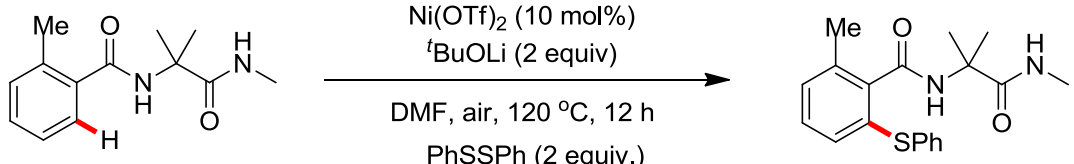
3u, 67%[e]



3v, 30%[e]

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Ni(OTf)_2$ (10 mol%), ^tBuOLi (0.4 mmol), DMF (1 mL) in air at 120 °C. [b] 15 h. [c] **2a** (0.6 mmol), $Ni(OTf)_2$ (15 mol%) and ^tBuOLi (0.6 mmol). [d] 100 °C. [e] $Ni(OTf)_2$ (20 mol%) and ^tBuOLi (0.6 mmol).

Scheme 2. Gram-scale C(sp^2)–H Thiolation.



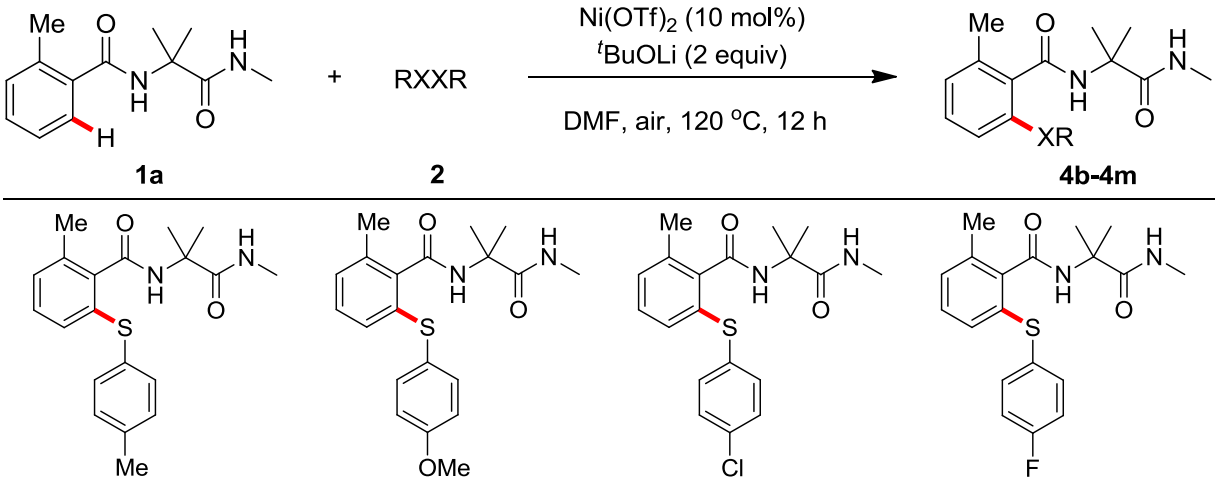
1a
5 mmol

3a
1.54 g, 90%

Next, the scope of disulfides was further tested (Table 3). In general, various disulfides and diselanes proceeded smoothly to provide the corresponding products. The introduction of electron-donating group at the *para*- or *meta*-position of diphenyl disulfides had no influence on the yield (**4b**, **4c** and **4f**), while *meta*-nitro substituted diphenyl disulfides gave a relative lower yield (**4h**). Contrastingly,

halogen-substituted diphenyl disulfides produced the corresponding products in excellent yields, guaranteeing further transformation (**4d** and **4g**). *Ortho*-substituted disulfide could also furnish the product with a slightly decreasing yield, probably because of interference with the oxidative addition process (**4i**). Importantly, heteroaromatic disulfide and diphenyl diselanes were also compatible with the reaction conditions, delivering the products in moderate to good yields (**4j**-**4m**). Unfortunately, no desired thiolated product was observed, when dibenzyldisulfane and dipropyldisulfane were applied (**4n** and **4o**).

Table 3. Scope of Disulfides[a]

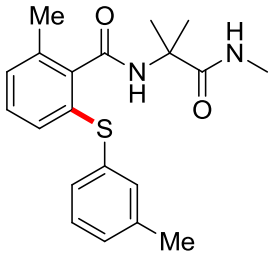


4b, 85%

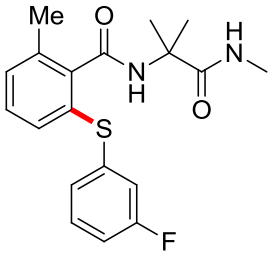
4c, 81%

4d, 98%

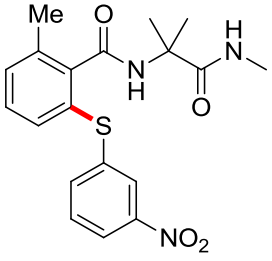
4e, 85%[b]



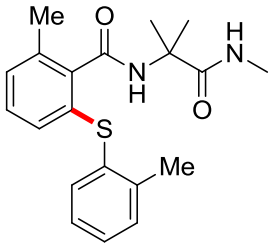
4f, 83%



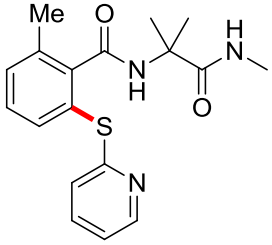
4g, 94%



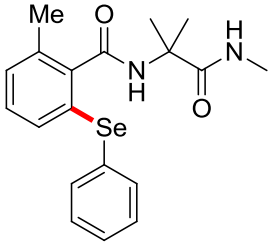
4h, 43%



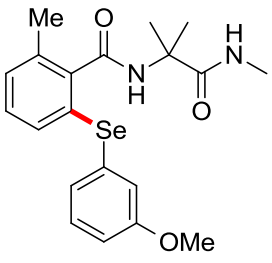
4i, 71%



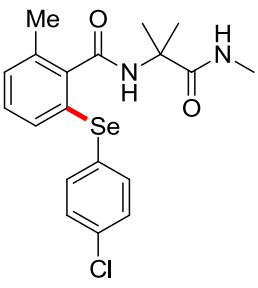
4j, 72%[b]



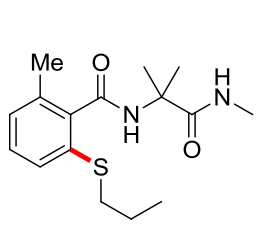
4k, 58%[b]



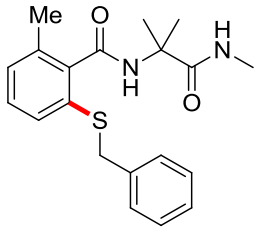
4l, 54%[b]



4m, 42%[b]



4n, 0%

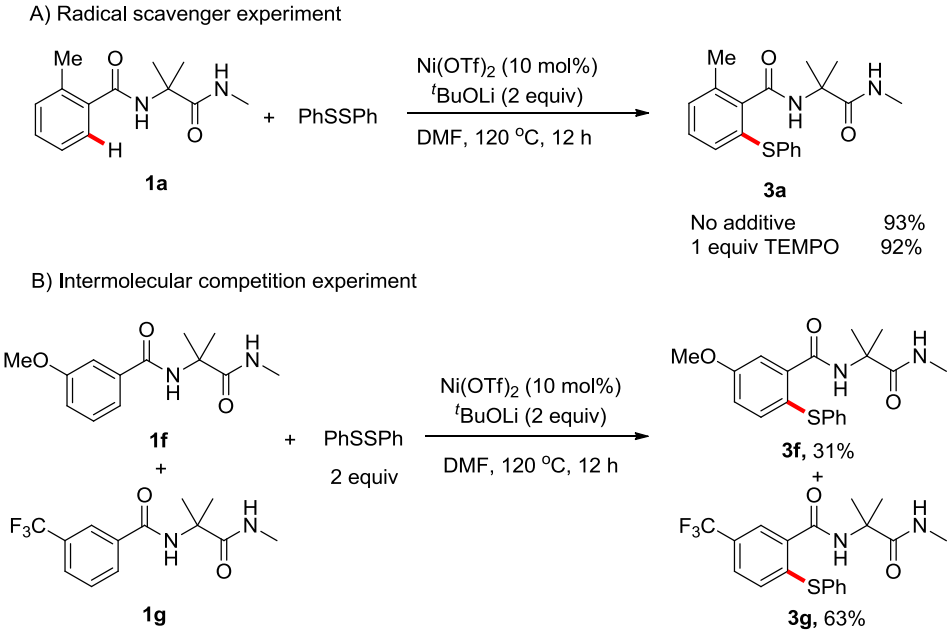


4o, 0%

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Ni(OTf)_2$ (10 mol%), ^tBuOLi (2 equiv), DMF (1 mL) in air at 120 °C. [b] 18 h.

To understand the reaction mechanism, we first performed a radical scavenger experiment (Scheme 3A). The result revealed that the reaction efficiency was not affected by TEMPO (1 equiv.), indicating that it likely did not involve a single electron transfer (SET) process. Furthermore, an intermolecular competition experiment between **1f** and **1g** was carried out and the substrate bearing an electron-withdrawing substituent reacted with higher relative rate (Scheme 3B), which suggested that C-H bond cleavage might be influenced by its acidity. A detailed mechanism remains to be elucidated.

Scheme 3. Mechanistic Investigations



Conclusion

In conclusion, we developed the first nickel-catalyzed direct *ortho*-thiolation of *N*-benzoyl α-amino acid derivatives. This method is widely applicable and shows high functional tolerance and high

regioselectivity. Dipeptide derivatives were also compatible, representing a potential protocol for the direct modification of peptide derivatives. It also provides a straightforward approach for the construction of *ortho*-thio substituted *N*-benzoyl α-amino acid derivatives, which are identified as privilege scaffolds with wide potential bioactivities in pharmaceuticals. Therefore, this modified strategy will be of importance to medicinal chemists.

Experimental Section

General Information. Unless otherwise noted, the reagents (chemicals) were purchased from commercial sources, and used without further purification. Water was deionized before used. Analytical thin layer chromatography (TLC) was HSGF 254 (0.15-0.2 mm thickness). Compound spots were visualized by UV light (254 nm). Column chromatography was performed on silica gel FCP 200-300. NMR spectra were run on 400 or 500 MHz instrument. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were measured on spectrometer.

General Procedure for the Preparation of Substrates 1a-v. To a mixture of 2-((*tert*-butoxycarbonyl)amino)-2-methylpropanoic acid (25.00 g, 123.01 mmol) and HOBt (18.28 g, 135.31 mmol) in 200 mL of DCM was added TEA (56.27 mL, 405.93 mmol), followed by addition of EDCI (25.94 g, 135.31 mmol). The resulting mixture was stirred for 10 min and then methanamine hydrochloride (8.31 g, 123.01 mmol) was added. The reaction was stirred overnight. The mixture was diluted with DCM and the organic layer was washed with saturated sodium carbonate, brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to give a white solid (23.10 g, 87%).

To a mixture of *tert*-butyl (2-methyl-1-(methylamino)-1-oxopropan-2-yl)carbamate (23.10 g, 106.81 mmol) in 150 mL of dioxane was added dropwise a solution of HCl in dioxane (4 N, 150 mL) at 0 °C.

The reaction was stirred at room temperature for 3 h. Then the mixture was concentrated under vacuum to give the crude product as a white solid (15.80 g, 97%).

To an ice-cooled solution of 2-amino-*N*,2-dimethylpropanamide hydrochloride (1.50 g, 9.83 mmol) in 40 mL of DCM was added TEA (4.09 mL, 29.48 mmol), followed by addition of corresponding benzoyl chloride (1.08 mmol) dropwise. The resulting mixture was stirred at room temperature for 6 h. Then the reaction was quenched by water and extracted with DCM. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column to afford the title compound as a white solid.

General Procedure for Nickel-Catalyzed *ortho*-C-H Thiolation of *N*-Benzoyl α-Amino Derivatives. A Schlenk tube equipped with a magnetic stir bar was charged with $Ni(OTf)_2$ (7.1 mg, 10 mol%), ^{t}BuOLi (32.1 mg, 0.40 mmol), substrate **1** (0.20 mmol) and disulfide **2** (0.4 mmol) and then capped with septa. 1 mL of DMF was charged to the vial via syringe, and then the resulting mixture was stirred in a pre-heated oil bath at 120 °C for 12 h. After the reaction was completed, the solvent was removed under vacuum and the residue was purified by silica gel column (PE/EA = 2:3) to afford desired thiolated product.

Analytical Characterization Data of Products.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(phenylthio)benzamide (3a): Compound **3a** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 64 mg, 93% yield. Mp: 144-146 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 7.37 – 7.20 (m, 8H), 7.13 (dd, J = 7.5, 0.8 Hz, 1H), 2.56 (d, J = 4.7 Hz, 3H), 2.30 (s, 3H), 1.41 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.3, 167.1, 141.2, 135.9, 135.7, 130.8, 130.6, 130.1, 129.9, 129.41, 129.37, 127.1, 56.6, 26.1, 25.0, 18.8. **LRMS** (ESI) $[M+H]^+$ found: 343.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{22}O_2N_2NaS$: 365.1294, found: 365.1288. Anal. Calcd for $C_{19}H_{22}O_2N_2S$: C, 66.64; H, 6.48; N, 8.18; found: C, 66.46; H, 6.51; N, 8.18.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-3-(phenylthio)-[1,1'-biphenyl]-2-carboxamide (3b):** Compound **3b** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 52 mg, 64% yield. Mp: 174-176 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.49 – 7.37 (m, 10H), 7.36 – 7.29 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 1H), 6.65 (q, *J* = 4.7 Hz, 1H), 2.44 (d, *J* = 4.7 Hz, 3H), 1.17 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.0, 166.5, 140.0, 139.42, 139.39, 134.9, 132.3, 131.3, 131.1, 129.51, 129.49, 129.1, 128.8, 128.0, 127.6, 56.7, 25.9, 24.6. **LRMS** (ESI) $[M+H]^+$ found: 405.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{24}H_{24}O_2N_2NaS$: 427.1451, found: 427.1445.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)-6-(trifluoromethyl)benzamide (3c):** Compound **3c** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 32 mg, 41% yield. Mp: 166-168 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.62 – 7.51 (m, 2H), 7.49 – 7.38 (m, 4H), 7.38 – 7.33 (m, 1H), 7.27 (d, *J* = 4.2 Hz, 1H), 2.58 (d, *J* = 4.5 Hz, 3H), 1.45 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, MeOD) δ 176.9, 167.7, 138.1, 137.5, 137.2, 135.2, 133.2, 131.3, 130.8, 128.6, 129.0 (q, *J* = 31.8 Hz), 126.5 (q, *J* = 4.7 Hz), 125.0 (q, *J* = 273.7 Hz), 59.1, 26.6. **LRMS** (ESI) $[M+H]^+$ found: 397.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{19}O_2N_2F_3NaS$: 419.1012, found: 419.1006.

2-Fluoro-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(phenylthio)benzamide (3d): Compound **3d** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 40 mg, 58% yield. Mp: 163-166 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.44 – 7.33 (m, 6H), 7.25 – 7.16 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 2.59 (d, *J* = 4.6 Hz, 3H), 1.43 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 173.8, 162.3, 158.5 (d, *J* = 247.7 Hz), 135.1 (d, *J* = 4.0 Hz), 133.9, 131.7, 131.0 (d, *J* = 8.8 Hz), 129.6, 128.0, 127.8 (d, *J* = 20.5 Hz), 127.4, 114.5 (d, *J* = 11.0 Hz), 56.8, 26.1, 25.0. **LRMS** (ESI) $[M+H]^+$ found: 347.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{18}H_{19}O_2N_2FNaS$: 369.1043, found: 369.1042.

5-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)benzamide (3e): Compound **3e** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 49 mg, 71%. Mp: 149-152 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.33 (s, 1H), 7.46 (d, J = 1.2 Hz, 1H), 7.42 (q, J = 4.6 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.32 – 7.24 (m, 3H), 7.19 (dd, J = 8.0, 1.3 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 2.56 (d, J = 4.6 Hz, 3H), 2.33 (s, 3H), 1.39 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.2, 167.0, 139.1, 136.8, 135.7, 132.1, 130.85, 130.79, 129.5, 129.4, 128.8, 127.2, 56.4, 26.1, 25.1, 20.4. **LRMS** (ESI) $[M+H]^+$ found: 343.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{22}O_2N_2NaS$: 365.1294, found: 365.1292.

5-Methoxy-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)benzamide (3f): Compound **3f** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 53 mg, 74% yield. Mp: 162-165 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.40 (q, J = 4.5 Hz, 1H), 7.33 – 7.26 (m, 3H), 7.23 – 7.17 (m, 4H), 7.02 (dd, J = 8.7, 2.9 Hz, 1H), 3.82 (s, 3H), 2.55 (d, J = 4.6 Hz, 3H), 1.35 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 166.7, 159.1, 142.4, 137.2, 135.9, 129.2, 128.9, 126.3, 121.4, 116.0, 113.9, 56.5, 55.6, 26.1, 25.0. **LRMS** (ESI) $[M+H]^+$ found: 359.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{19}H_{23}O_3N_2S$: 359.1424, found: 359.1422.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)-5-(trifluoromethyl)benzamide (3g):** Compound **3g** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 59 mg, 75% yield. Mp: 162-163 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.06 (d, J = 1.4 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.56 – 7.44 (m, 5H), 6.99 (d, J = 8.4 Hz, 1H), 2.60 (d, J = 4.6 Hz, 3H), 1.44 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 173.9, 165.6, 142.7, 135.6, 134.2, 131.9, 130.1, 129.3, 128.4, 126.6 (q, J = 3.5 Hz), 125.5 (q, J = 32.3 Hz), 125.2 (q, J = 3.5 Hz), 125.1 (q, J = 272.5 Hz), 56.6, 26.2, 25.2. **LRMS** (ESI) $[M+H]^+$ found: 396.9. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{19}O_2N_2F_3NaS$: 419.1012, found: 419.1007.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)benzamide (3h):** Compound **3h** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 22 mg, 34% yield (**3h** plus **3h'**, total 80% yield). Mp: 117-120 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.63 (dd, J = 7.4, 1.7 Hz, 1H), 7.46 (q, J = 4.6 Hz, 1H), 7.42 – 7.28 (m, 7H), 7.06 (dd, J = 7.7, 1.2 Hz, 1H), 2.58 (d, J = 4.6 Hz, 3H), 1.41 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.2, 166.9, 137.9, 134.5, 134.3, 132.1, 130.5, 130.2, 129.6, 128.3, 127.8, 126.4, 56.5, 26.1, 25.1. **LRMS** (ESI) $[M+H]^+$ found: 329.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{18}H_{20}O_2N_2NaS$: 351.1138, found: 351.1139.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2,6-bis(phenylthio)benzamide (3h'):** Compound **3h'** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 66 mg, 76% yield. Mp: 174-177 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.70 (s, 1H), 7.44 – 7.36 (m, 8H), 7.36 – 7.29 (m, 3H), 7.23 – 7.16 (m, 3H), 2.55 (d, J = 4.7 Hz, 3H), 1.43 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 165.6, 142.3, 134.5, 133.0, 131.8, 131.1, 130.3, 129.5, 127.7, 57.0, 25.9, 25.0. **LRMS** (ESI) $[M+H]^+$ found: 436.9. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{24}H_{24}O_2N_2NaS_2$: 459.1171, found: 459.1167. Anal. Calcd for $C_{24}H_{24}O_2N_2S_2$: C, 66.02; H, 5.54; N, 6.42; found: C, 64.20; H, 5.38; N, 6.22.

4-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2,6-bis(phenylthio)benzamide (3i): Compound **3i** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 68 mg, 76% yield. Mp: 204-206 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 7.42 – 7.35 (m, 8H), 7.34 – 7.26 (m, 2H), 7.17 (q, J = 4.2 Hz, 1H), 7.10 (s, 2H), 2.52 (d, J = 4.7 Hz, 3H), 2.16 (s, 3H), 1.40 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.2, 165.8, 140.6, 140.2, 134.9, 133.0, 132.3, 130.6, 129.5, 127.5, 56.9, 25.8, 25.0, 20.4. **LRMS** (ESI) $[M+H]^+$ found: 451.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{25}H_{26}O_2N_2NaS_2$: 473.1328, found: 473.1325.

4-(Dimethylamino)-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2,6-bis(phenylthio)benzamide (3j): Compound **3j** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 74 mg, 77% yield. Mp: 188-190 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.37 (s, 1H), 7.47 – 7.34 (m, 8H), 7.32 – 7.25 (m, 2H), 7.16 (q, J = 4.8 Hz, 1H), 6.56 (s, 2H), 2.74 (s, 6H), 2.51 (d, J = 4.8 Hz, 3H), 1.35 (s, 6H). **^{13}C {^{1}H} NMR** (100 MHz, DMSO-d_6) δ 174.3, 166.1, 150.6, 135.5, 132.6, 131.4, 130.1, 129.3, 127.1, 115.6, 56.7, 39.5, 25.8, 24.9. **LRMS** (ESI) $[M+H]^+$ found: 480.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{26}H_{29}O_2N_3NaS_2$: 502.1593, found: 502.1581.

2,4-Dimethyl-N-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(phenylthio)benzamide (3k): Compound **3k** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 85% yield. Mp: 180-182 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.36 (s, 1H), 7.35 – 7.27 (m, 4H), 7.27 – 7.22 (m, 2H), 7.07 (s, 1H), 7.00 (s, 1H), 2.55 (d, J = 4.6 Hz, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.40 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.2, 167.2, 138.9, 138.8, 136.2, 135.4, 131.3, 130.8, 129.8, 129.6, 129.2, 126.8, 56.5, 25.9, 25.0, 20.5, 18.6. **LRMS** (ESI) $[M+H]^+$ found: 357.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{24}O_2N_2NaS$: 379.1451, found: 379.1445.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)-1-naphthamide (3l):** Compound **3l** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 66 mg, 87% yield. Mp: 165-167 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 8.05 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.67 – 7.54 (m, 2H), 7.46 (q, J = 4.8 Hz, 1H), 7.42 – 7.23 (m, 6H), 2.64 (d, J = 4.6 Hz, 3H), 1.50 (s, 6H). **^{13}C {^{1}H} NMR** (100 MHz, DMSO-d_6) δ 174.1, 166.5, 138.9, 135.4, 132.0, 130.5, 130.2, 129.5, 129.3, 128.1, 127.8, 127.4, 127.2, 126.9, 125.5, 56.8, 26.1, 25.1. **LRMS** (ESI) $[M+H]^+$ found: 379.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{22}H_{22}O_2N_2NaS$: 401.1294, found: 401.1284.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-3-(phenylthio)thiophene-2-carboxamide (3m):** Compound **3m** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. Colorless oil, 23 mg, 35% yield. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.77 (d, J = 5.2 Hz, 1H), 7.74 (q, J = 4.5 Hz, 1H), 7.42 – 7.29 (m, 5H), 6.86 (d, J = 5.2 Hz, 1H), 2.60 (d, J = 4.5 Hz, 3H), 1.44 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 159.6, 136.7, 134.4, 132.0, 130.9, 130.3, 129.7, 129.6, 127.7, 56.8, 26.2, 24.6. **LRMS** (ESI) $[M+H]^+$ found: 335.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{16}H_{18}O_2N_2NaS_2$: 357.0702, found: 357.0692.

***N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-2-(phenylthio)benzo[*b*]thiophene-3-carboxamide (3n):** Compound **3n** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 79% yield. Mp: 186-189 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.95-7.89 (m, 2H), 7.53 – 7.33 (m, 8H), 2.61 (d, J = 4.6 Hz, 3H), 1.48 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 162.5, 139.7, 137.5, 136.2, 135.3, 134.4, 130.7, 129.6, 128.2, 125.4, 125.1, 123.4, 122.2, 56.7, 26.2, 25.1. **LRMS** (ESI) $[M+H]^+$ found: 385.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{20}N_2O_2NaS_2$: 407.0858, found: 407.0855.

2-Methyl-*N*-(1-(methylcarbamoyl)cyclopropyl)-6-(phenylthio)benzamide (3o): Compound **3o** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 90% yield. Mp: 183-186 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 9.05 (s, 1H), 7.38 – 7.19 (m, 9H), 2.60 (d, J = 4.8 Hz, 3H), 2.25 (s, 3H), 1.34 – 1.29 (m, 2H), 1.02 – 0.96 (m, 2H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 171.2, 168.9, 141.2, 135.7, 135.4, 131.4, 130.2, 129.8, 129.7, 129.5, 129.4, 127.0, 34.2, 26.1, 18.6, 15.7. **LRMS** (ESI) $[M+H]^+$ found: 341.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{19}H_{21}O_2N_2S$: 341.1318, found: 341.1315.

2-Methyl-*N*-(1-(methylcarbamoyl)cyclohexyl)-6-(phenylthio)benzamide (3p): Compound **3p** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 80% yield. Mp: 165-168 °C. **^{1}H NMR** (400 MHz, DMSO-d_6)

δ 8.30 (s, 1H), 7.37 – 7.21 (m, 8H), 7.15 (d, *J* = 7.3 Hz, 1H), 2.54 (d, *J* = 4.6 Hz, 3H), 2.36 (s, 3H), 2.16 (s, 1H), 2.12 (s, 1H), 1.72 – 1.62 (m, 2H), 1.61 – 1.42 (m, 5H), 1.26 – 1.12 (m, 1H). **^{13}C {^{1}H} NMR** (100 MHz, DMSO-d_6) δ 174.3, 167.7, 141.7, 136.2, 135.7, 131.1, 130.3, 130.0, 129.8, 129.3, 129.2, 126.7, 60.1, 31.7, 25.8, 25.0, 21.1, 19.2. **LRMS** (ESI) $[M+H]^+$ found: 383.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{22}H_{27}O_2N_2S$: 383.1788, found: 383.1789. Anal. Calcd for $C_{22}H_{26}O_2N_2S$: C, 69.08; H, 6.85; N, 7.32; found: C, 68.74; H, 6.91; N, 7.17.

2-Methyl-*N*-(1-(methylamino)-1-oxopropan-2-yl)-6-(phenylthio)benzamide (3q): Compound **3q** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 48 mg, 73% yield. Mp: 162-164 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ δ 8.52 (d, *J* = 7.5 Hz, 1H), 7.67 (q, *J* = 4.5 Hz, 1H), 7.36 – 7.29 (m, 4H), 7.29 – 7.22 (m, 2H), 7.20 (d, *J* = 7.4 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 4.46 – 4.37 (m, 1H), 2.59 (d, *J* = 4.6 Hz, 3H), 2.28 (s, 3H), 1.24 (d, *J* = 7.1 Hz, 3H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 172.2, 167.0, 140.8, 135.8, 135.5, 131.2, 130.5, 130.0, 129.4, 129.3, 129.2, 127.0, 48.4, 25.5, 18.9, 17.9. **LRMS** (ESI) $[M+H]^+$ found: 328.9. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{18}H_{21}O_2N_2S$: 329.1318, found: 329.1317. Anal. Calcd for $C_{18}H_{20}O_2N_2S$: C, 65.83; H, 6.14; N, 8.53; found: C, 66.43; H, 6.22; N, 8.33.

2-Methyl-*N*-(3-methyl-1-(methylamino)-1-oxobutan-2-yl)-6-(phenylthio)benzamide (3r): Compound **3r** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 85% yield. Mp: 140-143 °C. $[\alpha]^{20}_{D}$ = -65.4 (c 0.220, MeOH). **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.42 (d, *J* = 8.7 Hz, 1H), 7.78 (q, *J* = 4.6 Hz, 1H), 7.35 – 7.29 (m, 4H), 7.28 – 7.21 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 4.23 (dd, *J* = 8.3, 7.8 Hz, 1H), 2.59 (d, *J* = 4.6 Hz, 3H), 2.25 (s, 3H), 2.06 – 1.97 (m, 1H), 0.89 (d, *J* = 4.9 Hz, 3H), 0.88 (d, *J* = 4.9 Hz, 3H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 171.1, 167.5, 141.1, 136.0, 135.3, 131.3, 130.5, 130.0, 129.25, 129.21, 129.0, 127.0, 58.6, 29.9, 25.4, 19.4, 19.0, 18.5. **LRMS** (ESI) $[M+H]^+$ found: 357.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{20}H_{25}O_2N_2S$: 357.1631, found:

357.1628.

2-Methyl-*N*-(4-methyl-1-(methylamino)-1-oxopentan-2-yl)-6-(phenylthio)benzamide (3s): Compound **3s** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 56 mg, 76% yield. Mp: 178-180 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.53 (d, *J* = 8.1 Hz, 1H), 7.71 (q, *J* = 4.5 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.27 – 7.22 (m, 2H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 4.46 – 4.37 (m, 1H), 2.57 (d, *J* = 4.6 Hz, 3H), 2.27 (s, 3H), 1.76 – 1.62 (m, 1H), 1.59 – 1.50 (m, 1H), 1.44 – 1.36 (m, 1H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 172.2, 167.4, 141.1, 136.0, 135.4, 130.9, 130.3, 130.2, 129.4, 129.2, 129.1, 126.9, 51.2, 40.4, 25.5, 24.1, 23.1, 21.2, 18.9. **LRMS** (ESI) $[M+H]^+$ found: 371.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{21}H_{27}O_2N_2S$: 371.1788, found: 371.1785.

2-Methyl-*N*-(1-(methylamino)-1-oxo-3-phenylpropan-2-yl)-6-(phenylthio)benzamide (3t): Compound **3t** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 44 mg, 54% yield. Mp: 193-195 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.69 (d, *J* = 8.3 Hz, 1H), 7.74 (q, *J* = 4.4 Hz, 1H), 7.40 – 7.24 (m, 7H), 7.24 – 7.14 (m, 4H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 4.68 (td, *J* = 10.4, 4.6 Hz, 1H), 3.08 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.83 (dd, *J* = 13.8, 10.6 Hz, 1H), 2.58 (d, *J* = 4.6 Hz, 3H), 1.90 (s, 3H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 171.2, 167.4, 140.6, 138.0, 135.8, 135.4, 131.4, 130.6, 129.8, 129.3, 129.2, 129.1, 128.0, 127.1, 126.2, 54.3, 37.1, 25.5, 18.4. **LRMS** (ESI) $[M+H]^+$ found: 405.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{24}H_{23}O_2N_2S$: 403.1486, found: 403.1495.

2-(3-Methyl-2-(2-methyl-6-(phenylthio)benzamido)butanamido)acetic acid (3u): Compound **3u** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 52 mg, 67% yield. Mp: 183-186 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.58 (br, 1H), 8.50 (s, 1H), 7.63 (t, *J* = 5.5 Hz, 1H), 7.36 – 7.19 (m, 7H), 7.10 (d, *J* = 7.4 Hz,

1H), 3.73 (d, *J* = 5.5 Hz, 2H), 2.31 (s, 3H), 1.44 (s, 6H). **^{13}C {^{1}H} NMR** (100 MHz, DMSO-d_6) δ 174.0, 171.1, 167.2, 140.8, 135.8, 135.7, 131.0, 130.4, 129.6, 129.32, 129.26, 127.1, 56.5, 41.1, 24.8, 18.8. **LRMS** (ESI) $[M-H]^-$ found: 385.1. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{22}O_4N_2NaS$: 409.1192, found: 409.1183.

2-Methyl-N-(3-methyl-1-((2-(methylamino)-2-oxoethyl)amino)-1-oxobutan-2-yl)-6-(phenylthio)benzamide (3v): Compound **3v** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 24 mg, 30% yield. Mp: 168-172 °C. **^{1}H NMR** (400 MHz, MeOD) δ 7.41 – 7.08 (m, 8H), 3.80 (s, 2H), 2.50 (s, 3H), 2.41 (s, 3H), 1.54 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 173.8, 169.0, 168.3, 140.3, 135.83, 135.78, 130.9, 130.6, 129.9, 129.7, 129.5, 129.3, 126.9, 56.4, 42.9, 25.3, 24.8, 18.7. **LRMS** $[M+H]^+$ found 400.0. **HRMS** (ESI) $[M+H]^+$ calcd for $C_{21}H_{26}O_3N_3S$: 400.1689, found: 400.1679.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(p-tolylthio)benzamide (4b): Compound **4b** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 85% yield. Mp: 98-102 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.50 (s, 1H), 7.38 – 7.12 (m, 7H), 7.02 (d, *J* = 7.5 Hz, 1H), 2.57 (d, *J* = 4.4 Hz, 3H), 2.29 (s, 3H), 2.28 (s, 3H), 1.43 (s, 6H). **^{13}C {^{1}H} NMR** (150 MHz, DMSO-d_6) δ 174.2, 167.1, 140.3, 137.2, 135.4, 132.0, 131.6, 131.4, 130.1, 129.5, 129.2, 129.1, 56.6, 26.0, 25.0, 20.6, 18.7. **LRMS** (ESI) $[M+H]^+$ found: 357.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{24}O_2N_2NaS$: 379.1451, found: 379.1440.

2-((4-Methoxyphenyl)thio)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)benzamide (4c): Compound **4c** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 60 mg, 81% yield. Mp: 88-91 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.44 – 7.38 (m, 2H), 7.34 (q, *J* = 4.3 Hz, 1H), 7.21 – 7.16 (m, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 1H), 3.76 (s, 3H),

2.60 (d, *J* = 4.7 Hz, 3H), 2.28 (s, 3H), 1.46 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.2, 167.1, 159.5, 139.1, 135.1, 134.7, 133.8, 129.0, 128.4, 128.0, 124.4, 115.2, 56.6, 55.3, 26.0, 25.0, 18.6. **LRMS** (ESI) $[M+H]^+$ found: 373.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{24}O_3N_2NaS$: 395.1400, found: 395.1389.

2-((4-Chlorophenyl)thio)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)benzamide (4d): Compound **4d** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 74 mg, 98% yield. Mp: 173-176 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.48 (s, 1H), 7.41 – 7.36 (m, 2H), 7.33 – 7.23 (m, 5H), 7.19 (dd, *J* = 7.3, 1.2 Hz, 1H), 2.56 (d, *J* = 4.7 Hz, 3H), 2.31 (s, 3H), 1.40 (s, 6H). **^{13}C {^{1}H} NMR** (150 MHz, DMSO-d_6) δ 174.1, 166.9, 141.7, 135.8, 135.4, 131.6, 131.3, 131.2, 130.3, 129.6, 129.4, 129.2, 56.5, 26.0, 25.0, 18.7. **LRMS** (ESI) $[M+H]^+$ found: 377.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{21}O_2N_2ClNaS$: 399.0904, found: 399.0897.

2-((4-Fluorophenyl)thio)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)benzamide (4e): Compound **4e** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 61 mg, 85% yield. Mp: 138-140 °C. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.41 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.30 (q, *J* = 4.6 Hz, 1H), 7.27 – 7.23 (m, 1H), 7.23 – 7.18 (m, 3H), 7.09 (d, *J* = 7.7 Hz, 1H), 2.58 (d, *J* = 4.6 Hz, 3H), 2.30 (s, 3H), 1.43 (s, 6H). **^{13}C {^{1}H} NMR** (150 MHz, DMSO-d_6) δ 174.1, 167.0, 161.6 (d, *J* = 245.4 Hz), 140.7, 135.6, 133.3 (d, *J* = 8.3 Hz), 131.3, 131.0 (d, *J* = 2.9 Hz), 130.1, 129.6, 129.3, 116.4 (d, *J* = 23.4 Hz), 56.6, 26.0, 25.0, 18.7. **LRMS** (ESI) $[M+H]^+$ found: 361.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{21}O_2N_2FNaS$: 383.1200, found: 383.1190.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(m-tolylthio)benzamide (4f): Compound **4f** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 59 mg, 83% yield. Mp: 156-158 °C. **^{1}H**

NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.30 – 7.15 (m, 5H), 7.15 – 7.04 (m, 3H), 2.57 (d, *J* = 4.5 Hz, 3H), 2.30 (s, 3H), 2.26 (s, 3H), 1.41 (s, 6H). **^{13}C {^{1}H} NMR** (150 MHz, DMSO-d_6) δ 174.6, 167.5, 141.4, 139.2, 136.0, 135.8, 131.4, 131.2, 130.9, 130.1, 129.7, 128.4, 128.0, 57.0, 26.5, 25.5, 21.3, 19.2. **LRMS** (ESI) $[M+H]^+$ found: 357.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{24}O_2N_2NaS$: 379.1451, found: 379.1444.

2-((3-Fluorophenyl)thio)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)benzamide (4g): Compound **4g** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 68 mg, 94% yield. Mp: 177-180 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 7.38 – 7.29 (m, 3H), 7.27 (dd, *J* = 7.1, 1.4 Hz, 1H), 7.22 (q, *J* = 4.6 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 7.04 (ddd, *J* = 17.4, 9.1, 2.1 Hz, 2H), 2.56 (d, *J* = 4.6 Hz, 3H), 2.32 (s, 3H), 1.39 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 166.9, 162.3 (d, *J* = 246.5 Hz), 142.2, 139.4 (d, *J* = 7.9 Hz), 135.9, 132.1, 130.9 (d, *J* = 8.7 Hz), 130.8, 129.5, 128.6, 124.8, 115.4 (d, *J* = 23.6 Hz), 113.4 (d, *J* = 21.2 Hz), 56.5, 26.0, 24.9, 18.7. **LRMS** (ESI) $[M+H]^+$ found: 361.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{21}O_2N_2FNaS$: 383.1200, found: 383.1191.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-((3-nitrophenyl)thio)benzamide (4h): Compound **4h** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 33 mg, 43% yield. Mp: 202-204 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.46 (s, 1H), 8.03 (ddd, *J* = 8.1, 2.2, 1.0 Hz, 1H), 7.95 – 7.92 (m, 1H), 7.65 (ddd, *J* = 8.1, 1.6, 1.1 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.41 – 7.34 (m, 3H), 7.24 (q, *J* = 4.6 Hz, 1H), 2.56 (d, *J* = 4.6 Hz, 3H), 2.34 (s, 3H), 1.38 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.0, 166.7, 148.2, 142.6, 139.8, 136.18, 134.4, 132.4, 131.3, 130.4, 129.7, 127.6, 122.3, 121.1, 56.5, 26.0, 24.9, 18.8. **LRMS** (ESI) $[M+H]^+$ found: 388.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{21}O_4N_3NaS$: 410.1145, found: 410.1133.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(o-tolylthio)benzamide (4i):

Compound **4i** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 51 mg, 71% yield. Mp: 91-94 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.27 – 7.20 (m, 3H), 7.20 – 7.15 (m, 3H), 6.87 (d, *J* = 7.4 Hz, 1H), 2.57 (d, *J* = 4.7 Hz, 3H), 2.32 (s, 3H), 2.31 (s, 3H), 1.42 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 166.9, 140.1, 138.1, 135.5, 134.1, 131.7, 131.1, 130.5, 129.2, 129.1, 128.8, 127.6, 126.9, 56.5, 25.9, 24.9, 20.0, 18.7. **LRMS** (ESI) $[M+H]^+$ found: 357.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{20}H_{24}O_2N_2NaS$: 379.1451, found: 379.1441.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(pyridin-2-ylthio)benzamide (4j): Compound **4j** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 49 mg, 72% yield. Mp: 84-87 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.37 (d, *J* = 3.9 Hz, 1H), 8.26 (s, 1H), 7.64 (ddd, *J* = 10.8, 4.5 Hz, 1.4 Hz 1H), 7.50 – 7.44 (m, 1H), 7.43 – 7.37 (m, 2H), 7.24 (q, *J* = 4.4 Hz, 1H), 7.14 (dd, *J* = 6.9, 5.1 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 2.55 (d, *J* = 4.6 Hz, 3H), 2.32 (s, 3H), 1.31 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.0, 166.8, 160.1, 149.2, 143.4, 137.4, 136.1, 134.0, 131.6, 129.5, 125.9, 121.4, 120.4, 56.4, 26.0, 24.8, 18.8. **LRMS** (ESI) $[M+H]^+$ found: 344.0. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{18}H_{21}O_2N_3NaS$: 366.1247, found: 366.1238.

2-Methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)-6-(phenylselanyl)benzamide (4k): Compound **4k** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 45 mg, 58% yield. Mp: 107-109 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.49 (br, 2H), 7.32 (br, 4H), 7.27 -7.12 (m, 3H), 2.60 (d, *J* = 3.9 Hz, 3H), 2.31 (s, 3H), 1.44 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.1, 167.5, 141.2, 135.5, 132.9, 131.4, 130.8, 129.5, 129.3, 127.7, 127.6, 56.6, 25.9, 25.0, 19.0. **LRMS** (ESI) $[M+H]^+$ found: 390.9. **HRMS** (ESI) $[M+Na]^+$ calcd for $C_{19}H_{22}O_2N_2NaSe$: 413.0739, found: 413.0728.

2-((3-Methoxyphenyl)selanyl)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-

yl)benzamide (4l): Compound **4l** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 45 mg, 54% yield. Mp: 144-147 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 6.5, 2.1 Hz, 1H), 7.22 – 7.15 (m, 3H), 7.08 (s, 1H), 6.94 – 6.89 (m, 2H), 6.80 – 6.76 (m, 1H), 5.95 (s, 1H), 3.75 (s, 3H), 2.82 (d, *J* = 4.8 Hz, 3H), 2.37 (s, 3H), 1.52 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, $CDCl_3$) δ 174.5, 168.8, 160.4, 141.3, 136.3, 133.6, 132.9, 130.8, 130.6, 130.0, 126.2, 123.9, 117.3, 113.1, 58.3, 55.5, 26.5, 25.5, 19.5. **LRMS** (ESI) $[M+H]^+$ found: 420.9. **HRMS** (ESI) $[M-H]^-$ calcd for $C_{20}H_{23}O_3N_2Se$: 419.0879, found: 419.0833.

2-((4-Chlorophenyl)selanyl)-6-methyl-*N*-(2-methyl-1-(methylamino)-1-oxopropan-2-yl)benzamide (4m): Compound **4m** was prepared as described in general procedure for nickel catalyzed *ortho*-C-H thiolation of *N*-benzoyl α-amino derivatives. White solid, 36 mg, 42% yield. Mp: 86-89 °C. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 3.6 Hz, 1H), 7.26 -7.18 (m, 3H), 2.60 (d, *J* = 4.0 Hz, 3H), 2.32 (s, 3H), 1.43 (s, 6H). **^{13}C {^{1}H} NMR** (125 MHz, DMSO-d_6) δ 174.0, 167.5, 141.6, 135.6, 134.2, 132.4, 131.9, 130.0, 129.9, 129.44, 129.38, 126.9, 56.6, 26.0, 25.0, 19.0. **LRMS** (ESI) $[M+H]^+$ found: 424.9. **HRMS** (ESI) $[M-H]^-$ calcd for $C_{19}H_{20}O_2N_2ClSe$: 423.0384, found: 423.0386.

Author Information

Corresponding Author

E-mail: hliu@simm.ac.cn

Notes

The authors declare no competing financial interests.

Acknowledgements

F.G., W.Z., D.Z., S.L., J.W., and H.L. received funding from the National Natural Science Foundation

of China (91229204, 21632008, and 81620108027), the Major Project of Chinese National Programs for Fundamental Research and Development (2015CB910304), and National S&T Major Projects (2013ZX09507-001 and 2014ZX09507002-001).

Associated Content

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, LC/MS and HPLC experiments data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For selected papers, see: (a) Gershonov, E.; Granoth, R.; Tzehoval, E.; Gaoni, Y.; Fridkin, M. *J. Med. Chem.* **1996**, *39*, 4833-4843; (b) Kroona, H. B.; Peterson, N. L.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1991**, *34*, 1692-1699; (c) Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 473-476; (d) Kwak, S. Y.; Yang, J. K.; Kim, J. H.; Lee, Y. S. *Biopolymers* **2013**, *100*, 584-591; (e) Wang, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Products* **1995**, *58*, 93-99.

(2) Gutierrez, A.; Bernal, J.; Villacampa, M. D.; Cativiela, C.; Laguna, A.; Gimeno, M. C. *Inorg. Chem.* **2013**, *52*, 6473-6480.

(3) (a) Cacciola, J.; Fevig, J. M.; W. Stouten, P. F.; Alexander, R. S.; Knabb, R. M.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1253-1256; (b) Ling, Y.; Wang, X.; Wang, C.; Xu, C.; Zhang, W.; Zhang, Y.; Zhang, Y. *ChemMedChem* **2015**, *10*, 971-976; (c) Srivastava, P.; Schito, M.; Fattah, R. J.; Hara, T.; Hartman, T.; Buckheit, R. W. Jr.; Turpin, J. A.; Inman, J. K.; Appella, E. *Bioorg. Med. Chem.* **2004**, *12*, 6437-6450.

(4) For selected reviews, see: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596-1636; (b) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590-608; (c) Hartwig, J. F. *Acc. Chem. Res.*

2008, *41*, 1534-1544; (d) Kondo, T.; Mitsudo, Ta T. A. *Chem. Rev.* **2000**, *100*, 3205-3220; (e) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S.; Liu, X. *Chem. Soc. Rev.* **2015**, *44*, 291-314.

(5) For selected reviews, see: (a) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; (b) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740-4761; (c) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369-375; (d) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012**, *45*, 788-802; (e) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068-5083; (f) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744-5767.

(6) Castro, L. C. M.; Chatani, N. *Chem. – Eur. J.* **2014**, *20*, 4548-4553.

(7) (a) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J. Q.; *J. Am. Chem. Soc.* **2014**, *136*, 16940-16946; (b) Toba, T.; Hu, Y.; Tran, A. T.; Yu, J. Q. *Org. Lett.* **2015**, *17*, 5966-5969.

(8) Kim, J.; Sim, M.; Kim, N.; Hong, S. *Chem. Sci.* **2015**, *6*, 3611-3616.

(9) For select reviews, see: (a) Castro, L. C. M.; Chatani, N. *Chem. Lett.* **2015**, *44*, 410-421; (b) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299-309.

(10) For selected papers, see: (a) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308-5311; (b) Song, W.; Lackner, S.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 2477-2480; (c) Lin, C.; Li, D.; Wang, B.; Yao, J.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1328-1331; (d) Yan, S. Y.; Liu, Y. J.; Liu, B.; Liu, Y. H.; Shi, B. F. *Chem. Commun.* **2015**, *51*, 4069-4072; (e) Yang, K.; Wang, Y.; Chen, X.; Kadi, A. A.; Fun, H. K.; Sun, H.; Zhang, Y.; Lu, H.; *Chem. Commun.* **2015**, *51*, 3582-3585; (f) Ye, X.; Petersen, J. L.; Shi, X. *Chem. Commun.* **2015**, *51*, 7863-7866; (g) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340-1343; (h) Wang, X.; Qiu, R.; Yan, C.; Reddy, V. P.; Zhu, L.; Xu, X.; Yin, S. F. *Org. Lett.* **2015**, *17*, 1970-1973; (i) Yan, S. Y.; Liu, Y. J.; Liu, B.; Liu, Y. H.; Zhang, Z. Z.; Shi, B. F. *Chem. Commun.* **2015**, *51*, 7341-7344.