The Journal of Organic Chemistry

Article

Palladium-catalyzed ortho-alkoxylation of N-benzoyl #-amino acid derivatives at room temperature

Shuangjie Li, Wei Zhu, Feng Gao, Chunpu Li, Jiang Wang, and H. Liu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02257 • Publication Date (Web): 21 Nov 2016

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

Palladium-catalyzed *ortho*-alkoxylation of *N*-benzoyl *α*-amino acid derivatives at room temperature

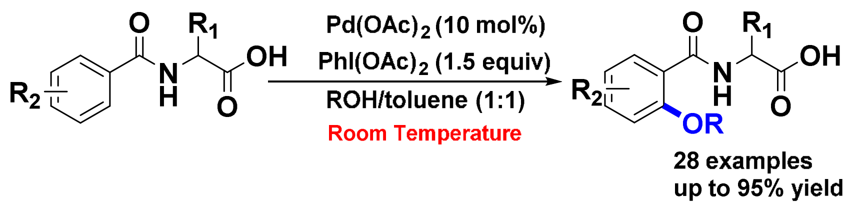
Shuangjie Li,[†] Wei Zhu,[‡] Feng Gao,[‡] Chunpu Li,[‡] Jiang Wang,[‡] and Hong Liu[*‡]

[†]School of Pharmacy, China Pharmaceutical University, Jiangsu, Nanjing 210009, P. R. China

[‡]Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China.

hliu@simm.ac.cn (Hong Liu)

Graphic Abstract



Abstract

An efficient palladium-catalyzed *ortho*-alkoxylation of *N*-benzoyl *α*-amino acid derivatives under room temperature has been explored. This novel transformation, using amino acids as directing groups, $Pd(OAc)_2$ as catalyst, alcohols as the alkoxylation reagents and $PhI(OAc)_2$ as the oxidant, showed wide generality, good functional tolerance, high mono-selectivity and regioselectivity.

Introduction

Functionalized amino acid derivatives representing as important class of privilege structures have been widely found in numerous biologically active compounds and natural products (Fig. 1).[1] Among them, *ortho*-alkoxyl substituted *N*-benzoyl *α*-amino acid derivatives serve as useful intermediates in drug discovery and medicinal chemistry.[2] The construction of such scaffolds is mainly achieved by Ullmann reaction, while the traditional methods often suffer from harsh reaction conditions, pre-functionalization of substrates and limited generality.[3] Thus, there remains the need to develop efficient and economical methodologies for elaborating amino acid derivatives under mild condition.

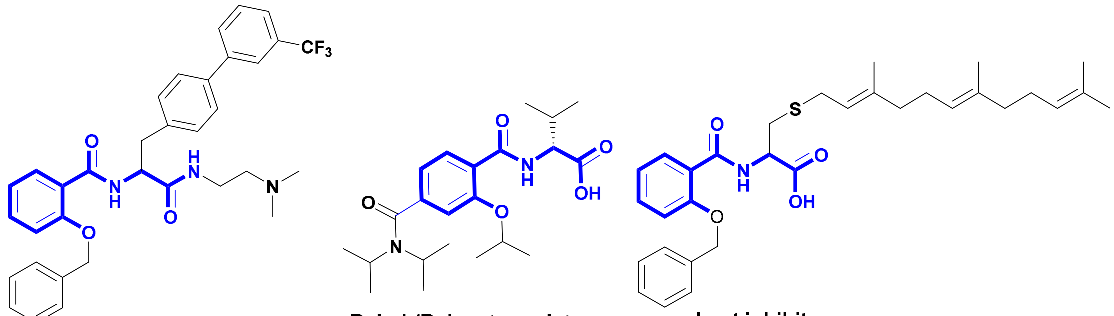
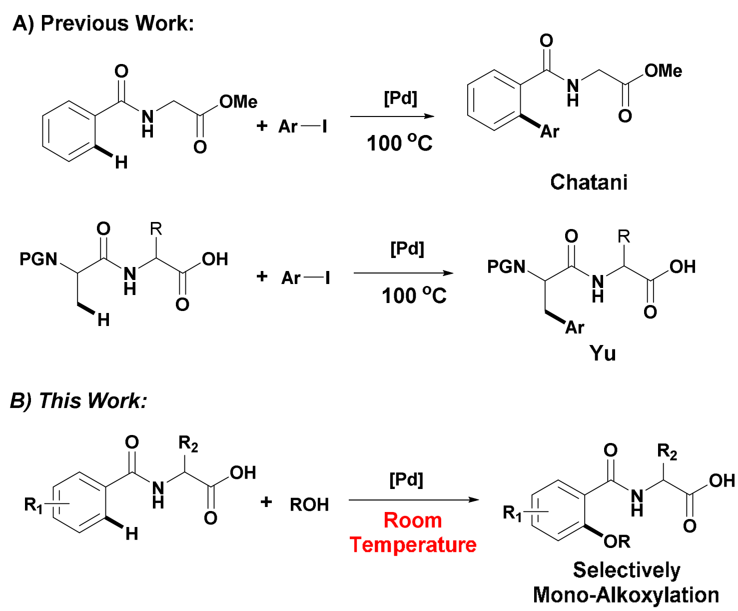


Figure 1. Bioactive *ortho*-alkoxyl substituted derivatives.

In past decades, selective C–H functionalization, assisted by directing-group has drawn considerable attention and emerged as a powerful tool to construct C-C or C-X bonds.[4] Very recently, environmentally friendly and inexpensive amino acid moieties have been employed as novel directing groups in C-H activation for the modification of amino acid derivatives (Scheme 1A).[5] The special structure of amino acid made itself as a feasible directing group without the necessary of being removed and the products are very useful building blocks for making bioactive molecules.

Scheme 1. Palladium-catalyzed C-H activation of amino acid derivatives.

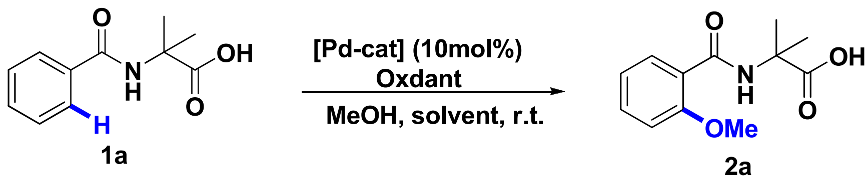


Despite the great progress of Pd-catalyzed direct *ortho*-alkoxylation of the C(sp^2)−H bonds has been achieved,[6] huge challenges still remain in the development of environmentally friendly and efficient transformation systems for the selective mono-alkoxylation of C−H bonds under mild conditions. Given the importance of *α*-amino acid derivatives, we herein report the palladium-catalyzed alkoxylation of *N*-benzoyl *α*-amino acid derivatives under room temperature (Scheme 1B).

Results and Discussion

To verify the hypothesis, we initiated our investigation of the direct *ortho*-methoxylation of *N*-benzoyl *α*-amino acid **1a**. After extensive attempts, 2-(2-methoxybenzamido)-2-methylpropanoic acid **2a** was afforded in 29% yield with $Pd(OAc)_2$ as catalyst and DMP as oxidant under room temperature (Table 1, entry 1). As shown in Table 1, various oxidants, palladium catalysts and solvents were screened for the best reaction condition. The oxidant had a remarkable impact on the reaction yield, and the $PhI(OAc)_2$ gave the best yield (Table 1, entry 4). The effect of different solvents on the transformation was subsequently investigated. Among them, the mixed solvent of toluene led to slightly increase in yields, while other mixed solvents resulted in decrease in yields (entries 5-9). Meanwhile, choosing toluene as co-solvent is due to solubility. The yield was slightly decreased with the presence of oxygen, which was consistent with earlier findings (entries 10−11).[7] Compared with $PdCl_2$, $Pd(OAc)_2$ was proved to be the better catalyst (entry 12).

Table 1. Optimization of reaction conditions[a]

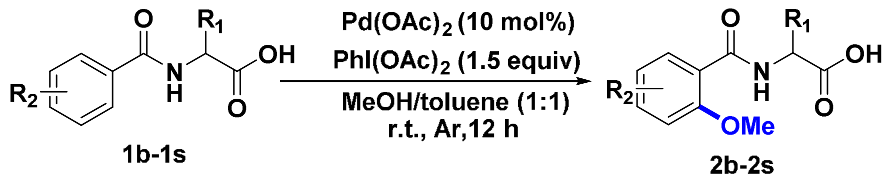


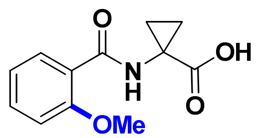
Entry	Pd-cat	Oxidant	Solvent	Yield (%)
1	$Pd(OAc)_2$	DMP	MeOH	29
2	$Pd(OAc)_2$	$NaIO_3$	MeOH	NR[b]
3	$Pd(OAc)_2$	$Na_2S_2O_8$	MeOH	NR[b]
4	$Pd(OAc)_2$	$PhI(OAc)_2$	MeOH	83
5	$Pd(OAc)_2$	$PhI(OAc)_2$	DCE/MeOH(1:1)	85
6	$Pd(OAc)_2$	$PhI(OAc)_2$	CH_3CN/MeOH(1:1)	78
7	$Pd(OAc)_2$	$PhI(OAc)_2$	DMF/MeOH(1:1)	54
8	$Pd(OAc)_2$	$PhI(OAc)_2$	THF/MeOH(1:1)	NR[b]
9	**$Pd(OAc)_2$**	**$PhI(OAc)_2$**	**PhMe/MeOH(1:1)**	**87**
10[c]	$Pd(OAc)_2$	$PhI(OAc)_2$	PhMe/MeOH(1:1)	76
11[d]	$Pd(OAc)_2$	$PhI(OAc)_2$	PhMe/MeOH(1:1)	78
12	$PdCl_2$	$PhI(OAc)_2$	PhMe/MeOH(1:1)	65

[a] Unless otherwise specified, all the reactions were carried out with 0.2 mmol of **1a**, 0.02 mmol of Pd-cat and 0.3 mmol of oxidant under argon atmosphere at room temperature for 12 h. All listed yields are isolated ones. [b]NR = no reaction. [c]The reaction were carried out under O_2 atmosphere. [d]The reaction were carried out under Air.

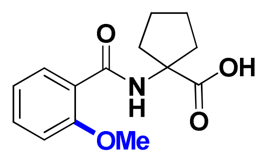
With the optimal condition in hands, the substrates scope of *N*-benzoyl *α*-amino acid derivatives was investigated (Table 2). Generally, various substituents both on the aromatic ring and *α*-amino acid moieties were well tolerated in this direct alkoxylation reaction, and afforded the corresponding mono-methoxyl products in moderate to high yields (Table 2).

Table 2. Scope of N-benzoyl α-amino acid derivatives[a]

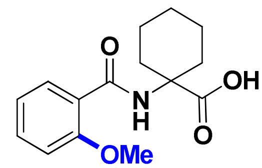




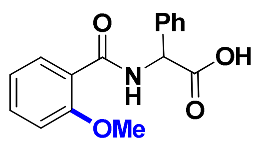
2b, 75%



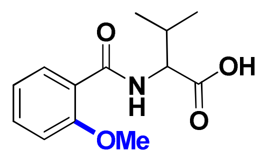
2c, 73%



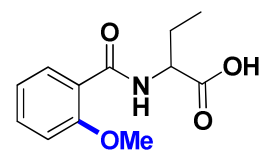
2d, 92%



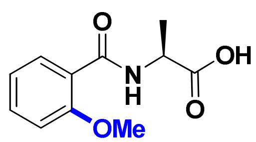
2e, 73%



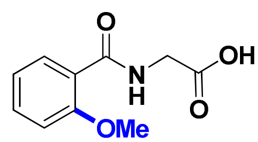
2f, 75%



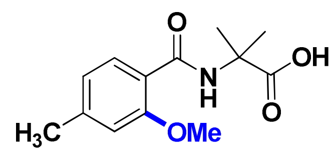
2g, 90%



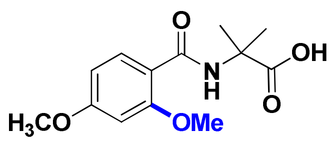
2h, 89% (ee% >99%)



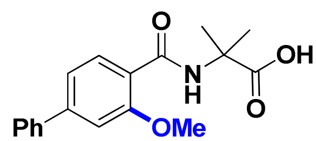
2i, 62%



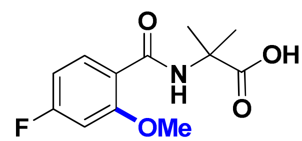
2j, 67%



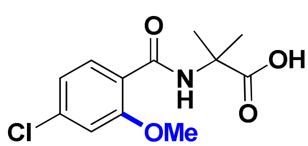
2k, 72%



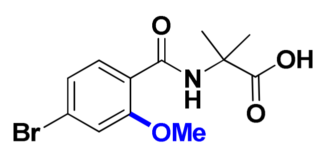
2l, 55%



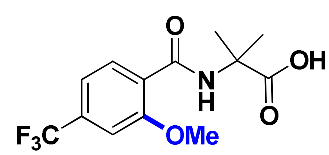
2m, 64%



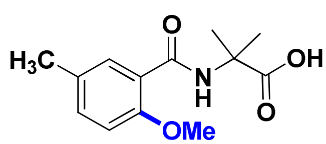
2n, 55%



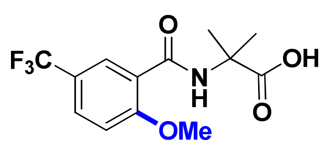
2o, 62%



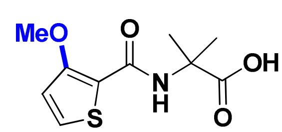
2p, 57%



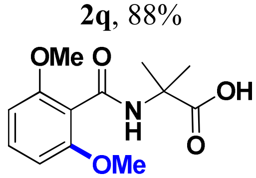
2q, 88%



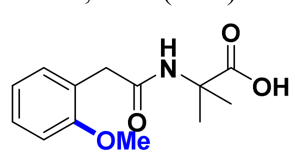
2r, 60% (90%)[b]



2s, 49%



NR[c]



NR[c]

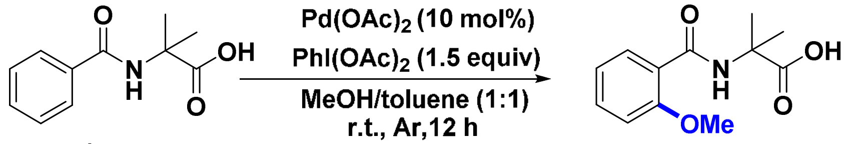
[a]Unless otherwise specified, all the reactions were carried out with 0.2 mmol of **1**, 0.02 mmol of $Pd(OAc)_2$, 0.3 mmol of $PhI(OAc)_2$, MeOH/toluene (1:1) as solvent

under argon atmosphere at room temperature for 12 h. All listed yields are isolated ones. [b]The reaction was performed at 80 ^{o}C.[c]NR = no reaction.

Cyclic amino acid derivatives worked well under standard conditions with high yields (**2b-2d**); *α*-mono-substituted amino acids derivatives proceeded smoothly with moderate to high yields (**2e-2h**), while glycine derivative gave slightly lower yield (**2i**). Notably, the chirality of the amino acids substrate was not influenced under this mild transformation condition (**2h**, *ee* > 99%), guaranteeing further applications.

The influence of different substituents at aromatic ring was evaluated. To our delight, both electron-rich and electron-poor amino acids derivatives were well tolerated without di-methoxyl products dectected. The protocol was found to be broadly applicable for this type of derivatives bearing electron-donating or withdrawing substituents on the phenyl ring (**2j-2l**). Moreover, halogens, such as F, Cl, Br, were well tolerated under the standard reaction conditions (**2m-2o**). The broad functional group tolerance highlights the potential utility of this reaction in the late-stage modification of complex molecules as well as in the total synthesis of natural products. The cleavage of C-H bonds in meta-substituted substrates occurred predominantly at less-hindered sites to give moderate to good yields and excellent regio-selectivity, irrespective of the electronic nature of the substituents (**2q** and **2r)**. The thiophene substrate also provided the desired products in moderate yields (**2s**). However, substrate 2-(2-methoxybenzamido)-2-methylpropanoic acid did not afford corresponding product. The alkoxylation reaction didn't proceed when amino acid is protected higher chain length analogues like phenyl acetyl. Importantly, we also carried it out on a gram scale without any additives to afford **2a** in 87% yield (Scheme 2).

Scheme 2. Gram-scale reaction.

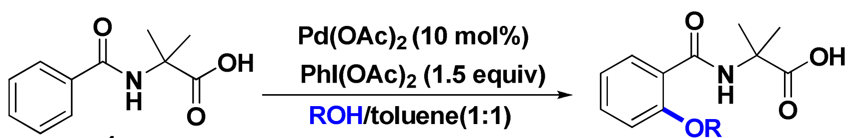


1a **2a**

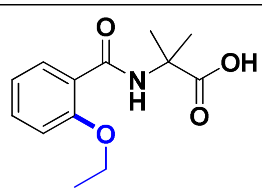
1g 0.99g (87%)

Next, we investigated a variety of linear and branched alcohols as coupling partners, which demonstrated wide generality and moderate to high yields. Generally, the primary alcohols, such as ethanol, propanol, 3-trifluoro-1-propanol and phenylethanol could be transformed into the corresponding ethers in excellent yields (**3a-3d**). The increased steric hindrance of benzyl alcohol and branched alcohols led to decrease in yields, while the corresponding products could be afforded in good yields under elevated temperature (**3e-3i**). Unfortunately, the *tert*-butoxy substituted product could not be achieved under these reaction conditions, which indicated the important influence of the steric effect.

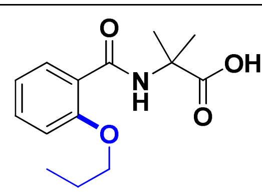
Table 3. Scope of various alcohols[a]



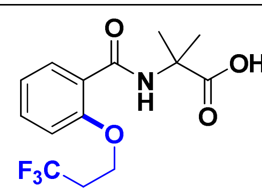
1a **3a-3i**



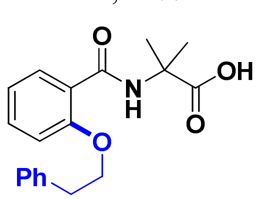
3a, 95%



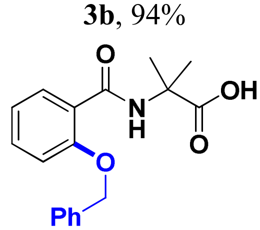
3b, 94%



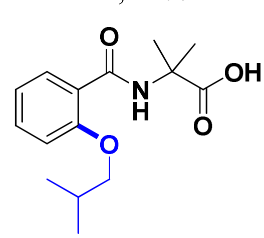
3c, 83%



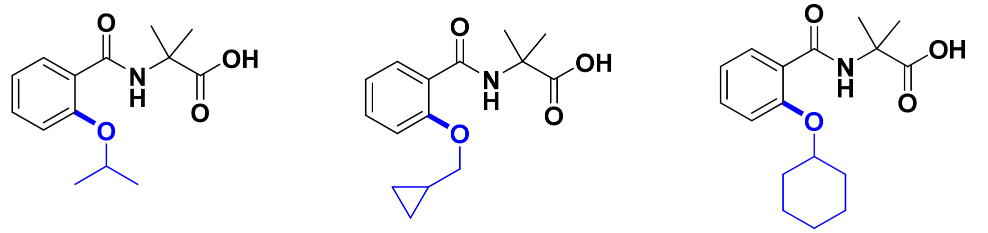
3d, 76%



3e, 46% (70%)[b]



3f, 72%

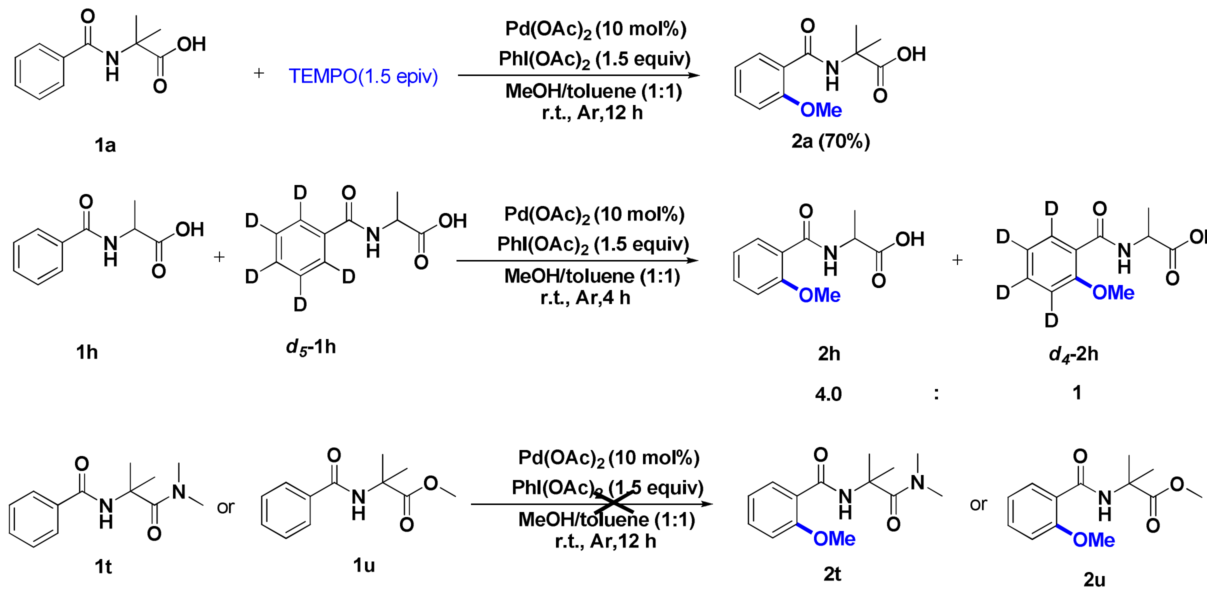


3g, 49%(82%)[b] **3h**, 35% (85%)[b] **3i**, 50%

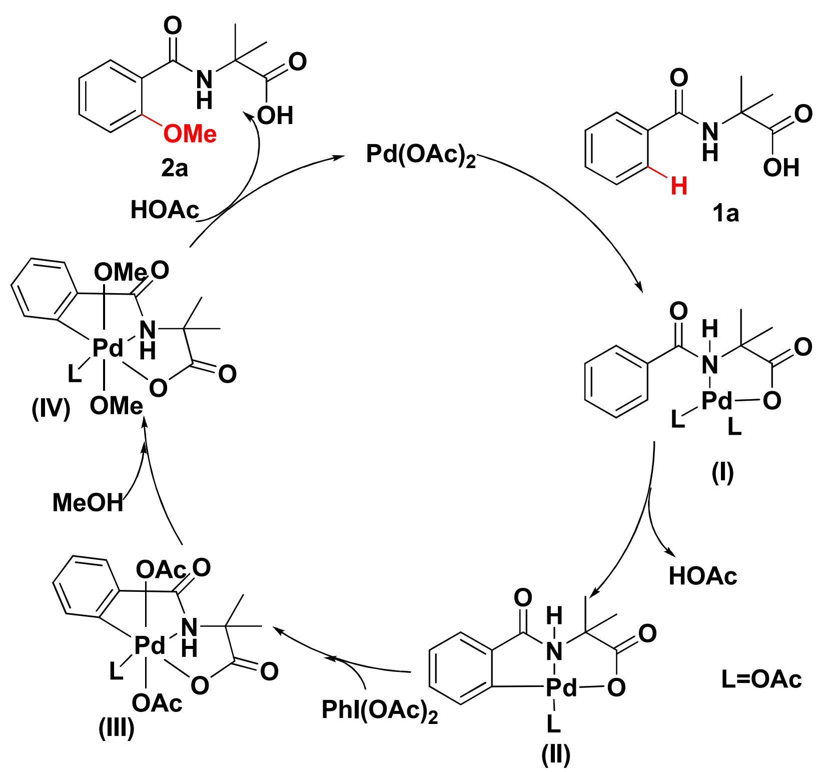
[a]Unless otherwise specified, all the reactions were carried out with 0.2 mmol of **1**, 0.02 mmol of $Pd(OAc)_2$, 0.3 mmol of $PhI(OAc)_2$, ROH/toluene (1:1) under argon atmosphere at room temperature for 12 h. All listed yields are isolated ones. [b]The reaction was performed at 80 °C.

To obtain more insight into the mechanism, some controlled experiments were performed. The addition of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) as a radical quencher slightly inhibited the reaction (Scheme 3, eq 1), suggesting that the reaction doesn't involve a radical pathway. As shown in Scheme 3, the KIE was observed to be 4.0 (Scheme 3, eq 2), indicating that the C−H bond cleavage at the *ortho*-position of *N*-benzoyl *α*-amino acid is most likely involved with the rate-limiting step. The carboxyl group of substrate was crucial to the reaction based on the fact that substrate **1t or 1u** was not transformed into corresponding products under the standard reaction conditions (Scheme 3, eq 3). On the basis of previous literatures,[6c, 7b, 8] a plausible mechanism was proposed in Scheme 4. First, the coordination of nitrogen atom and oxygen atom to the Pd Catalyst generates a palladium intermediate (**I**) followed by concerted metalation deprotonation (CMD) process to produce the palladacycle complexes (**II**). Cyclopalladated intermediate (**II**) is then oxidized to a high-valent Pd intermediate (**III**) by $PhI(OAc)_2$. In the presence of alcohol solvent, the OAc ligands of (**III**) could be exchanged to form intermediate (**IV**), which could undergo C−OR RE to give alkoxylated products.

Scheme 3. Control Experiments



Scheme 4. Plausible reaction mechanism.



Conclusion

In conclusion, we have successfully developed an efficient and environmentally friendly palladium-catalyzed alkoxylation of $C(sp^2)$−H bonds in α-amino acid derivatives under room temperature. This reaction features broad substrate scopes, good tolerance, high mono-selectivity and regioselectivity. This mild procedure 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 synthesis of substrates (1a-1s).

2-Amino-2-methylpropionic acid (2 g, 19.4 mmol) was dissolved in 1M NaOH aqueous solution (20 mL). The mixture was cooled to 0 °C, then benzoyl chloride (2.30 mL, 19.4 mmol) and 1M NaOH aqueous solution (20 mL) were added dropwise simultaneously. The resulting mixture was stirred for 5 hours at room temperature. Then 1M HCl (60 mL) was added to the reaction mixture and stirred for 10 minutes. The resulting solid was collected by filtration, washed with water and Et_2O. The desired product **1a** was obtained as a white solid (3.02 g, 72%). Compounds **1b-1s** were prepared in a similar manner with different yields (45%-70%).

General procedure for the alkoxylation of substrates

Substrate **1** (0.2 mmol), $PhI(OAc)_2$ (97 mg, 0.3 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), alcohol (1 mL) and toluene (1 mL) were added in a 25 mL tube under argon. The tube was sealed and the mixture was stirred at room temperature for 12 h. After completion of the reaction, the solution was concentrated by vacuum. The residue was purified by silica gel column using (DCM/MeOH/HAc=100:5:1) as eluent to give the corresponding pure products.

Determination of Intermolecular Kinetic Isotope Effect

Substrate benzoylalanine (**1h)** (0.2 mmol, 19 mg), (benzoyl-2,3,4,5,6-d_5)alanine (***d*$_5$-1h**) (0.2 mmol, 20 mg), $PhI(OAc)_2$ (97 mg, 0.3 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), methanol (1 mL) and toluene (1 mL) were added in a 25 mL tube under argon. The mixture was stirred at room temperature for 4 h, The solution was concentrated by vacuum. The residue was purified by silica gel column using（DCM/MeOH/HAc=100:5:1）as eluent to give the corresponding pure product. The ratio of **2h/ *d*$_4$-2h** was determined to be 8.00/2.00 (KIE = 4.0) by ^{1}H NMR spectroscopy.

Chiral HPLC analysis of products

Sample A [rac-2-benzamidopropanoic acid (were prepared under epimerization-free condition from rac-2-aminopropanoic acid)], Sample B [D-2-benzamidopropanoic acid (were prepared under epimerization-free condition from D-2-aminopropanoic acid), Sample C synthesized from Sample A (which is the product of direct C-H alkoxylation of rac-2-benzamidopropanoic acid under standard protocol)] and Sample D synthesized from Sample B (which is the product of direct C-H alkoxylation of D-2-benzamidopropanoic acid under standard protocol)] were separated by Chiral HPLC using a Chiralcel-IC column (25% *i*-PrOH and 0.5% CF_3COOH in hexanes, flow rate 0.3 mL/min, UV lamp 215 or 254 nm). In the HPLC profile of Sample A, the two peaks correspond to 1: 1 mixture of D-2-benzamidopropanoic acid (t_R = 17.3 min) and L-2-benzamidopropanoic acid (t_R = 20.1 min). In the HPLC profile of Sample B, the peak corresponds to D-2-benzamidopropanoic acid

(t_R = 17.3 min). In the HPLC profile of Sample C, peak corresponds to 1: 1 mixture of D-2-(2-methoxybenzamido)propanoicacid (t_R = 39.1 min) and L-2-(2-methoxybenzamido)propanoic acid (t_R = 48.6 min). In the HPLC profile of Sample D, peak corresponds to D-2-(2-methoxybenzamido)propanoic acid, which indicates that no diastereomer of product was observed.

Analytical Characterization Data of Products.

2-(2-methoxybenzamido)-2-methylpropanoic acid (1a): This compound is known.[9a] ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.46 (s, 1H), 7.82 (d, J = 7.2 Hz, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 1.61 (s, 6H).

1-benzamidocyclopropane-1-carboxylic acid (1b): This compound is known.[9a] Compound **1b** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.95 (s, 1H), 7.86 – 7.82 (m, 2H), 7.52 (d, J = 7.3 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 1.40 (dd, J = 7.7, 4.4 Hz, 2H), 1.09 (dd, J = 7.7, 4.4 Hz, 2H).

1-benzamidocyclopentane-1-carboxylic acid (1c): This compound is known.[9b] Compound **1c** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 1H), 8.50 (s, 1H), 7.86 – 7.81 (m, 2H), 7.55 – 7.50 (m, 1H), 7.46 (t, J = 7.5 Hz, 2H), 2.13 (m, 2H), 2.09 – 2.00 (m, 2H), 1.75 – 1.61 (m, 4H).

1-benzamidocyclohexane-1-carboxylic acid (1d): This compound is known.[9c] Compound **1d** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H), 8.26 (s, 1H), 7.87 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 6.8 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 2.16 (m, 2H), 1.83 – 1.70 (m, 2H), 1.57 (m, 5H), 1.32 (m, 1H).

2-benzamido-2-phenylacetic acid (1e): This compound is known.[9d] Compound **1e** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 9.06 (d, J = 7.4 Hz, 1H), 7.93 (d, J = 7.5 Hz, 2H), 7.50 (m, 5H), 7.37 (m, 3H), 5.61 (d, J = 7.4 Hz, 1H).

Benzoylvaline (1f): This compound is known.[9e] Compound **1f** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.42 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.47 (d, J = 7.3 Hz, 2H), 4.28 (dd, J = 8.0, 6.0 Hz, 1H), 2.19 (m, 1H), 0.97 (m, 6H).

2-benzamidobutanoic acid (1g): This compound is known.[9e] White Compound **1g** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 8.55 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.47(m, 2H), 4.30 (ddd, J = 9.2, 7.8, 5.1 Hz, 1H), 1.92 – 1.81 (m, 1H), 1.81 – 1.73 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H).

benzoyl-*L*-alanine (1h): This compound is known.[9e] White Compound **1h** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.53 (s, 1H), 8.65 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.3 Hz, 1H), 7.47 (m, 2H), 4.44 – 4.40 (m, 1H), 1.39 (d, J = 7.4 Hz, 3H).

(benzoyl-2,3,4,5,6-d_5)alanine (d_5-1h): ^{1}H NMR (400 MHz, MeOD-d_4) 1H NMR (400 MHz, MeOD-d_4) δ 4.62 (q, J = 7.3 Hz, 1H), 1.54 (d, J = 7.3 Hz, 3H).

benzoylglycine(1i): This compound is known.[9e] Compound **1i** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.90 – 7.79 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 7.4 Hz, 1H), 7.49 – 7.37 (m, 2H), 4.09 (s, 2H).

2-methyl-2-(4-methylbenzamido)propanoic acid (1j): This compound is known.[9f] Compound **1j** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (s, 1H), 8.36 (s, 1H), 7.77 (d, J = 8.1 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.35 (s, 3H), 1.45 (s, 6H).

2-(4-methoxybenzamido)-2-methylpropanoic acid (1k): This compound is known.[9f] Compound **1k** was prepared in a similar manner as described for compound **1a**. ^{1}H NMR (400 MHz, DMSO-d_6)

δ 12.12 (s, 1H), 8.28 (s, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 1.43 (s, 6H).

2-([1,1'-biphenyl]-4-carboxamido)-2-methylpropanoic acid (1l): Compound **1l** was prepared in a similar manner as described for compound **1a**. White solid, 2.3 g, 56% yield. Mp: 156-158 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.52 (s, 1H), 7.96 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 1H), 1.47 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 176.0, 165.9, 143.1, 139.6, 129.5, 128.6, 127.3, 126.8, 55.9, 25.5. LRMS (ESI) $[M-H]^+$ m/z found: 282.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{17}H_{16}NO_3$ 282.1136, found 282.1132.

2-(4-fluorobenzamido)-2-methylpropanoic acid (1m): Compound **1m** was prepared in a similar manner as described for compound **1a**. White solid, 1.6 g, 46% yield. Mp: 167-169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H), 8.49 (s, 1H), 7.93 (dd, *J* = 12.3, 5.3 Hz, 2H), 7.29 (dd, *J* = 12.3, 5.3 Hz, 2H), 1.45 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 176.0, 165.2, 165.1, 163.5, 131.2, 131.1, 130.7, 130.6, 115.5, 115.4, 55.9, 25.4. LRMS (ESI) $[M-H]^+$ m/z found: 224.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{11}H_{11}FNO_3$ 224.0728, found 224.0724.

2-(4-chlorobenzamido)-2-methylpropanoic acid (1n): Compound **1n** was prepared in a similar manner as described for compound **1a**. White solid, 2.5 g, 56% yield. Mp: 185-187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 2H, 7.53 (d, *J* = 8.5 Hz, 2H), 1.45 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 175.96, 165.31, 136.54, 133.41, 129.90, 128.71, 56.00, 25.40. LRMS (ESI) $[M-H]^+$ m/z found: 240.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{11}H_{11}ClNO_3$ 240.0433, found 240.0429.

2-(4-bromobenzamido)-2-methylpropanoic acid (1o): Compound **1o** was prepared in a similar manner as described for compound **1a**. White solid, 1.3 g, 55% yield. Mp: 162-165 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.55 (s, 1H), 7.80 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.68(dd, *J* = 8.8, 2.0 Hz, 2H), 1.45 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 175.9, 165.3, 133.7, 131.6, 130.1, 125.4, 55.9, 25.4. LRMS (ESI) $[M-H]^+$ m/z found: 283.9. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{11}H_{11}BrNO_3$ 283.9928, found 283.9924.

2-methyl-2-(4-(trifluoromethyl)benzamido)propanoic acid (1p): Compound **1p** was prepared in a similar manner as described for compound **1a**. White solid, 3.1 g, 60% yield. Mp: 134-136 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.73 (s, 1H), 8.05 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.2 Hz, 2H), 1.47 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 175.8, 165.2, 138.5, 131.6, 131.4, 128.8, 125.7, 125.6, 125.3, 123.5, 56.1, 25.3. LRMS (ESI) $[M-H]^+$ m/z found: 274.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{11}F_3NO_3$ 274.0697, found 274.0690.

2-methyl-2-(3-methylbenzamido)propanoic acid (1q): Compound **1q** was prepared in a similar manner as described for compound **1a**. White solid, 2.4 g, 44% yield. Mp: 165-167 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.67 (s, 1H), 7.62 (d, J = 6.9 Hz, 1H), 7.41 – 7.32 (m, 2H), 2.43 (s, 3H), 1.62 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 176.1, 166.1, 141.5, 131.9, 129.1, 127.9, 55.8, 25.5, 21.4. LRMS (ESI) $[M-H]^+$ m/z found: 220.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{14}NO_3$ 220.0979, found 220.0975.

2-methyl-2-(3-(trifluoromethyl)benzamido)propanoic acid (1r): Compound **1r** was prepared in a similar manner as described for compound **1a**. White solid, 2.1 g, 34% yield. Mp: 145-147 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.71 (s, 1H), 8.11 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.64 (t, J = 7.8 Hz, 1H), 1.57 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, DMSO-d_6) δ 175.8, 164.8, 135.4, 132.1, 130.0, 129.5, 129.3, 128.3, 125.4, 124.5, 124.4, 123.5, 56.1, 25.3. LRMS (ESI) $[M-H]^+$ m/z found: 274.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{11}F_3NO_3$ 274.0697, found 274.0693.

2-methyl-2-(thiophene-2-carboxamido)propanoic acid (1s): Compound **1s** was prepared in a similar manner as described for compound **1a**. White solid, 2.3 g, 56% yield. Mp: 134-136 °C. ^{1}H

NMR (400 MHz, MeOD-d_4) δ 8.40 (s, 1H), 7.76 (d, J = 3.7 Hz, 1H), 7.64 (d, J = 5.0 Hz, 1H), 7.12 (dd, J = 4.9, 3.8 Hz, 1H), 1.58 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 175.9, 161.1, 140.3, 131.3, 129.0, 128.3, 55.9, 25.5. LRMS (ESI) $[M-H]^+$ m/z found: 212.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_9H_{10}NO_3S$ 212.0387, found 212.0381.

2-(2-methoxybenzamido)-2-methylpropanoic acid (2a): This compound is known.[9g] White solid, 41 mg, 87% yield. Mp: 142-144 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.99 (s, 1H), 7.91 (dd, J = 7.8, 1.7 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.14 (dd, J = 8.3, 1.7 Hz, 1H), 7.04 (t, J = 8.1 Hz, 1H), 3.99 (s, 3H), 1.63 (s, 6H). $^{13}C\{^1H\}$ NMR (125 MHz, MeOD-d_4) δ 178.5, 167.3, 159.7, 134.8, 132.5, 123.3, 122.5, 113.5, 58.2, 57.1, 25.6. LRMS (ESI) $[M-H]^+$ m/z found: 236.0. LRMS (ESI) $[M-H]^+$ m/z found: 236.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{14}NO_4$ 236.0923, found 236.0919.

1-(2-methoxybenzamido)cyclopropane-1-carboxylic acid (2b); Compound **2b** was prepared in a similar manner as described for compound **2a.** White solid, 35 mg, 75% yield. Mp: 108-110 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 7.93 – 7.82 (m, 3H), 7.48 (dd, J = 8.8, 2.2 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.04 (t, J = 7.5 Hz, 1H), 3.95 (s, 3H), 1.61 – 1.54 (m, 2H), 1.21 – 1.26 (m, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, MeOD-d_4) δ 169.8, 159.7, 134.7, 132.6, 123.5, 122.3, 113.4, 57.0, 18.4. LRMS (ESI) $[M-H]^+$ m/z found: 234.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{12}NO_4$ 234.0766, found 234.0760.

1-(2-methoxybenzamido)cyclopentane-1-carboxylic acid (2c): Compound **2c** was prepared in a similar manner as described for compound **2a.** White solid, 38 mg, 73% yield. Mp: 106-108 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 7.87 (dd, J = 7.7, 1.6 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 3.98 (s, 3H), 2.25 – 2.34 (m, 2H), 2.14 – 2.07 (m, 2H), 1.80 – 1.89 (m, 4H). $^{13}C\{^1H\}$ NMR (125 MHz, MeOD-d_4) δ 178.3, 167.9, 159.6, 134.7, 132.43, 123.4, 122.5, 113.5, 67.8, 57.1, 38.7, 26.2. LRMS (ESI) $[M-H]^+$ m/z found: 262.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{14}H_{16}NO_4$ 262.1079, found 262.1073.

1-(2-methoxybenzamido)cyclohexane-1-carboxylic acid (2d): This compound is known.[9d] Compound **2d** was prepared in a similar manner as described for compound **2a.** White solid, 51 mg, 92% yield. Mp: 103-105 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.50 (s, 1H), 7.93 – 7.78 (m, 1H), 7.50 (ddd, J = 11.0, 8.9, 2.3 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 4.02 (s, 3H), 2.13 – 2.24 (m, 2H), 1.81 – 1.90 (m, 2H), 1.64 – 1.76 (m, 4H), 1.47 – 1.61 (m, 2H). ^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 182.3, 171.2, 163.6, 138.8, 136.5, 126.5, 119.3, 117.5, 64.5, 61.2, 37.7, 30.8, 27.1. LRMS (ESI) [M-H]$^+$ m/z found: 276.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{15}H_{18}NO_4$ 276.1236, found 276.1228.

2-(2-methoxybenzamido)-2-phenylacetic acid (2e): Compound **2e** was prepared in a similar manner as described for compound **2a.** White solid, 42 mg, 73% yield. Mp: 173-175 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.97 (dd, J = 7.8, 1.6 Hz, 1H), 7.52 – 7.55 (m, 1H), 7.49 – 7.51 (m, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.30 (d, J = 7.2 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 5.53 (s, 1H), 4.06 (s, 3H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 172.4, 164.6, 157.6, 137.7, 132.7, 130.4, 127.7, 127.0, 126.3, 120.2, 120.0, 111.2, 57.4, 54.0. LRMS (ESI) [M-H]$^+$ m/z found: 284.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{16}H_{14}NO_4$ 284.0923, found 284.0915.

(2-methoxybenzoyl)valine (2f): Compound **2f** was prepared in a similar manner as described for compound **2a.** White solid, 37 mg, 75% yield. Mp: 133-135 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.00 – 7.89 (m, 1H), 7.56 – 7.48 (m, 1H), 7.18 (d, J = 8.4 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.59 (d, J = 4.6 Hz, 1H), 4.02 (s, 3H), 2.38 – 2.23 (m, 1H), 1.03 (dd, J = 6.8, 1.4 Hz, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 175.6, 167.9, 159.8, 135.0, 132.9, 122.7, 122.6, 113.6, 59.9, 57.3, 32.8, 20.1, 18.7. LRMS (ESI) [M-H]$^+$ m/z found: 250.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{13}H_{16}NO_4$ 250.1079 found 250.1075.

2-(2-methoxybenzamido)butanoic acid (2g): Compound **2g** was prepared in a similar manner as described for compound **2a.** White solid, 43 mg, 90% yield. Mp: 126-128 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.00 – 7.88 (m, 1H), 7.52 (ddd, J = 8.9, 8.0, 2.3 Hz, 1H), 7.19 (dd, J = 8.6, 3.2 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 4.67 – 4.51 (m, 1H), 4.02 (s, 3H), 2.09 – 1.97 (m, 1H), 1.83 – 1.94(m, 1H), 1.00 (td, J = 7.4, 3.1 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (125 MHz, MeOD-d_4) δ 176.0, 167.8, 159.8, 135.0, 132.7, 127.6, 122.5, 113.6, 57.2, 55.9, 26.7, 10.3. LRMS (ESI) $[M-H]^+$ m/z found: 236.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{14}NO_4$ 236.0923, found 236.0924.

(2-methoxybenzoyl)-L-alanine (2h): Compound **2h** was prepared in a similar manner as described for compound **2a.** White solid, 40 mg, 89% yield. Mp: 120-122 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.00 – 7.88 (m, 1H), 7.51 (ddd, J = 10.2, 8.7, 2.3 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.68 – 4.52 (m, 1H), 4.01 (d, J = 1.7 Hz, 3H), 1.52 (d, J = 7.1 Hz, 3H). $^{13}C\ \{^1H\}$ NMR (125 MHz, MeOD-d_4) δ 167.6, 159.9, 135.0, 132.7, 122.7, 122.5, 113.5, 57.1, 19.1. LRMS (ESI) $[M-H]^+$ m/z found: 222.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{11}H_{12}NO_4$ 222.0766, found 222.0760.

(2-methoxybenzoyl)glycine (2i): This compound is known.[9i] Compound **2i** was prepared in a similar manner as described for compound **2a.** White solid, 26 mg, 62% yield. Mp: 117-119 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.00 (dd, J = 7.8, 1.8 Hz, 1H), 7.51 (ddd, J = 8.4, 7.3, 1.9 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 4.14 (s, 2H), 3.99 (s, 3H). $^{13}C\ \{^1H\}$ NMR (101 MHz, MeOD-d_4) δ 173.6, 168.3, 159.9, 135.0, 132.8, 122.4, 113.4, 57.0, 43.1. LRMS (ESI) $[M-H]^+$ m/z found: 208.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{10}H_{10}NO_4$ 208.0610, found 208.0607.

2-(2-methoxy-4-methylbenzamido)-2-methylpropanoic acid (2j): Compound **2j** was prepared in a similar manner as described for compound **2a.** White solid, 34 mg, 67% yield. Mp: 98-100 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.90 (s, 1H), 7.84 (d, J = 7.9 Hz, 1H), 6.98 (s, 1H), 6.89 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 2.40 (s, 3H), 1.65 (s, 6H). $^{13}C\ \{^1H\}$ NMR (150 MHz, MeOD-d_4) δ 165.3, 157.8, 144.1, 130.7, 121.4, 118.5, 114.4, 112.2, 61.2, 55.1, 23.7, 20.3. LRMS (ESI) $[M-H]^+$ m/z found: 250.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1029.

2-(2,4-dimethoxybenzamido)-2-methylpropanoic acid (2k): Compound **2k** was prepared in a similar manner as described for compound **2a.** White solid, 38 mg, 72% yield. Mp: 112-114 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.91 (d, J = 8.9, 1H), 6.63 (m, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 1.64 (s, 6H).^{13}C {^{1}H} NMR (100 MHz, MeOD-d_4) δ 178.6, 166.9, 165.9, 161.2, 134.3, 115.6, 107.3, 99.9, 57.12, 56.5, 25.7. LRMS (ESI) [M-H]$^+$ m/z found: 266.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{13}H_{16}NO_5$ 266.1028, found 266.1024.

2-(3-methoxy-[1,1'-biphenyl]-4-carboxamido)-2-methylpropanoic acid (2l): Compound **2l** was prepared in a similar manner as described for compound **2a.** White solid, 34 mg, 55% yield. Mp: 156-158 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 9.01 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.68 (dd, J = 8.3, 1.3 Hz, 2H), 7.48 – 7.44 (m, 2H), 7.39 (d, J = 7.4 Hz, 1H), 7.34 (d, J = 1.5 Hz, 1H), 7.32 (dd, J = 8.1, 1.6 Hz, 1H), 4.08 (s, 3H), 1.66 (s, 6H).^{13}C {^{1}H} NMR (100 MHz, MeOD-d_4) δ 166.9, 160.07, 148.0, 141.7, 133.2, 130.5, 129.7, 128.7, 122.1, 122.0, 121.0, 111.9, 58.5, 57.2, 25.6. LRMS (ESI) [M-H]$^+$ m/z found: 312.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{18}H_{18}NO_4$ 312.1236, found 312.1234.

2-(4-fluoro-2-methoxybenzamido)-2-methylpropanoic acid (2m): Compound **2m** was prepared in a similar manner as described for compound **2a.** White solid, 33 mg, 64% yield. Mp: 86-88 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.81 (s, 1H), 7.97 (dd, J = 8.6, 7.1 Hz, 1H), 6.97 (dd, J = 11.0, 2.3 Hz, 1H), 6.82 (td, J = 8.3, 2.3 Hz, 1H), 4.02 (s, 3H), 1.65 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 174.7, 163.5, 157.3, 130.6, 115.9, 105.1, 97.5, 54.3, 53.6, 21.6. LRMS (ESI) [M-H]$^+$ m/z found: 254.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{12}H_{13}NO_4F$ 254.0829, found 254.0829.

2-(4-chloro-2-methoxybenzamido)-2-methylpropanoic acid (2n): Compound **2n** was prepared in a similar manner as described for compound **2a.** White solid, 30 mg, 55% yield. Mp: 112-114 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.91 (s, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.09 (dd, J = 8.4, 1.8 Hz, 1H), 4.03 (s, 3H), 1.65 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 165.0, 159.0, 138.9, 132.6, 121.4, 121.3, 112.9, 56.4, 24.3. LRMS (ESI) $[M-H]^+$ m/z found: 270.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{13}NO_4Cl$ 270.0533, found 270.0531.

2-(4-bromo-2-methoxybenzamido)-2-methylpropanoic acid (2o): Compound **2o** was prepared in a similar manner as described for compound **2a.** White solid, 39 mg, 62% yield. Mp: 116-118 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.90 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.33 (s, 1H), 7.23 (dd, J = 8.3, 1.4 Hz, 1H), 4.02 (s, 3H), 1.65 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, MeOD-d_4) δ 166.3, 160.0, 133.9, 128.3, 125.7, 122.8, 117.0, 58.6, 57.6, 25.5. LRMS (ESI) $[M-H]^+$ m/z found: 314.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{12}H_{13}BrNO_4$ 314.0028, found 314.0019, 316.003.

2-(2-methoxy-4-(trifluoromethyl)benzamido)-2-methylpropanoic acid (2p): Compound **2p** was prepared in a similar manner as described for compound **2a.** White solid, 35 mg, 57% yield. Mp: 160-162 °C.^{1}H NMR (400 MHz, MeOD-d_4) δ 8.99 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.37 (d, J = 8.3 Hz, 1H), 4.07 (s, 3H), 1.66 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 177.7, 164.9, 158.4, 134.52, 132.0, 126.6, 124.2, 117.7, 109.23,57.5, 56.4, 24.3. LRMS (ESI) $[M-H]^+$ m/z found: 304.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{13}H_{13}NO_4F_3$ 304.0797, found 304.0793.

2-(2-methoxy-5-methylbenzamido)-2-methylpropanoic acid (2q): Compound **2q** was prepared in a similar manner as described for compound **2a.** White solid, 44 mg, 88% yield. Mp: 142-144 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.93 (s, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 1.65 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 178.8, 167.31, 157.6, 135.1, 132.7, 131.9, 122.8, 113.5, 58.3, 57.1, 25.6, 20.9. LRMS (ESI) $[M-H]^+$ m/z found: 250.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1074.

2-(2-methoxy-5-(trifluoromethyl)benzamido)-2-methylpropanoic acid (2r): Compound **2r** was prepared in a similar manner as described for compound **2a.** White solid, 37 mg, 60% yield. Mp: 177-179 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.19 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.7, 2.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 4.09 (s, 3H), 1.66 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ

178.6, 165.8, 162.0, 131.4, 129.4, 126.1, 124.4, 124.4, 114.2, 58.5, 57.6, 25.5. LRMS (ESI) $[M-H]^+$ m/z found: 304.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{13}H_{13}NO_4F_3$ 304.0797, found 304.0790.

2-(3-methoxythiophene-2-carboxamido)-2-methylpropanoic acid (2s): Compound **2s** was prepared in a similar manner as described for compound **2a.** White solid, 24 mg, 49% yield. Mp: 137-139 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.13 (s, 2H), 7.61 (d, J = 5.5 Hz, 1H), 7.08 (d, J = 5.5 Hz, 1H), 4.08 (s, 3H), 1.65 (s, 6H). ^{13}C {^1H} NMR (125 MHz, MeOD-d_4) δ 178.5, 163.6, 159.4, 131.1, 117.6, 117.2, 60.3, 58.1, 25.7. LRMS (ESI) $[M-H]^+$ m/z found: 242.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{10}H_{12}NO_4S$ 242.0487, found 242.0482.

2-(2-ethoxybenzamido)-2-methylpropanoic acid(3a): Compound **3a** was prepared in a similar manner as described for compound **2a.** White solid, 49 mg, 95% yield. Mp: 137-139 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 9.02 (s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.5 Hz 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.6 Hz, 1H), 4.26 (q, J = 6.9 Hz, 2H), 1.66 (s, 6H), 1.56 (t, J = 7.0 Hz, 3H).^{13}C {^1H} NMR (125 MHz, MeOD-d_4) δ 167.2, 159.1, 134.7, 132.5, 123.2, 122.4, 114.40, 66.6, 25.7, 15.6. LRMS (ESI) $[M-H]^+$ m/z found: 250.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{13}H_{16}NO_4$ 250.1079, found 250.1078.

2-methyl-2-(2-propoxybenzamido)propanoic acid (3b): Compound **3b** was prepared in a similar manner as described for compound **2a.** White solid, 50 mg, 94% yield. Mp: 167-169 °C. ^1H NMR (400 MHz, MeOD-d_4) δ 8.86 (s, 1H), 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.55 – 7.33 (m, 1H), 7.12 (d, J = 8.3 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 4.13 (t, J = 6.4 Hz, 2H), 1.99 – 1.88 (m, 2H), 1.63 (s, 6H), 1.10 (t, J = 7.4 Hz, 3H).^{13}C {^1H} NMR (125 MHz, MeOD-d_4) δ 178.5, 167.3, 159.1, 134.8, 132.5, 123.2, 122.3, 114.3, 72.5, 58.2, 25.9, 24.0, 11.6. LRMS (ESI) $[M-H]^+$ m/z found: 264.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1240.

2-methyl-2-(2-(3,3,3-trifluoropropoxy)benzamido)propanoic acid (3c): Compound **3c** was prepared in a similar manner as described for compound **2a.** White solid, 53 mg, 83% yield. Mp:

175-177 °C.^{1}H NMR (400 MHz, MeOD-d_4) δ 8.74 (s, 1H), 7.91 (dd, J = 7.8, 1.4 Hz, 1H), 7.56 – 7.43 (m, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 4.41 (t, J = 5.9 Hz, 2H), 2.96 – 2.80 (m, 1H), 1.64 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 178.8, 167.0, 158.1, 134.7, 132.7, 123.9, 123.0, 114.0, 63.9, 58.5, 34.9, 25.4. LRMS (ESI) [M-H]$^+$ m/z found: 318.0. HRMS (ESI-TOF) [M-H]+ m/z calcd for $C_{14}H_{15}NO_4F_3$ 318.0953, found 318.0945.

2-methyl-2-(2-phenethoxybenzamido)propanoic acid (3d): Compound **3d** was prepared in a similar manner as described for compound **2a.** White solid, 50 mg, 76% yield. Mp: 183-185 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.73 (s, 1H), 7.93 (d, J = 7.7 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.21 (m, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 4.48 (t, J = 6.7 Hz, 2H), 3.27 (t, J = 6.7 Hz, 2H), 1.51 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 167.1, 158.7, 139.7, 134.7, 132.7, 130.3, 130.3, 130.1, 128.1, 123.4, 122.5, 114.4, 70.9, 36.5, 25.6. LRMS (ESI) [M-H]$^+$ m/z found: 326.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for C_{19}H20NO_4 326.1392, found 326.1393.

2-(2-(benzyloxy)benzamido)-2-methylpropanoic acid (3e): Compound **3e** was prepared in a similar manner as described for compound **2a.** White solid, 29 mg, 46% yield. Mp: 178-180 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.67 (s, 1H), 7.95 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 7.1 Hz, 2H), 7.47 – 7.54 (m, 1H), 7.40 – 7.49 (m, 2H), 7.38 – 7.44 (m, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 5.27 (s, 2H), 1.38 (s, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 167.2, 158.9, 137.9, 134.7, 132.6, 130.3, 130.1, 130.1, 123.6, 122.7, 114.9, 73.0, 25.8. LRMS (ESI) [M-H]$^+$ m/z found: 312.0. HRMS (ESI-TOF) [M-H]$^+$ m/z calcd for $C_{18}H_{18}NO_4$ 312.1236, found 312.1230.

2-(2-isobutoxybenzamido)-2-methylpropanoic acid (3f): Compound **3f** was prepared in a similar manner as described for compound **2a.** White solid, 40 mg, 72% yield. Mp: 143-145 °C.^{1}H NMR (400 MHz, MeOD-d_4) δ 8.77 (s, 1H), 7.92 (dd, J = 7.8, 1.7 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 3.97 (d, J = 6.5 Hz, 2H), 2.18 – 2.30 (m, 1H), 1.65 (s, 6H), 1.11 (d, J = 6.1 Hz, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 178.4, 167.5, 159.1, 134.7, 132.5, 123.3, 122.3, 114.2, 77.2, 58.1, 29.9, 25.9, 20.2. LRMS (ESI) $[M-H]^+$ m/z found: 278.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{15}H_{20}NO_4$ 278.1392, found 278.1385.

2-(2-isopropoxybenzamido)-2-methylpropanoic acid (3g): Compound **3g** was prepared in a similar manner as described for compound **2a.** White solid, 26 mg, 49% yield. Mp: 137-139 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 9.00 (s, 1H), 7.94 (dd, J = 7.8, 1.7 Hz, 1H), 7.51 – 7.38 (m, 1H), 7.15 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 4.82 – 4.91 (m, 1H), 1.64 (s, 6H), 1.44 (d, J = 6.1 Hz, 6H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 176.5, 165.5, 165.4, 156.1, 132.7, 130.8, 122.3, 120.6, 114.3, 72.1, 23.8, 20.9. LRMS (ESI) $[M-H]^+$ m/z found: 264.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{14}H_{18}NO_4$ 264.1236, found 264.1229.

2-(2-(cyclopropylmethoxy)benzamido)-2-methylpropanoic acid (3h): Compound **3h** was prepared in a similar manner as described for compound **2a.** White solid, 19 mg, 35% yield. Mp: 146-148 °C.^{1}H NMR (400 MHz, MeOD-d_4) δ 9.05 (s, 2H), 7.97 (dd, J = 7.8, 1.7 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.13 – 6.99 (m, 2H), 4.03 (d, J = 7.2 Hz, 2H), 1.65 (s, 6H), 1.37 – 1.47 (m, 1H), 0.73 – 0.66 (m, 2H), 0.43 – 0.56 (m, 2H).^{13}C {^{1}H} NMR (125 MHz, MeOD-d_4) δ 178.5, 167.2, 159.2, 134.9, 132.6, 122.9, 122.4, 114.5, 75.8, 58.0, 26.0, 11.5, 4.3. LRMS (ESI) $[M-H]^+$ m/z found: 276.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{15}H_{18}NO_4$ 276.1236, found 276.1231.

2-(2-(cyclohexyloxy)benzamido)-2-methylpropanoic acid (3i): Compound **3i** was prepared in a similar manner as described for compound **2a.** White solid, 31 mg, 50% yield. Mp: 150-152 °C. ^{1}H NMR (400 MHz, MeOD-d_4) δ 8.96 (s, 1H), 7.94 – 7.88 (dd, J = 8.4, 1.2, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 4.59 – 4.49 (m, 1H), 2.04 – 2.14(m, 2H), 1.79 – 1.89 (m, 2H), 1.62-1.68 (m, 8H), 1.50 – 1.43 (m, 2H), 1.42 – 1.32 (m, 2H).^{13}C {^{1}H} NMR (100 MHz, MeOD-d_4) δ 167.5, 157.7, 134.4, 132.7, 124.6, 122.3, 116.0, 79.1, 33.4, 27.0, 25.8, 25.4.

LRMS (ESI) $[M-H]^+$ m/z found: 304.0. HRMS (ESI-TOF) $[M-H]^+$ m/z calcd for $C_{17}H_{22}NO_4$ 304.1549, found 304.1545.

Author Information

Corresponding Author

E-mail: hliu@simm.ac.cn

Notes

The authors declare no competing financial interests.

Acknowledgements

S.L., W.Z., F.G., J.W., and H.L. received funding from the National Natural Science Foundation of China (81220108025, 21472209, and 91229204), the Major Project of Chinese National Programs for Fundamental Research and Development (2015CB910304), the National Basic Research Program of China (2012CB518005), and National S&T Major Projects (2013ZX09507-001, and 2014ZX09507002-001).

Associated Content

Supporting Information

Copies of ^{1}H and ^{13}C {^{1}H} NMR spectra 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) Majmudar, J. D.; Hodges-Loaiza, H. B.; Hahne, K.; Donelson, J. L.; Song, J.; Shrestha, L.; Harrison, M. L.; Hrycyna, C. A.; Gibbs, R. A. *Bioorg. Med. Chem.* **2012,** *20*, 283-295. (b) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011,** *54*, 3451-3479. (c) Takeuchi, Y.; Ozaki, S.; Satoh, M.; Mimura, K.; Hara, S.; Abe, H.; Nishioka, H.; Harayama, T. *Chem. Pharm. Bull.* **2010,** *58*, 1552-1553. (d) Wang, S.; Beck, R.; Blench, T.; Burd, A.; Buxton, S.; Malic, M.; Ayele, T.;

Shaikh, S.; Chahwala, S.; Chander, C.; Holland, R.; Merette, S.; Zhao, L.; Blackney, M.; Watts, A. *J. Med. Chem.* **2010,** *53*, 1465-1472.

2. (a) Imramovsky, A.; Jorda, R.; Pauk, K.; Reznickova, E.; Dusek, J.; Hanusek, J.; Krystof, V. *Eur. J. Med. Chem.* **2013,** *68*, 253-259. (b) Yang, B.; Lamb, M. L.; Zhang, T.; Hennessy, E. J.; Grewal, G.; Sha, L.; Zambrowski, M.; Block, M. H.; Dowling, J. E.; Su, N.; Wu, J.; Deegan, T.; Mikule, K.; Wang, W.; Kaspera, R.; Chuaqui, C.; Chen, H. *J. Med. Chem.* **2014,** *57*, 9958-9970.

3. (a) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006,** *128*, 4594-4595. (b) Shintou, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **2004,** *126*, 7359-7367. (c) Vo, C. V.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011,** *133*, 14082-14089.

4. (a) Ackermann, L. *Chem. Rev.* **2011,** *111*, 1315-1345. (b) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012,** *45*, 788-802. (c) Peron, F.; Fossey, C.; Sopkova-de Oliveira Santos, J.; Cailly, T.; Fabis, F. *Chem. - Eur. J.* **2014,** *20*, 7507-7513. (d) Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.; Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D. *J. Am. Chem. Soc.* **2015,** *137*, 11888-11891. (e) Bera, M.; Maji, A.; Sahoo, S. K.; Maiti, D. *Angew. Chem.* **2015,** *54*, 8515-8519. (f) Kolle, S.; Batra, S. *Org. Biomol. Chem.* **2015,** *13*, 10376-10385. (g) Maji, A.; Bhaskararao, B.; Singha, S.; Sunoj, R. B.; Maiti, D. *Chem. Sci.* **2016,** *7*, 3147-3153. (h) Bera, M.; Sahoo, S. K.; Maiti, D. *ACS. Catal.* **2016,** *6*, 3575-3579.

5. (a) Castro, L. C. M.; Chatani, N. *Chem. Eur. J.* **2014,** *20*, 4548-4553. (b) Gong, W.; Zhang, G.; Liu, T.; Giri, R.; Yu, J. Q. *J. Am. Chem. Soc.* **2014,** *136*, 16940-16946. (c) Kim, J.; Sim, M.; Kim, N.; Hong, S. *Chem Sci* **2015,** *6*, 3611-3616. (d) Toba, T.; Hu, Y.; Tran, A. T.; Yu, J. Q. *Org. Lett.* **2015,** *17*, 5966-5969.

6. (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004,** *126*, 2300-2301. (b) Gao, T.; Sun, P. *J. Org. Chem.* **2014,** *7*, 9888-9893. (c) Jiang, T. S.; Wang, G. W. *J. Org. Chem.* **2012,** *77*, 9504-9509. (d) Shi, S.; Kuang, C. *J. Org. Chem.* **2014,** *79*, 6105-6112. (e) Siciliano, C.; Barattucci,

A.; Bonaccorsi, P.; Di Gioia, M. L.; Leggio, A.; Minuti, L.; Romio, E.; Temperini, A. *J. Org. Chem.* **2014,** *79*, 5320-5326. (f) Yin, Z.; Jiang, X.; Sun, P. *J. Org. Chem.* **2013,** *78*, 10002-10007. (g) Zhang, C.; Sun, P. *J. Org. Chem.* **2014,** *79*, 8457-8461. (h) Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, K.; Ren, B.; Gong, J. F.; Niu, J. L.; Song, M. P. *J. Org. Chem.* **2014,** *79*, 10399-10409.

7. (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013,** *4*, 4187-4192. (b) Zhang, S. Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012,** *134*, 7313-7316.

8. (a) Li, H.; Li, P.; Wang, L. *Org. Lett.* **2013,** *15*, 620-623. (b) Lian, B.; Zhang, L.; Chass, G. A.; Fang, D. C. *J. Org. Chem.* **2013,** *78*, 8376-8385.

9. (a) Lucchesi, C; Arbore, A; Pascual, S; Fontaine, L; Maignan, C; Dujardin, G. *Carbohydr. Res.* **2010**, *345*, 844-849. (b) Satyanarayana, B; Sumalatha, Y; Sridhar, C; Venkatraman, S; Reddy, P, P. *Heterocycl. Commun.* **2006**, *12*, 323-328. (c) Saavedra, C; Hernandez, R; Boto, A; Alvarez, E. *J. Org. Chem.* **2009**, 74, 4655-4665. (d) Sofia; Chakravarty; Katzenellenbogen. *J. Org. Chem.* **1983**, *48*, 3318-3325 (e) Saavedra, C; Hernandez, R; Boto, A; Alvarez, E. *J. Org. Chem.* **2009**, *74*, 4655-4665. (f) Reinaud; Capdevielle; Maumy. Synthesis. **1990**, *7*, 612-614. (g) Buijs, W; Comba, P; Corneli, D; Pritzkow, H. *J. Organomet. Chem.* **2002**, *461*, 71-80. (h) Schaefer, G; Bode, J, W. *Org. Let.* **2014**, *16*, 1526-1529. (i) Jin, C; Chen, J; Su, W. *Heterocycles.* **2011**, *83*, 153-161.