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Pd-Catalyzed Coupling of γ-C(sp^3)−H Bonds of Oxalyl Amide-Protected Amino Acids with Heteroaryl and Aryl Iodides

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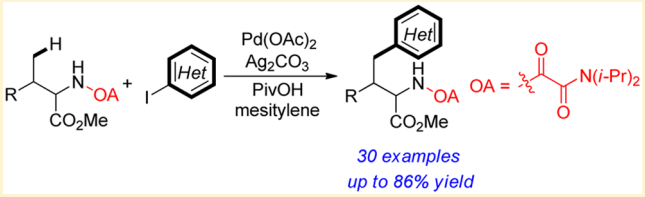
Supporting Information

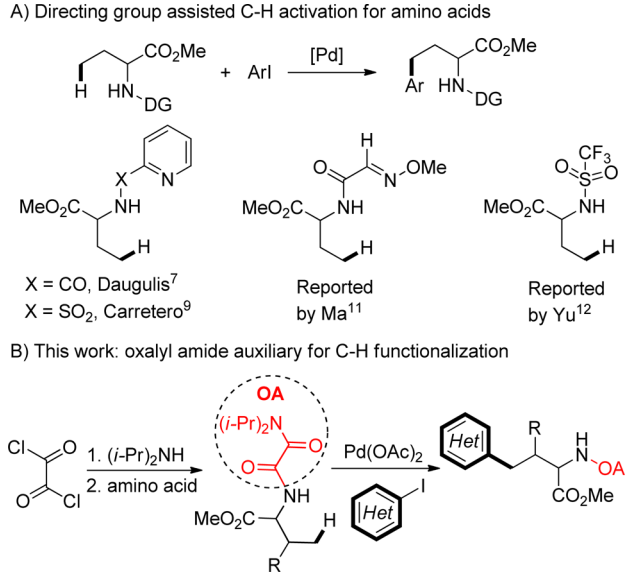
ABSTRACT: Pd-catalyzed regioselective coupling of γ-C(sp^3)−H bonds of oxalyl amide-protected amino acids with heteroaryl and aryl iodides is reported. A wide variety of iodides are tolerated, giving the corresponding products in moderate to good yields. Various oxalyl amide-protected amino acids were compatible in this C−H transformation, thus representing a practical method for constructing non-natural amino acid derivatives.



In the past decade, direct C−H functionalization methodology has aroused widespread interest since it offers a concise pathway toward the synthesis of key structures present in drugs and natural products.[1,2] Recently, significant progress has been made in the area of transition-metal-catalyzed functionalization of unactivated simple C(sp^3)−H bonds assisted by directing groups.[3,4] The direct arylation of alkyl C−H bonds, which is recognized as a powerful strategy to construct various arylated alkyl compounds,[5,6] could help streamline the synthetic process and reduce the formation of byproducts. In 2005, Daugulis and co-workers had reported the use of *N*,*N*-bidentate directing groups in realizing the γ-arylation of amine derivatives.[7] Chen and co-worker also described an elegant Pd-catalyzed picolinamide-directed γ-functionalization of natural amino acids.[8] Ever since, different examples of *N*,*N*-bidentate directing groups for palladium-catalyzed γ-C(sp^3)−H bonds arylation of amine/amino acid derivatives have emerged in literature[9−11] (Scheme 1A). Very recently, Yu and co-workers reported the γ-arylation of triflyl-protected amino acids with arylboron reagents using *N*-acetyl-L-isoleucine as a ligand.[12]

Heteroaryl compounds forms the core of many drugs, pesticides, dyes and plastics, and they usually play an important role in synthetic chemistry and pharmacochemistry.[13] However, reports on the direct functionalization of γ-C(sp^3)−H bonds of amine derivatives with heteroaryl iodides are still few. It is probable that heteroaryl compounds might coordinate with palladium intermediate which could inhibit the C−H bond activation. Our group had previously demonstrated that oxalyl amide could serve as an effective directing group for amine derivatives in promoting remote C−H transformation.[14] As a result, we proceed to address the challenge of γ-arylation of amino acids with heteroaryl iodides. This transformation would represent a vital process since the resultant compounds frequently form the core of proteins, peptides, and pharmaceutical agents.[15,16] Herein, we report a new protocol for Pd-catalyzed selective coupling of γ-C(sp^3)−H bonds of oxalyl amide-protected amino acids with heteroaryl and aryl iodides under mild conditions (Scheme 1B). Both inert γ-CH_3 and -CH_2 bonds could be well functionlized, giving synthetically useful arylated products in moderate to good yields.

Scheme 1. Protecting Droup Directed C−H Activation



We began our initial study by treating amino ester **1a** with 4-iodoanisole **2a** in the presence of $Pd(OAc)_2$ (5 mol %) and Ag_2CO_3 (1.5 equiv) in mesitylene at 100 °C for 24 h. Gratifyingly, 80% of highly selective γ-arylated amino ester **3a**

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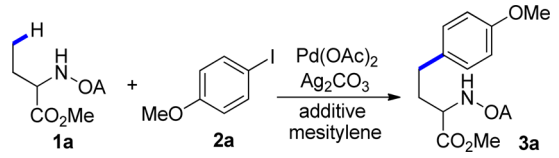
was obtained (Table1, entry 1). However, a reduction in the catalyst loading resulted in only 55% yield of **3a** (Table1, entry 2). The introduction of pivalic acid[17] as an additive slightly improved the reactivity of Pd-catalyzed γ-arylation, affording **3a** in 85% yield. Further screening of other well-known additives,[18] such as $(BnO)_2PO_2H$, HOAc, 1-AdCO$_2$H, Ac-Gly-OH, *ortho*-phenyl benzoic acid (*o*-PBA) and $KHCO_3$, revealed their inefficacy under this process (Table 1, entries 4−9). Inexpensive oxidants including $K_2S_2O_8$, BQ, TBHP and $Cu(OAc)_2$ were also tested but none gave a better result. Much to our delight, we observed that reducing both the amount of Ag_2CO_3 used and lowering the temperature to 90 °C further increased the yield of **3a** to 89%. Control experiment revealed that the reaction could not proceed without a palladium catalyst, indicating the irreplaceable role of Pd-$(OAc)_2$ in this newly developed protocol (entry 15). Finally, we found that ArBPin could not replace aryl iodide as a coupling partner, which suggested that the Ag_2CO_3 and PivOH could not promote C(sp^3)−H arylation through a Pd(0)/Pd(II) catalytic manifold (entry 16).

Table 1. Optimization Studies for Pd-Catalyzed C(sp^3)−H Bond Arylation[a]

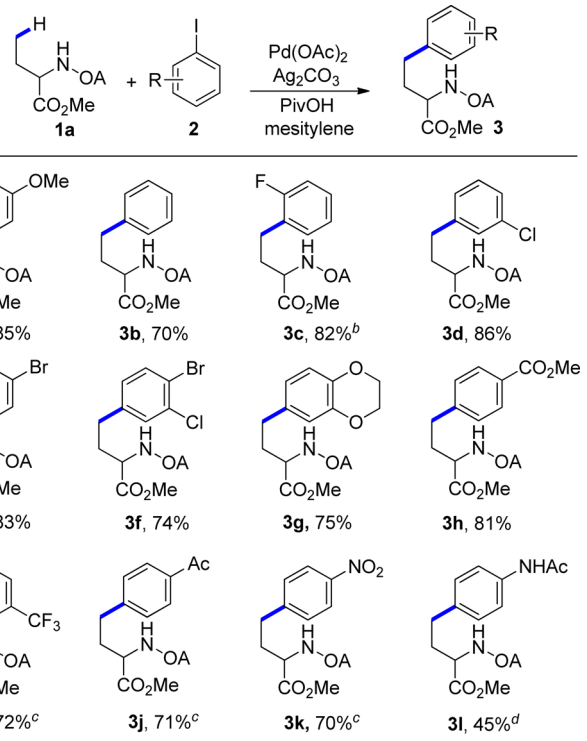


entry	oxidant	additive	yield (%)[b]
1	Ag_2CO_3	none	80
2[c]	Ag_2CO_3	none	55
3	Ag_2CO_3	PivOH	85
4	Ag_2CO_3	$(BnO)_2PO_2H$	66
5	Ag_2CO_3	HOAc	62
6	Ag_2CO_3	1-AdOH	73
7	Ag_2CO_3	Ac-Gly-OH	51
8	Ag_2CO_3	*o*PBA	57
9	Ag_2CO_3	$KHCO_3$	68
10	$K_2S_2O_8$	PivOH	23
11	BQ	PivOH	0
12	TBHP	PivOH	15
13	$Cu(OAc)_2$	PivOH	<5
14[d]	Ag_2CO_3	PivOH	89 (85)[e]
15[f]	Ag_2CO_3	PivOH	0
16[g]	Ag_2CO_3	PivOH	0

[a]Conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $Pd(OAc)_2$ (5 mol %), oxidant (0.15 mmol), additive (0.03 mmol), mesitylene (0.3 mL), 100 °C, 24 h. [b]GC yield determined using tridecane as internal standard. [c]$Pd(OAc)_2$ (2.5 mol %). [d]Oxidant (0.1 mmol), 90 °C. [e]Isolated yield. [f]No catalyst. [g]Phenylboronic acid pinacol ester instead of **2a**.

With the optimized conditions in hand, various types of iodides were coupled with amino ester **1a** (Table 2). Satisfyingly, aryl iodides containing electron-donating or -withdrawing groups were well tolerated giving the corresponding products in moderate to good yields (**3a**−**l**). It was worth noting that the compatibility of F, Cl and Br functional groups with this protocol offered a great opportunity for further functionalization. The use of 1-iodo-4-nitrobenzene also afforded the product **3k** in good yield albeit under increased temperature and extended time (110 °C, 36 h). Interestingly, the acetyl amide **2l**, which contained another coordination center for palladium catalyst[12] also underwent arylation with **1a**, giving an acceptable synthetic yield of **3l** under modified conditions.

Table 2. Substrate Scope of Aryl Iodides[a]



[a]Reaction conditions: **1a** (0.2 mmol), ArI (0.3 mmol), $Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.2 mmol), PivOH (0.06 mmol), mesitylene (0.6 mL), 90 °C, 24 h. Isolated yields. [b]110 °C. [c]Ag_2CO_3 (0.3 mmol), 110 °C, 36 h. [d]Ag_2CO_3(0.6 mmol), 130 °C, 36 h.

Encouraged by the excellent coupling ability of substrate **1a** with aryl iodides, we extended this protocol to heteroaryl iodides. We were pleased to find that several types of heteroaryl iodides could also undergo γ-arylation with **1a**, as illustrated in Table 3. In general, the heteroaryl iodides were less reactive compared with aryl iodides. The reaction could only proceed at 110 °C with 10 mol % $Pd(OAc)_2$ and 1.5 equiv Ag_2CO_3. For example, heteroaryl iodides **2m** and **2n** coupled well with **1a** affording the arylated products **3m** and **3n** in good yields, respectively. The use of 2-acetyl-5-iodothiophene gave the γ-functionalized product **3o** in 65% yield. Iodopyridines bearing strong electron-withdrawing substituents also provided the desired products in good yields (**3p**,**q**). Surprisingly, iodopyridines bearing the F, Cl, Br, and I groups were also successfully incorporated into the alkyl scaffolds of amino acid esters under harsher conditions (**3r**−**u**). We reasoned that the iodopyridine derivatives (**2r**−**u**) might coordinate with the palladium center and then enwrap/decompose the catalyst during the catalytic cycle, thus resulting in the observed poor yields. To our delight, the coupling reaction of substrate **1a** with methyl 5-bromo-2-furoate could also give 42% yield of the product (**3w**). Notably, all reactions proceeded quite cleanly, just unreacted starting materials and products were observed in the transformation.

The substrate scope of amino acids was next explored, and the results are shown in Table 4. We found that arylation reaction of oxalyl amide protected isoleucine with **2a** occurred at the γ-C(sp^3)−H position by employing $Pd(TFA)_2$ as catalyst, the monoarylated product **4a** was obtained in 55%

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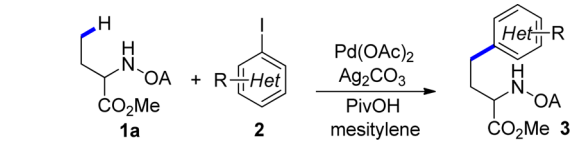
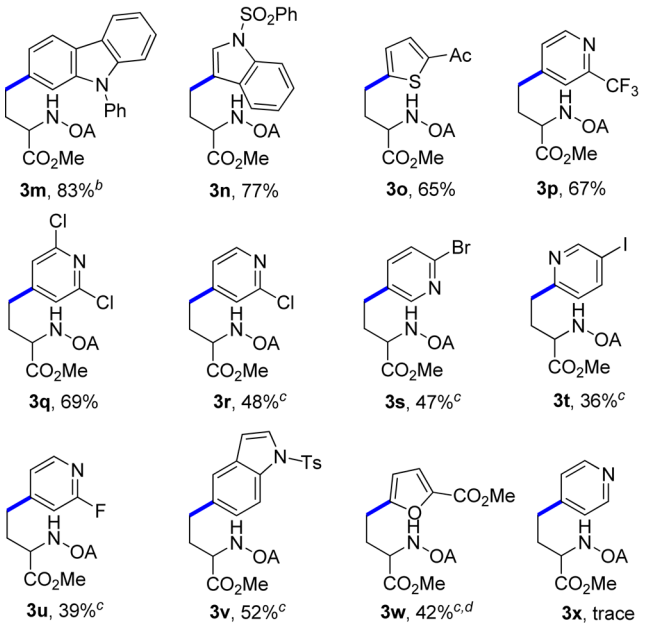
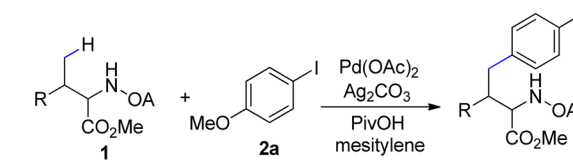
Table 3. Substrate Scope of Heteroaryl Iodides[a]

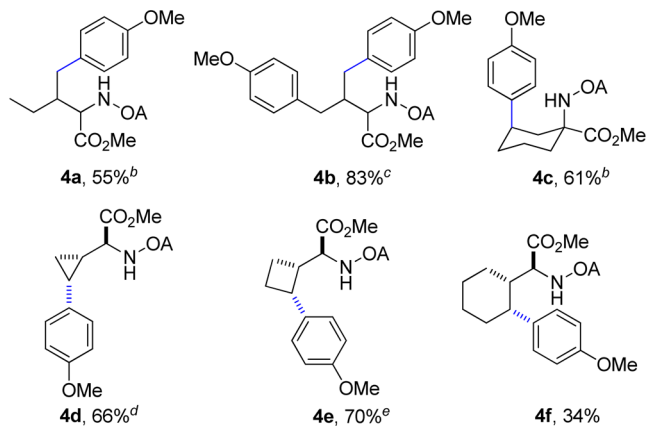




[a]Reaction conditions: **1a** (0.2 mmol), heteroaryl iodide (0.3 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.3 mmol), PivOH (0.06 mmol), mesitylene (0.6 mL), 24 h, 110 °C. Isolated yields. [b]90 °C. [c]$Pd(OAc)_2$ (15 mol %), 150 °C. [d]Bromide (0.3 mmol).

Table 4. Substrate Scope of Amino Acids[a]



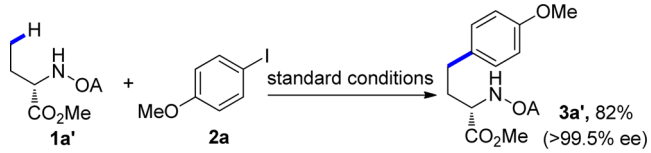


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.6 mmol), PivOH (0.06 mmol), mesitylene (0.6 mL), 130 °C, 36 h. Isolated yields. [b]$Pd(TFA)_2$ (10 mol %), 60 °C. [c]**2a** (0.6 mmol). [d]$Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.3 mmol), 60 °C. [e]$Pd(OAc)_2$ (5 mol %), Ag_2CO_3 (0.3 mmol), 90 °C.

yield at 60 °C. When we employed the $Pd(OAc)_2$ as catalyst, the product **4a** was isolated in lower yield, accompanied by the diarylated product. As expected, the coupling of valine derivative with 4-iodoanisole (3 equiv) in the presence of $Pd(OAc)_2$ (10 mol %) after 36 h gave the diarylated product **4b** in 83% yield. The 1-aminocyclohexane-carboxylic acid derivative afforded the γ-monoarylated product in 61% yield (**4c**). Attempts to increase the yield by increasing the reaction temperature resulted in the formation of both mono and diarylated products. To further probe the substrate scope, a series of glycine derivatives were tested (**4d–f**).[6c] Unsurprisingly, cyclopropylglycine and cyclobutylglycine gave the γ-arylated products (**4d,e**) in good yields under slightly modified reaction conditions. Cyclohexylglycine could only give low yield of **4f** after 36 h at 130 °C due to incomplete conversion of starting material. These results indicated the difference in reactivity with the substrates of different ring sizes.

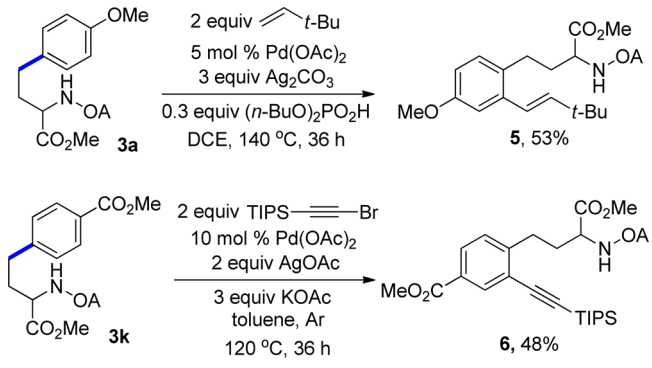
To show the practical importance of this protocol, oxalyl amide protected L-amino ester **1a′** was reacted with 4-iodoanisole under standard reaction conditions. There was no significant racemization at the chiral center, as determined by high-performance liquid chromatography (Scheme 2). The

Scheme 2. Aryaltion of Oxalyl Amide Protected L-Amino Ester 1a′



significance of this Pd-catalyzed γ-arylation reaction was further demonstrated by the preparation of homophenylalanine derivatives.[19] For example, compound **3a** could undergo a Pd-catalyzed *ortho*-olefination reaction[14b] to give the alkenylated homophenylalanine derivative **5** in moderate yield. Compound **3k** could also be transformed to the synthetically useful alkynylated product **6** in moderate yield by coupling with bromoalkyne[14e] (Scheme 3). As we known, alkenes and alkynes

Scheme 3. Synthesis of 3-Arylamino Acid Derivatives



are special building blocks in synthetic chemistry and in materials chemistry because of their versatile transformation into multiple functional groups or linear structural motifs.

On the basis of our previous studies and recent reports,[14,20] a plausible mechanism is proposed in Scheme 4. The oxalyl amide **1a** reaction with $Pd(OAc)_2$ generated the palladium amide complex **7**, followed by C–H activation to give the

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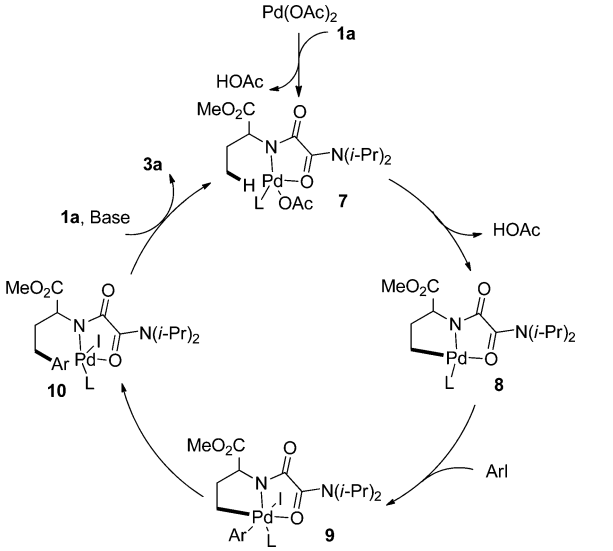
Scheme 4. Proposed Catalytic Cycle



intermediate **8**. Oxidative addition of aryl iodide to **8** produced a high-valent Pd intermediate **9**. Subsequent rapid reductive elimination followed by ligand exchange afforded the product, accompanied by active species of palladium intermediate **7**. Ag_2CO_3 played an important role in catalyst regeneration via halide abstraction from a putative PdI_2 species.[21]

In summary, we have developed a highly effective palladium-catalyzed coupling of γ-C(sp^3)−H bonds in oxalyl amide-protected amino acids with heteroaryl and aryl iodides. A wide variety of iodides are tolerated in this transformation. Both unactivated γ-CH_3 and -CH_2 bonds are activated, thus affording synthetically useful functionalized products in moderate to good yields. This new development in the functionalization of C(sp^3)−H bonds offers a new strategy toward building non-natural amino acids derivatives.

EXPERIMENTAL SECTION

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. HRMS analysis was carried out using TOF-MS instrument with ESI source. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br s = broad singlet, m = multiplet. General procedures for the synthesis of products are represented as follows.

Preparation of S1. A solution of diisopropylamine (7.01 mL, 50 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise to a solution of oxalyl chloride (6.44 mL, 75 mmol, 1.5 equiv) in CH_2Cl_2 (100 mL) at 0 °C. After 5 min of stirring, triethylamine (7.30 mL, 52.5 mmol, 1.05 equiv) was added dropwise. The solution was warmed to room temperature and stirred for 6 h. Excess oxalyl chloride and solvent were removed under reduced pressure, and CH_2Cl_2 (30 mL) was added and evaporated. This operation was performed twice to give **S1** as a pale yellow solid. The crude product was used in the next step without any purification.

N,N-Diisopropyloxamoyl chloride ***S1***. Yield 95% (8.4 g); pale yellow solid; ^{1}H NMR (400 MHz, CDCl3) δ 3.77 (m, 1H), 3.51 (m, 1H), 1.41 (d, J = 6.9 Hz, 6H), 1.24 (d, J = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 158.8, 51.0, 46.5, 20.3, 19.8; HRMS calcd for $C_8H_{14}ClNO_2Na$ [M + Na^+] 214.0611; found 214.0609.

General Procedures for Preparation of Oxalyl Amide Protected Amino Acid (1a−1h).[22,23] $SOCl_2$ (4.35 mL, 60 mmol, 3.0 equiv) was added dropwise to a solution of amino acid (20 mmol, 1.0 equiv) in MeOH (30 mL) at 0 °C. The resulting mixture was allowed to stir from 0 °C to room temperature overnight. The solvent was removed under reduced pressure to give white solid, which was used directly for next step. A solution of amino ester (20 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was added dropwise to a solution of *N,N*-diisopropyloxamoyl chloride **S1** (25 mmol, 1.25 equiv) in CH_2Cl_2 (50 mL) at 0 °C. After 30 min of stirring, triethylamine (5.84 mL, 42 mmol, 2.1 equiv) was added dropwise, and then the mixture was stirred for 6 h at room temperature before being quenched by water (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic phase was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel afforded corresponding amide substrates as white solid of colorless oil >70% yield.

Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)butanoate ***(1a)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; Yield 81% (4.41 g); off-white solid; mp = 88−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.2 Hz, 1H), 4.65−4.58 (m, 1H), 4.51−4.46 (m, 1H), 3.73 (s, 3H), 3.52−3.45 (m, 1H), 1.94−1.88 (m, 1H), 1.80−1.73 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.20 (dd, J = 6.6, 2.6 Hz, 6H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 163.1, 162.6, 53.5, 52.5, 49.8, 46.7, 25.5, 21.0, 20.9, 20.2, 20.1, 9.7; HRMS Calcd for $C_{13}H_{24}N_2NaO_4$ [M + Na^+] 295.1634, found 295.1636.

Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-3-methylpentanoate ***(1b)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; Yield 71% (4.26 g); off-white solid; mp = 54−56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (br s, 1H), 4.69−4.63 (m, 1H), 4.52 (dd, J = 8.8, 5.0 Hz, 1H), 3.74 (s, 3H), 3.54−3.47 (m, 1H), 1.97−1.90 (m, 1H), 1.49−1.41 (m, 7H), 1.25−1.18 (m, 7H), 0.94−0.90 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 163.0, 162.6, 56.6, 52.3, 49.8, 46.7, 38.0, 25.3, 20.98, 20.96, 20.3, 20.2, 15.6, 11.7; HRMS Calcd for $C_{15}H_{28}N_2NaO_4$ [M + Na^+] 323.1947, found 323.1949.

Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-3-methylbutanoate ***(1c)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; Yield 79% (4.29 g); off-white solid; mp = 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.4 Hz, 1H), 4.68−4.61 (m, 1H), 4.47 (dd, J = 8.9, 5.0 Hz, 1H), 3.74 (s, 3H), 3.54−3.47 (m, 1H), 2.25−2.17 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.21 (dd, J = 6.6, 3.9 Hz, 6H), 0.95 (dd, J = 9.7, 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 163.2, 162.6, 57.2, 52.2, 49.7, 46.5, 31.2, 20.8, 20.1, 20.0, 19.0, 18.0; HRMS Calcd for $C_{14}H_{26}N_2NaO_4$ [M + Na^+] 309.1790, found 309.1790.

Methyl 1-(2-(diisopropylamino)-2-oxoacetamido)cyclohexanecarboxylate ***(1d)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent; Yield 80% (4.99 g); off-white solid; mp = 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (br s, 1H), 4.72−4.65 (m, 1H), 3.71 (s, 3H), 3.54−3.47 (m, 1H), 2.07 (d, J = 13.5 Hz, 2H), 1.89−1.82 (m, 2H), 1.68−1.60 (m, 3H), 1.53−1.46 (m, 2H), 1.42 (d, J = 6.8 Hz, 6H), 1.33−1.27 (m, 1H), 1.21 (d, J = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 162.9, 162.7, 59.1, 52.5, 49.6, 46.7, 32.2, 25.2, 21.4, 21.0, 20.2; HRMS Calcd for $C_{16}H_{28}N_2NaO_4$ [M + Na^+] 335.1947, found 335.1951.

Methyl 2-cyclopropyl-2-(2-(diisopropylamino)-2-oxoacetamido)-acetate ***(1e)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; Yield 71% (4.03 g); off-white solid; mp = 62−63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 6.7 Hz, 1H), 4.57−4.50 (m, 1H), 3.86−3.82 (m, 1H), 3.70 (s, 3H), 3.48−3.41 (m, 1H), 1.36 (d, J = 6.7 Hz, 6H), 1.16 (d, J = 6.5 Hz, 6H), 1.12−1.05 (m, 1H), 0.59−0.47 (m, 3H), 0.40−0.36 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 163.0, 162.7, 56.1, 52.3, 49.6, 46.4, 20.8, 20.7, 20.1, 19.9, 13.3, 3.4, 3.3; HRMS Calcd for $C_{14}H_{24}N_2NaO_4$ [M + Na^+] 307.1634, found 307.1639.

Methyl 2-cyclobutyl-2-(2-(diisopropylamino)-2-oxoacetamido)-acetate ***(1f)***. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; Yield 74% (4.41 g); off-white solid; mp = 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (br s, 1H), 4.63−4.57 (m, 1H), 4.47 (t, J = 8.2 Hz, 1H), 3.70 (s, 3H), 3.52−3.45 (m, 1H), 2.71−2.62 (m, 1H), 2.01−1.76 (m, 6H), 1.40 (d, J = 6.8 Hz, 6H), 1.19 (dd, J = 6.6, 2.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 163.3, 162.7, 55.9, 52.3, 49.8, 46.6, 37.7,

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25.1, 24.8, 20.9, 20.2, 20.1, 18.0; HRMS Calcd for $C_{15}H_{26}N_2NaO_4$ [M + Na^+] 321.1790, found 321.1799.

*Methyl 2-cyclohexyl-2-(2-(diisopropylamino)-2-oxoacetamido)-acetate (**1g**).* Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; Yield 76% (5.20 g); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 1H), 4.68−4.61 (m, 1H), 4.45 (dd, J = 8.9, 5.5 Hz, 1H), 3.73 (s, 3H), 3.53−3.46 (m, 1H), 1.87−1.81 (m, 1H), 1.75−1.61 (m, 5H), 1.42 (d, J = 6.8 Hz, 6H), 1.24−1.04 (m, 11H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 163.0, 162.6, 57.0, 52.3, 49.8, 46.7, 41.0, 29.6, 28.4, 26.0, 26.0, 20.97, 20.94, 20.2, 20.1; HRMS Calcd for $C_{18}H_{34}N_2NaO_4$ [M + Na^+] 365.2416, found 365.2428.

General Procedure for Palladium-Catalyzed Arylation of 1a with Aryl Iodides (Table 2) (3a, 3b, 3d−3h, 3i−3k, 3l). A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), ArI (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (55.2 mg, 1.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 90 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(4-methoxyphenyl)butanoate (**3a**).* 4-Iodoanisole was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 85% (64.3 mg); off-white solid; mp = 91−93 °C; H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 7.9 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 4.68−4.62 (m, 1H), 4.59−4.54 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.55−3.48 (m, 1H), 2.63 (t, J = 7.9 Hz, 2H), 2.23−2.14 (m, 1H), 2.07−1.98 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.4, 4.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 163.2, 162.6, 158.2, 132.5, 129.5, 114.0, 55.3, 52.6, 52.0, 49.8, 46.7, 34.0, 30.8, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{20}H_{30}N_2NaO_5$ [M + Na^+] 401.2052, found 401.2066.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-phenylbutanoate (**3b**).* Iodobenzene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 70% (48.7 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.21 (m, 3H), 7.16 (d, J = 6.9 Hz, 3H), 4.88−4.83 (m, 1H), 4.43−4.37 (m, 1H), 3.72 (s, 3H), 3.51−3.44 (m, 1H), 3.21−3.16 (dd, J = 13.9, 5.7 Hz, 1H), 3.11−3.06 (m, 1H), 1.74−1.72 (m, 2H), 1.40 (dd, J = 6.8, 3.2 Hz, 6H), 1.16 (dd, J = 6.6, 1.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 162.9, 162.6, 135.7, 129.4, 128.8, 127.3, 53.3, 52.6, 49.8, 46.6, 38.2, 21.0, 20.9, 20.2; HRMS Calcd for $C_{19}H_{28}N_2NaO_4$ [M + Na^+] 371.1947, found 371.1954.

*Methyl 4-(3-chlorophenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3d**).* 3-Chloroiodobenzene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent; Yield 86% (65.7 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.0 Hz, 1H), 7.22−7.15 (m, 3H), 7.05 (d, J = 7.1 Hz, 1H), 4.67−4.55 (m, 2H), 3.73 (s, 3H), 3.56−3.46 (m, 1H), 2.70−2.62 (m, 2H), 2.26−2.17 (m, 1H), 2.09−2.00 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.5, 5.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 163.2, 162.5, 142.5, 134.3, 129.9, 128.7, 126.8, 126.6, 52.7, 51.9, 49.9, 46.8, 33.6, 31.4, 20.98, 20.95, 20.2, 20.1; HRMS Calcd for $C_{19}H_{27}ClN_2NaO_4$ [M + Na^+] 405.1557, found 405.1554.

*Methyl 4-(4-bromophenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3e**).* 1-Bromo-4-iodobenzene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 83% (70.9 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.36 (m, 3H), 7.05 (d, J = 8.3 Hz, 2H), 4.67−4.60 (m, 1H), 4.59−4.54 (m, 1H), 3.72 (s, 3H), 3.56−3.49 (m, 1H), 2.68−2.60 (m, 2H), 2.24−2.15 (m, 1H), 2.07−1.98 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.6, 4.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 163.1, 162.5, 139.4, 131.7, 130.3, 120.2, 52.7, 51.9, 49.8, 46.8, 33.7, 31.2, 20.99, 20.95, 20.2, 20.1; HRMS Calcd for $C_{19}H_{27}BrN_2NaO_4$ [M + Na^+] 449.1052, found 449.1057.

*Methyl 4-(4-bromo-3-chlorophenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3f**).* 4-Bromo-3-chloroiodobenzene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 74% (68.1 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.47 (m, 2H), 7.26 (d, J = 2.0 Hz, 1H), 6.94−6.92 (m, 1H), 4.65−4.53 (m, 2H), 3.73 (s, 3H), 3.55−3.48 (m, 1H), 2.65−2.61 (m, 2H), 2.23−2.15 (m, 1H), 2.07−1.98 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.24−1.21 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 163.2, 162.6, 141.5, 134.4, 133.8, 130.5, 128.3, 120.1, 52.7, 51.8, 49.9, 46.8, 33.4, 31.0, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{19}H_{26}BrClN_2NaO_4$ [M + Na^+] 483.0662, found 483.0669.

*Methyl 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3g**).* 6-Iodo-1,4-benzodioxane was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 75% (60.9 mg); pale yellow solid; mp = 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 8.2 Hz, 1H), 6.67−6.61 (m, 2H), 4.66−4.52 (m, 2H), 4.21 (s, 4H), 3.72 (s, 3H), 3.54−3.48 (m, 1H), 2.57 (t, J = 8.0 Hz, 2H), 2.21−2.12 (m, 1H), 2.05−1.95 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 6.6, 3.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 163.1, 162.6, 143.5, 142.0, 133.7, 121.4, 117.3, 117.1, 64.5, 64.4, 52.6, 52.0, 49.8, 46.7, 33.9, 31.0, 21.0, 20.2, 20.1; HRMS Calcd for $C_{21}H_{30}N_2NaO_6$ [M + Na^+] 429.2002, found 429.2013.

*Methyl 4-(3-(2-(diisopropylamino)-2-oxoacetamido)-4-methoxy-4-oxobutyl)benzoate. (**3h**).* Methyl 4-iodobenzoate was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 81% (65.8 mg); pale yellow solid; mp = 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 4.64−4.54 (m, 2H), 3.88 (s, 3H), 3.71 (s, 3H), 3.54−3.47 (m, 1H), 2.73 (t, J = 7.8 Hz, 2H), 2.28−2.19 (m, 1H), 2.11−2.02 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 6.6, 4.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 167.1, 163., 162.6, 146.0, 129.9, 128.6, 128.3, 52.67, 52.1, 51.9, 49.9, 46.7, 33.4, 31.8, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{21}H_{30}N_2NaO_6$ [M + Na^+] 429.2002, found 429.2012.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(2-fluorophenyl)butanoate (**3c**).* A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), 2-fluoroiodobenzene **2c** (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (55.2 mg, 1.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 110 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) to give the corresponding product **3c**. Yield 82% (60.0 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 7.9 Hz, 1H), 7.19−7.14 (m, 2H), 7.06−6.96 (m, 2H), 4.66−4.56 (m, 2H), 3.72 (s, 3H), 3.55−3.48 (m, 1H), 2.73−2.69 (t, J = 7.9 Hz, 2H), 2.28−2.19 (m, 1H), 2.10−2.00 (m, 1H), 1.43 (dd, J = 6.8, 0.9 Hz, 6H), 1.23 (dd, J = 6.7, 2.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 163.2, 162.6, 161.2 (d, J_{C-F} = 243.0 Hz), 130.8 (d, J_{C-F} = 4.8 Hz), 128.2 (d, J_{C-F} = 8.1 Hz), 127.3 (d, J_{C-F} = 15.7 Hz), 124.2 (d, J_{C-F} = 3.6 Hz), 115.4 (d, J_{C-F} = 22.0 Hz), 52.6, 52.0, 49.9, 46.7, 32.3, 25.2, 21.0, 20.2, 20.2; HRMS Calcd for $C_{19}H_{27}FN_2NaO_4$ [M + Na^+] 389.1853, found 389.1855.

General Procedure for Palladium-Catalyzed Arylation of 1a with Aryl Iodides (Table 2) (3i−3k). A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), ArI (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (82.8 mg, 1.5equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly-(tetrafluoroethylene) (PTFE) cap] was heated at 110 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite.

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The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(3-(trifluoromethyl)phenyl)butanoate (**3i**).* 3-Iodobenzotrifluoride was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 72% (59.9 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 5H), 4.70−4.64 (m, 1H), 4.62−4.57 (m, 1H), 3.73 (s, 3H), 3.56−3.50 (m, 1H), 2.81−2.69 (m, 2H), 2.30−2.21 (m, 1H), 2.12−2.03 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.24 (dd, J = 6.3, 5.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 163.1, 162.5, 141.4, 132.0 (d, J_{C-F} = 1.0 Hz), 130.9 (q, J_{C-F} = 32.0 Hz), 129.1, 125.3 (q, J_{C-F} = 32.0 Hz), 124.3 (q, J_{C-F} = 270.0 Hz), 123.3 (q, J_{C-F} = 4.0 Hz), 52.7, 51.9, 49.9, 46.8, 33.7, 31.6, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{20}H_{27}F_3N_2NaO_4$ [M + Na$^+$] 439.1821, found 439.1829.

*Methyl 4-(4-acetylphenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3j**).* 4-Iodoacetophenone was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 71% (55.4 mg); pale yellow solid; mp = 102−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 8.1 Hz, 2H), 4.65−4.55 (m, 2H), 3.72 (s, 3H), 3.55−3.48 (m, 1H), 2.74 (t, J = 7.9 Hz, 2H), 2.56 (s, 3H), 2.28−2.19 (m, 1H), 2.12−2.02 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 6.1, 5.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 171.8, 163.2, 162.6, 146.3, 135.5, 128.8, 52.7, 51.9, 49.9, 46.7, 33.4, 31.7, 26.7, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{21}H_{30}N_2NaO_5$ [M + Na$^+$] 413.2052, found 413.2058.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(4-nitrophenyl)butanoate (**3k**).* 4-Iodo-1-nitrobenzene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 70% (55.1 mg); pale yellow solid; mp = 70−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.1 Hz, 1H), 7.34 (d, J = 8.6 Hz, 2H), 4.64−4.55 (m, 2H), 3.74 (s, 3H), 3.55−3.49 (m, 1H), 2.82−2.78 (m, 2H), 2.30−2.21 (m, 1H), 2.13−2.02 (m, 1H), 1.42 (dd, J = 6.8, 1.9 Hz, 6H), 1.24−1.21 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 163.3, 162.5, 148.3, 146.7, 129.4, 123.9, 52.8, 51.8, 49.9, 46.8, 33.3, 31.7, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{19}H_{27}N_3NaO_6$ [M + Na$^+$] 416.1798, found 416.1792.

*Methyl 4-(4-acetamidophenyl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3l**).* A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), 4-iodoacetanilide **2l** (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (165.6 mg, 3.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 130 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (4/1) as an eluent to give the corresponding product **3c**. Yield 45% (36.5 mg); pale yellow solid; mp = 194−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (br s, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 4.57−4.50 (m, 2H), 3.70 (s, 3H), 3.54−3.47 (m, 1H), 2.60 (t, J = 7.9 Hz, 2H), 2.11 (s, 3H), 2.04−1.97 (m, 2H), 1.42 (d, J = 6.8 Hz, 6H), 1.21 (dd, J = 6.6, 3.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 168.8, 163.5, 162.9, 136.4, 136.2, 128.9, 120.3, 52.6, 51.9, 50.0, 46.6, 33.6, 31.1, 24.5, 20.9, 20.9, 20.2, 20.1; HRMS Calcd for $C_{21}H_{31}N_3NaO_5$ [M + Na$^+$] 428.2161, found 428.2170.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(9-phenyl-9H-carbazol-2-yl)butanoate (**3m**).* A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), 3-iodo-9-phenylcarbazole **2m** (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2CO_3 (82.8 mg, 1.5 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 90 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent to give the corresponding product **3m**. Yield 83% (85.3 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.7 Hz, 1H), 7.95 (d, J = 1.0 Hz, 1H), 7.61−7.54 (m, 4H), 7.47−7.43 (m, 1H), 7.39 (dd, J = 4.5, 1.0 Hz, 2H), 7.35−7.32 (m, 2H), 7.29−7.27 (m, 1H), 7.25−7.21 (m, 1H), 4.72−4.64 (m, 2H), 3.75 (s, 3H), 3.56−3.49 (m, 1H), 2.89 (t, J = 8.0 Hz, 2H), 2.39−2.30 (m, 1H), 2.22−2.13 (m, 1H), 1.44 (dd, J = 6.8, 2.1 Hz, 6H), 1.24 (dd, J = 6.6, 2.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 163.2, 162.6, 141.3, 139.8, 137.9, 132.1, 123.0, 127.5, 127.1, 126.7, 126.0, 123.7, 123.3, 120.4, 120.0, 109.92, 109.88, 52.6, 52.2, 49.8, 46.8, 34.7, 31.9, 21.01, 20.99, 20.24, 20.17; HRMS Calcd for $C_{31}H_{35}N_3NaO_4$ [M + Na$^+$] 536.2525, found 536.2521.

General Procedure for Palladium-Catalyzed Arylation of 1a with Heteroaryl Iodides (Table 2) (3n−3q). A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), heteroaryl iodides (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2CO_3 (82.8 mg, 1.5 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 110 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(1-(phenylsulfonyl)-1H-indol-3-yl)butanoate (**3n**).* 3-Iodo-1-(phenylsulfonyl)-indole was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 77% (81.3 mg); white oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.88−7.86 (m, 2H), 7.52 (t, J = 7.4 Hz, 1H), 7.46−7.41 (m, 3H), 7.38−7.29 (m, 3H), 7.23 (t, J = 7.5 Hz, 2H), 4.73−4.66 (m, 1H), 4.65−4.60 (m, 1H), 3.70 (s, 3H), 3.57−3.50 (m, 1H), 2.81−2.68 (m, 2H), 2.34−2.25 (m, 1H), 2.16−2.07 (m, 1H), 1.61 (s, 2H), 1.45 (d, J = 6.8 Hz, 6H), 1.24 (dd, J = 6.6, 3.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 163.1, 162.4, 138.3, 135.4, 133.8, 130.7, 129.4, 126.9, 125.0, 123.3, 123.2, 121.6, 119.5, 113.9, 52.7, 52.0, 49.9, 46.8, 31.6, 21.03, 21.00, 20.3, 20.2; HRMS Calcd for $C_{27}H_{33}N_3NaO_6S$ [M + Na$^+$] 550.1988, found 550.1984.

*Methyl 4-(5-acetylthiophen-2-yl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3o**).* 5-Acetyl-2-iodothiophene was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 77% (81.3 mg); yellow solid; mp = 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 3.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 3.8 Hz, 1H), 4.67−4.58 (m, 2H), 3.75 (s, 3H), 3.56−3.49 (m, 1H), 2.99−2.87 (m, 2H), 2.50 (s, 3H), 2.35−2.26 (m, 1H), 2.16−2.09 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.24−1.21 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.6, 170.6, 162.2, 161.4, 151.9, 141.8, 132.0, 125.5, 51.8, 50.6, 48.9, 45.8, 32.7, 25.8, 25.6, 19.99, 19.95, 19.2, 19.1; HRMS Calcd for $C_{19}H_{28}N_2NaO_5S$ [M + Na$^+$] 419.1617, found 419.1620.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(2-(trifluoromethyl)pyridin-4-yl)butanoate (**3p**).* 4-Iodo-2-(trifluoromethyl)pyridine was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 67% (55.9 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 5.0 Hz, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.31 (d, J = 4.8 Hz, 1H), 4.59−4.51 (m, 2H), 3.71 (s, 3H), 3.54−3.47 (m, 1H), 2.79 (t, J = 8.1 Hz, 2H), 2.30−2.21 (m, 1H), 2.15−2.05 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.21 (dd, J = 6.6, 4.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 163.5, 162.8, 151.7, 150.2, 148.5 (q, J_{C-F} = 34.0 Hz), 126.6, 121.6 (q, J_{C-F} = 273.0 Hz), 120.7, (q, J_{C-F} = 2.0 Hz), 52.7, 51.8, 50.0, 46.7, 32.3, 31.2, 20.9, 20.8, 20.2, 20.1; HRMS Calcd for $C_{19}H_{26}F_3N_3NaO_4$ [M + Na$^+$] 440.1773, found 440.1783.

*Methyl 4-(2,6-dichloropyridin-4-yl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3q**).* 2,6-Dichloro-4-iodopyridine was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 69% (57.7 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 1H), 7.11 (s, 2H), 4.66−4.56 (m, 2H), 3.76 (s, 3H), 3.56−3.50 (m, 1H), 2.75−2.62 (m, 2H), 2.28−2.19 (m, 1H), 2.10−2.03 (m, 1H), 1.43 (d, J = 6.8 Hz, 6H), 1.24 (t, J = 6.7 Hz, 6H); ^{13}C

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NMR (101 MHz, $CDCl_3$) δ 171.3, 163.2, 162.4, 155.5, 150.8, 123.0, 52.9, 51.7, 49.9, 46.8, 32.4, 30.7, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{18}H_{25}Cl_2N_3NaO_4$ [M + Na^+] 440.1120, found 440.1121.

General Procedure for Palladium-Catalyzed Arylation of 1a with Heteroaryl Iodides (Table 2) (3r−3x). A mixture of **1a** (54.5 mg, 0.2 mmol, 1.0 equiv), heteroaryl iodides (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (6.6 mg, 15 mol %), Ag_2CO_3 (82.8 mg, 1.5 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 150 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel to give the corresponding product.

*Methyl 4-(2-chloropyridin-4-yl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3r**).* 2-Chloro-4-iodopyridine was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 48% (36.9 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 5.1 Hz, 1H), 7.71 (d, J = 7.9 Hz, 1H), 7.14 (s, 1H), 7.03 (d, J = 5.0 Hz, 1H), 4.59−4.53 (m, 2H), 3.72 (s, 3H), 3.54−3.47 (m, 1H), 2.70−2.66 (m, 2H), 2.25−2.17 (m, 1H), 2.11−2.01 (m, 1H), 1.40 (d, J = 6.8 Hz, 6H), 1.21 (t, J = 6.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 163.4, 162.7, 153.0, 151.8, 149.7, 124.3, 122.7, 52.7, 51.7, 49.9, 46.7, 32.3, 30.8, 20.9, 20.9, 20.2, 20.1; HRMS Calcd for $C_{18}H_{26}ClN_3NaO_4$ [M + Na^+] 406.1510, found 406.1504.

*Methyl 4-(6-bromopyridin-3-yl)-2-(2-(diisopropylamino)-2-oxoacetamido)butanoate (**3s**).* 2-Bromo-5-iodopyridine was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 47% (40.3 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.44 (d, J = 1.6 Hz, 2H), 4.70−4.59 (m, 2H), 3.79 (s, 3H), 3.61−3.54 (m, 1H), 2.75−2.67 (m, 2H), 2.30−2.21 (m, 1H), 2.14−2.04 (m, 1H), 1.47 (d, J = 6.8 Hz, 6H), 1.28 (t, J = 6.3 Hz, 6H); ^{13}C NMR (101 MHz, CDCl3) δ 171.6, 163.2, 162.5, 150.3, 140.1, 138.8, 135.3, 128.0, 52.8, 51.7, 49.9, 46.8, 33.4, 28.3, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{18}H_{26}BrN_3NaO_4$ [M + Na^+] 450.1004, found 450.1001.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(5-iodopyridin-2-yl)butanoate (**3t**).* 2,5-Diiodopyridinewas used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent; Yield 36% (34.2 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 1.8 Hz, 1H), 7.87 (dd, J = 8.2, 2.2 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 6.97 (d, J = 8.2 Hz, 1H), 4.63−4.54 (m, 2H), 3.72 (s, 3H), 3.54−3.47 (m, 1H), 2.82 (t, J = 7.5 Hz, 2H), 2.38−2.30 (m, 1H), 2.23−2.14 (m, 1H), 1.43 (dd, J = 6.8, 1.8 Hz, 6H), 1.21 (dd, J = 6.6, 2.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 163.4, 162.8, 159.1, 155.3, 144.9, 125.2, 90.6, 52.6, 52.0, 49.8, 46.6, 33.3, 31.0, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{18}H_{26}IN_3NaO_4$ [M + Na^+] 498.0866, found 498.0863.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(3-fluoropyridin-4-yl)butanoate (**3u**).* 2-Fluoro-4-iodopyridine was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent; Yield 39% (28.7 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 5.2 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.01−6.99 (m, 1H), 6.75 (s, 1H), 4.63−4.55 (m, 2H), 3.55−3.48 (m, 1H), 2.79−2.67 (m, 2H), 2.26−2.21 (m, 1H), 2.12−2.04 (m, 1H), 1.41 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 6.5, 5.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 164.3 (d, J_{C-F} = 237.0 Hz), 163.3, 162.6, 155.6 (d, J_{C-F} = 8.0 Hz), 147.7 (d, J_{C-F} = 15.0 Hz), 121.7 (d, J_{C-F} = 4.0 Hz), 109.3 (d, J_{C-F} = 37.0 Hz), 52.8, 51.7, 49.9, 46.7, 32.4, 30.98, 30.95, 20.94, 20.88, 20.2, 20.1; HRMS Calcd for $C_{18}H_{26}FN_3NaO_4$ [M + Na^+] 390.1805, found 390.1816.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(1-tosyl-1H-indol-5-yl)butanoate (**3v**).* 5-Iodo-1-(4-methylphenylsulfonyl)indole was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 52% (56.4 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 7.11 (dd, J = 8.5, 1.5 Hz, 1H), 6.58 (d, J = 3.6 Hz, 1H), 4.70−4.63 (m, 1H), 4.60−4.55 (m, 1H), 3.68 (s, 3H), 3.56−3.49 (m, 1H), 2.75−2.71 (m, 2H), 2.33 (s, 3H), 2.27−2.18 (m, 1H), 2.10−1.99 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.6, 3.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 163.1, 162.5, 145.0, 135.6, 135.4, 133.6, 131.2, 130.0, 126.9, 126.7, 125.4, 121.0, 113.6, 109.0, 52.6, 52.0, 49.8, 46.8, 34.3, 31.5, 21.7, 21.0, 21.0, 20.3, 20.2; HRMS Calcd for $C_{28}H_{35}N_3NaO_6S$ [M + Na^+] 564.2144, found 564.2162.

*Methyl 5-(3-(2-(diisopropylamino)-2-oxoacetamido)-4-methoxy-4-oxobutyl)furan-2-carboxylate (**3w**).* Methyl 5-bromo-2-furoate was used as arylation reagent. Purified by column chromatography on silica gel with petroleum ester/ethyl acetate (7/1) as an eluent; Yield 42% (33.3 mg); brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.2 Hz, 1H), 7.07 (d, J = 3.4 Hz, 1H), 6.19 (d, J = 3.4 Hz, 1H), 4.68−4.57 (m, 2H), 3.86 (s, 3H), 3.74 (s, 3H), 3.55−3.48 (m, 1H), 2.81−2.77 (m, 2H), 2.36−2.27 (m, 1H), 2.16−2.06 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.22 (dd, J = 6.6, 4.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 163.1, 162.3, 159.3, 159.0, 143.5, 119.3, 108.7, 52.8, 51.9, 51.6, 49.8, 46.8, 30.4, 24.6, 20.99, 20.95, 20.2, 20.1; HRMS Calcd for $C_{19}H_{28}N_2NaO_7$ [M + Na^+] 419.1794, found 419.1808.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-3-(4-methoxybenzyl)pentanoate (**4a**).* A mixture of **1b** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(TFA)_2$ (6.0 mg, 10 mol %), Ag_2CO_3 (165.6 mg, 3.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 60 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gelwith petroleum ester/ethyl acetate (8/1) as an eluent to give the corresponding product **4a**. Yield 55% (44.7 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11−7.07 (m, 3H), 6.84−6.81 (m, 2H), 4.64−4.58 (m, 2H), 3.77 (s, 3H), 3.71 (s, 3H), 3.56−3.49 (m, 1H), 2.61−2.47 (m, 2H), 2.21−2.15 (m, 1H), 1.46−1.35 (m, 8H), 1.23 (t, J = 6.4 Hz, 6H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 163.4, 162.9, 158.2, 131.7, 130.2, 114.0, 55.3, 53.7, 52.5, 49.9, 46.7, 45.0, 36.1, 22.9, 21.02, 20.96, 20.3, 20.2, 11.9; HRMS Calcd for $C_{22}H_{34}N_2NaO_5$ [M + Na^+] 429.2365, found 429.2364.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-3-(4-methoxybenzyl)-4-(4-methoxyphenyl)butanoate (**4b**).* A mixture of **1c** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.6 mmol, 3.0 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2CO_3 (165.6 mg, 3.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 130 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (8/1) as an eluent to give the corresponding product **4b**. Yield 83% (82.8 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 9.0 Hz, 1H), 7.06 (t, J = 8.5 Hz, 4H), 6.83−6.78 (m, 4H), 4.62−4.59 (m, 2H), 3.77 (d, J = 5.4 Hz, 6H), 3.61 (s, 3H), 3.56−3.49 (m, 1H), 2.65−2.54 (m, 5H), 1.46 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 7.9, 7.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 163.5, 162.9, 158.3, 158.2, 131.5, 131.15, 130.2, 130.2, 114.0, 55.33, 55.29, 53.6, 52.4, 49.8, 46.6, 45.5, 36.1, 35.5, 21.1, 20.9, 20.3, 20.2; HRMS Calcd for $C_{28}H_{38}N_2NaO_6$ [M + Na^+] 521.2628, found 521.2624.

*Methyl 1-(2-(diisopropylamino)-2-oxoacetamido)-3-(4-methoxyphenyl)cyclohexanecarboxylate (**4c**).* A mixture of **1d** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(TFA)_2$ (6.0 mg, 10 mol %), Ag_2CO_3 (165.6 mg, 3.0equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 60 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent to give the corresponding product **4c**. Yield 61% (51.1 mg); yellow soid; mp = 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (br s, 1H), 7.12 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H),

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4.71−4.64 (m, 1H), 3.77 (d, J = 1.2 Hz, 6H), 3.52−3.45 (m, 1H), 3.01−2.95 (m, 1H), 2.68 (d, J = 12.9 Hz, 1H), 2.49 (d, J = 12.6 Hz, 1H), 1.89−1.80 (m, 2H), 1.73−1.69 (m, 1H), 1.58−1.49 (m, 2H), 1.43−1.34 (m, 7H), 1.19 (t, J = 6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9, 162.5, 162.2, 158.1, 138.1, 127.8, 113.9, 59.5, 55.4, 52.4, 49.6, 46.7, 41.7, 39.1, 34.1, 33.1, 22.7, 21.0, 20.9, 20.2; HRMS Calcd for $C_{23}H_{34}N_2NaO_5$ [M + Na^+] 441.2365, found 441.2373.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-2-(2-(4-methoxyphenyl)cyclopropyl)acetate (**4d**).* A mixture of **1e** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (82.8 mg, 1.5 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 60 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent to give the corresponding product **4d**. Yield 66% (51.5 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 7.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 4.67−4.60 (m, 1H), 3.79−3.75 (m, 4H), 3.60 (s, 3H), 3.53−3.47 (m, 1H), 2.33 (dd, J = 15.2, 8.4 Hz, 1H), 1.53−1.46 (m, 1H), 1.42 (d, J = 6.8 Hz, 6H), 1.20 (dd, J = 9.7, 6.7 Hz, 6H), 1.14−1.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.6, 162.9, 162.6, 158.4, 130.1, 129.0, 113.7, 55.3, 52.3, 51.9, 49.7, 46.7, 22.0, 21.5, 21.0, 20.9, 20.2, 20.1, 8.0; HRMS Calcd for $C_{21}H_{31}N_2O_5$ [M + H^+] 391.2233, found 391.2226.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-2-(2-(4-methoxyphenyl)cyclobutyl)acetate (**4e**).* A mixture of **1f** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (82.8 mg, 1.5 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 90 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (10/1) as an eluent to give the corresponding product **4e**. Yield 70% (56.6 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2H), 6.83−6.81 (m, 2H), 6.65 (d, J = 7.6 Hz, 1H), 4.53−4.46 (m, 1H), 4.13 (dd, J = 10.1, 7.9 Hz, 1H), 3.78−3.72 (m, 4H), 3.65 (s, 3H), 3.48−3.41 (m, 1H), 3.10−3.01 (m, 1H), 2.41−2.25 (m, 2H), 2.15 (dd, J = 15.6, 7.9 Hz, 2H), 1.39 (dd, J = 8.7, 6.9 Hz, 6H), 1.13 (t, J = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 162.3, 161.9, 158.4, 132.0, 129.2, 114.0, 55.3, 53.5, 52.3, 49.4, 46.6, 41.3, 40.9, 23.7, 22.4, 21.0, 20.9, 20.2, 20.1; HRMS Calcd for $C_{22}H_{32}N_2NaO_5$ [M + Na^+] 427.2209, found 427.2204.

*Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-2-(2-(4-methoxyphenyl)cyclohexyl)acetate (**4f**).* A mixture of **1g** (0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), Ag_2CO_3 (165.6 mg, 3.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 130 °C with vigorous stirring for 36 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate(8/1) as an eluent to give the corresponding product **4f**. Yield 34% (29.4 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.40 (d, J = 8.0 Hz, 1H), 4.52−4.45 (m, 1H), 4.41 (t, J = 8.6 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.44−3.37 (m, 1H), 3.03−3.01 (m, 1H), 2.41−2.35 (m, 1H), 1.90−1.73 (m, 5H), 1.52−1.44 (m, 3H), 1.34 (dd, J = 13.1, 6.8 Hz, 6H), 1.14 (dd, J = 22.0, 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 162.4, 161.9, 158.3, 135.7, 129.6, 114.0, 55.2, 54.5, 52.2, 49.4, 46.5, 42.7, 42.3, 27.5, 23.6, 23.4, 20.9, 20.9, 20.0; HRMS Calcd for $C_{24}H_{36}N_2NaO_5$ [M + Na^+] 455.2522, found 455.2521.

*(S)-Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-phenylbutanoate (**3a′**).* A mixture of oxalyl amide protected L-amino ester **1a′** (54.5 mg, 0.2 mmol, 1.0 equiv), 4-iodoanisole (0.3 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (55.2 mg, 1.0 equiv), PivOH (6.1 mg, 0.3 equiv) and mesitylene (0.6 mL) in a 15 mL glass vial [sealed with poly(tetrafluoroethylene) (PTFE) cap] was heated at 90 °C with vigorous stirring for 24 h. The reaction mixture was cooled to room temperature, diluted with ethyl acetate and filtered through Celite. The filtrate was concentrated in vacuo and purified by column chromatography on silica gel with petroleum ester/ethyl acetate (9/1) as an eluent to give the corresponding product **3a′**. Yield 82% (62.1 mg); yellow oil; >99.5% ee [Daicel Chiralcel OD-H, hexanes/i-PrOH = 85/15, flow rate: 1.0 mL·min^{-1}, λ = 254.4 nm, t (major)= 5.857, t (minor)= 6.330]. $[\alpha]_D^{25}$ = 14.03 (c 1.06, acetone).

*(E)-Methyl 2-(2-(diisopropylamino)-2-oxoacetamido)-4-(2-(3,3-dimethylbut-1-en-1-yl)-4-methoxyphenyl)butanoate (**5**).* A mixture of **3a** (75.7 mg, 0.2 mmol), 3,3-dimethyl-1-butene (2 equiv), $Pd(OAc)_2$ (2.2 mg, 5 mol %), Ag_2CO_3 (165.6 mg, 3 equiv), $(n\text{-}BuO)_2PO_2H$ (12.6 mg, 0.3 equiv) and DCE (1 mL) in a 15 mL glass tube (sealed with PTFE cap) was heated at 140 °C for 36 h. The reaction mixture was cooled to room tempreture, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel with petroleum ester/ethyl acetate (12/1) as an eluent to give the alkenylated product **5**. Yield 53% (48.8 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.7 Hz, 1H), 6.70 (dd, J = 8.4, 2.7 Hz, 1H), 6.44 (d, J = 15.9 Hz, 1H), 6.10 (d, J = 15.9 Hz, 1H), 4.76−4.69 (m, 1H), 4.60−4.55 (m, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.56−3.49 (m, 1H), 2.74−2.61 (m, 2H), 2.17−2.08 (m, 1H), 1.98−1.91 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.6, 2.3 Hz, 6H), 1.12 (s, 9H); ^{13}C NMR (101 MHz, CDCl3) δ 172.0, 163.0, 162.3, 158.5, 144.5, 138.2, 130.6, 130.0, 120.0, 112.6, 111.6, 55.4, 52.6, 52.3, 49.7, 46.8, 33.8, 33.6, 29.7, 28.8, 21.0, 20.2, 20.2; HRMS Calcd for $C_{26}H_{40}N_2NaO_5$ [M + Na^+] 483.2835, found 483.2835.

*Methyl 4-(3-(2-(diisopropylamino)-2-oxoacetamido)-4-methoxy-4-oxobutyl)-3-((triisopropylsilyl)ethynyl)benzoate (**6**).* A mixture of **3k** (81.3 mg, 0.2 mmol), bromoalkyne (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), AgOAc (0.4 mmol, 2.0 equiv), KOAc (0.6 mmol, 3.0 equiv) and toluene (1 mL) under Ar atmospherein a 15 mL glass tube (sealed with PTFE cap) was heated at 120 °C for 36 h. The reaction mixture was cooled to room tempreture, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel with petroleum ester/ethyl acetate (30/1) as an eluent to give the alkynylated product **6**. Yield 48% (48.8 mg); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 1.7 Hz, 1H), 7.89 (dd, J = 8.0, 1.8 Hz, 1H), 7.30−7.25 (m, 3H), 4.74−4.68 (m, 1H), 4.57−4.51 (m, 1H), 3.91 (s, 3H), 3.69 (s, 3H), 3.56−3.49 (m, 1H), 2.95 (t, J = 7.8 Hz, 2H), 2.41−2.32 (m, 1H), 2.11−2.02 (m, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.23 (dd, J = 6.6, 2.0 Hz, 6H), 1.14 (d, J = 2.4 Hz, 21H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 166.5, 163.1, 162.3, 147.7, 134.4, 129.7, 129.3, 128.6, 123.5, 104.2, 96.3, 52.6, 52.3, 52.0, 49.7, 46.8, 32.3, 31.2, 21.03, 20.99, 20.23, 20.16, 18.8, 11.4; HRMS Calcd for $C_{23}H_{29}BrN_2NaO_6$ [M + Na^+] 531.1107, found 531.1118.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00649.

^{1}H and ^{13}C NMR spectra of all new compounds and HPLC trace for compound **3a′**. (PDF)

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Notes

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