JOC The Journal of Organic Chemistry

Article

Pd(II)-Catalyzed Directed #-C(sp3)–H Arylation between Free #2-Amino Esters and #3-Amino Esters and Aryl Iodides Using a Catalytic Transient Directing Group

Zhaohui Wang, Yangjie Fu, Qiyu Zhang, Hong Liu, and Jiang Wang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00115 • Publication Date (Web): 19 May 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

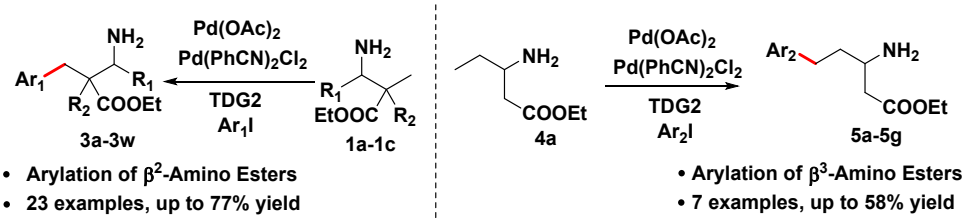
Pd(II)-Catalyzed Directed γ-C(sp³)–H Arylation between Free β²-Amino Esters and β³-Amino Esters and Aryl Iodides Using a Catalytic Transient Directing Group

Zhaohui Wang, [a,b] Yangjie Fu, [a,b] Qiyu Zhang,[a,b] Hong Liu, *,[a,b] and Jiang Wang*,[b]

[a] Jiangsu Key Laboratory of Drug Design and Optimization, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

[b] State Key Laboratory of Drug Research and Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, China.

Supporting Information Placeholder

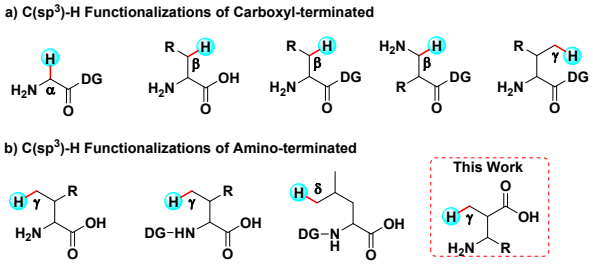


ABSTRACT: Pd(II)-catalyzed directed γ-C(sp³)-H arylation coupling with free β²-amino esters and β³-amino esters using a commercially available catalytic transient directing group has been developed. This approach features high efficiency, broad substrate tolerance, easily accessible starting materials and mild reaction conditions.

INTRODUCTION

β-amino acids (β-AAs) are significant and rewarding functional moieties in various peptides, peptidomimetics, proteins, antibiotics, and other biologically active compounds[1] and being increasingly used in the pharmaceutical, agrochemical, and healthcare industries.[1-2] Traditionally, the synthesis of β-AAs and their derivatives were mainly carried out by the carbonylation of enamines.[3] In recent years, using transition-metal-catalyzed direct C−H functionalization strategy to modify simple amino acids is an efficient and valuable route to obtain unnatural amino acids.[4] This C–H functionalization strategy has two pivotal methods: carboxy-terminal and amino-terminal assisted directing groups.[5-6] The former implements modification of α-amino acids via α-, β-, and γ-C(sp³)-H activation or β-amino acids via β- C(sp³)-H activation[5] and the latter through γ- and δ-C(sp³)-H activation to achieve unnatural α-amino acid. [6] A few special examples can directly realize C-H functionalization by free carboxyl or amino groups,[5d,6c] most of which require an additional directing group including pyridine, 8-aminoquinoline, 2-picolinamide, oxazolines, and coordinating amide directing groups, with transition-metal forming monodentate, bidentate, and tridentate metallacyclic intermediate to achieve site-selective activation of C-H bonds (**Scheme 1**).[7]

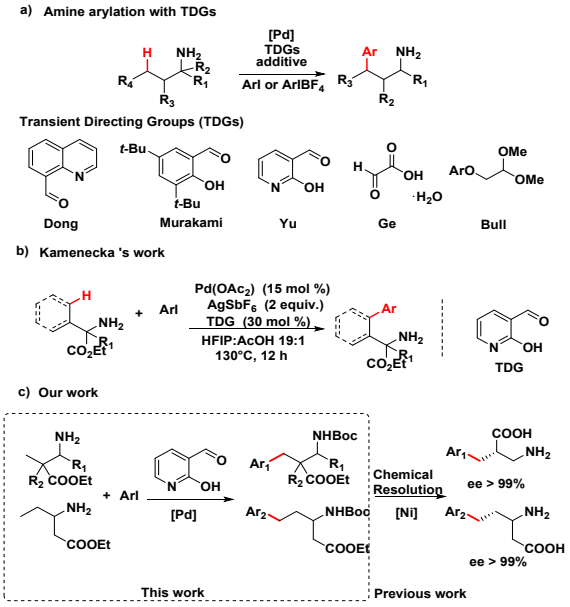
Scheme 1. C(sp³)-H Functionalizations of Amino Acids



Recently, transient directing groups (TDGs) catalyzed site-selective C–H functionalization have received significant attention, due to the absence of additional directing groups installed and removed in situ.[8-9] And free primary amines used as substrates have been realized Pd(II)-catalyzed γ-C(sp²)-H, γ-C(sp³)-H or δ-C(sp³)-H arylation by employing TDGs.[9] Dong et al. used 8-formylquinoline as exo-imine-type directing group to achieve arylation of free primary amines.[9a] Murakami's group produced γ-arylated primary amines employing salicylaldehydes as directing group.[9b] Although these two types of aldehyde-directing groups were used in the reaction without catalytic amount, they had the characteristic of easily installable and removable. Yu *et al.* discribed that free amines could react with the TDG 2-hydroxynicotinaldehyde producing the reversible imine intermediate to realize γ-C(sp³)-H and δ-C(sp³)-H arylation.[9c-9d] Ge and his co-workers developed the Pd(II)-catalyzed γ-C(sp³)–H arylation of primary aliphatic amines using a catalytic amount of glycoylic acid as TDG.[9e] And Bull's group presented the use of novel TDG

alkyl acetals as transient activators to obtain γ-C(sp^3)-H arylation of primary amines (**Scheme 2a**).[9f] Recently, Kamenecka *et al.* reported the cross-coupling reactions of C(sp^2)-H or C(sp^3)-H bonds of α-amino esters with arenes and heteroarenes in the presence of 2-hydroxynicotinaldehyde (**Scheme 2b**).[9g] In C–H activation, the transition-metal-catalyzed γ-C(sp^3)–H arylation of free β-amino esters are rarely reported. At the same time, our groups havereported a chemical method for the resolution of racemic β^2-AAs and β^3-AAs using chiral Ni(II)-complexes in our previous work. Therefore, various chiral β^2-AAs and β^3-AAs can be obtained by the C–H functionalization of simple β-AAs and chemical resolution.[10] Herein, we report Pd(II)-catalyzed directed γ-C(sp^3)–H arylation of free β^2-amino esters and β^3-amino esters by catalytic TDGs (**Scheme 2c**).

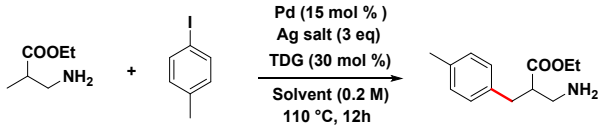
Scheme 2. γ-C(sp^3)-H Arylation of Free Amines with TDGs



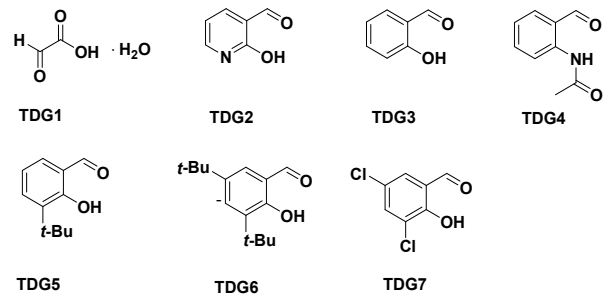
RESULTS AND DISCUSSION

Initially, ethyl 3-amino-2-methylpropanoate **1a** was chosen as prototypical substrate for arylation with 4-iodotoluene **2a** due to its applicability and abundancy. After we commenced our investigation of the reaction conditions by screening TDGs using $Pd(OAc)_2$ and AgTFA in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 110 °C for 12 h (Table 1). Interestingly, relative to the other TDGs, which yielded trace product **3a**, a 48% ^{1}H NMR yield was obtained when **TDG2** was employed (Table 1, entries 1-7). Using other silver salts instead of AgTFA reduced the yield (Table 1, entries 8-10). No reaction was observed in the absence of a silver salt (Table 1, entry 11). Screening of the solvents showed that acidic conditions could promote this reaction, although using AcOH and TFA gained the lower yield (Table 1, entries 12-14). Furthermore, we carried out survey of the palladium source to optimize the reaction conditions, however, none of them provided a better yield than $Pd(OAc)_2$ (Table 1, entries 15-17). In recent years, cooperative metal catalytic systems produced numerous applications in oxidative addition and reductive elimination reaction.[11-12] The strategy of combining palladium with other metals, such as Pd/Rh[11a, 11b], Pd/Au[11d], Pd/Ni[11e], Pd/Cu[11d, 11f, 11g]and Pd/Pd[12a, 12d, 12f], have been extensively studied in depth. Double Pd(II)-catalyzed were commonly used in cross-coupling reactions for example Heck reaction, Suzuki-coupling reaction or C−H functionalization, which can potentially lower activation barriers of chemical transformations compared to single Pd(II)-catalyzed system.[12-13] A further investigation revealed that co-catalyst combined the $Pd(OAc)_2$ and $Pd(PhCN)_2Cl_2$ was the best choice, affording the desired product **3a** in 70% isolated yield (Table 1, entries 18-20). Simultaneously, when the 2 equiv. or 10 equiv. of H_2O were additional added in the similar reaction conditions, the yields are lower than without water (Table 1, entries 21 and 22). And the reaction under argon atmosphere was obtained slightly lower yield (Table 1, entry 23). The reaction with a mixture of HFIP and TFA was obtained 54% yield, which was lower than using the mixture of HFIP and AcOH in the similar reaction conditions (Table 1, entry 24).

Table 1. Optimizing the Conditions for γ-C(sp^3)-H Arylation of Free β^2-Amino Ester [a]



Transient Directing Groups (TDGs)



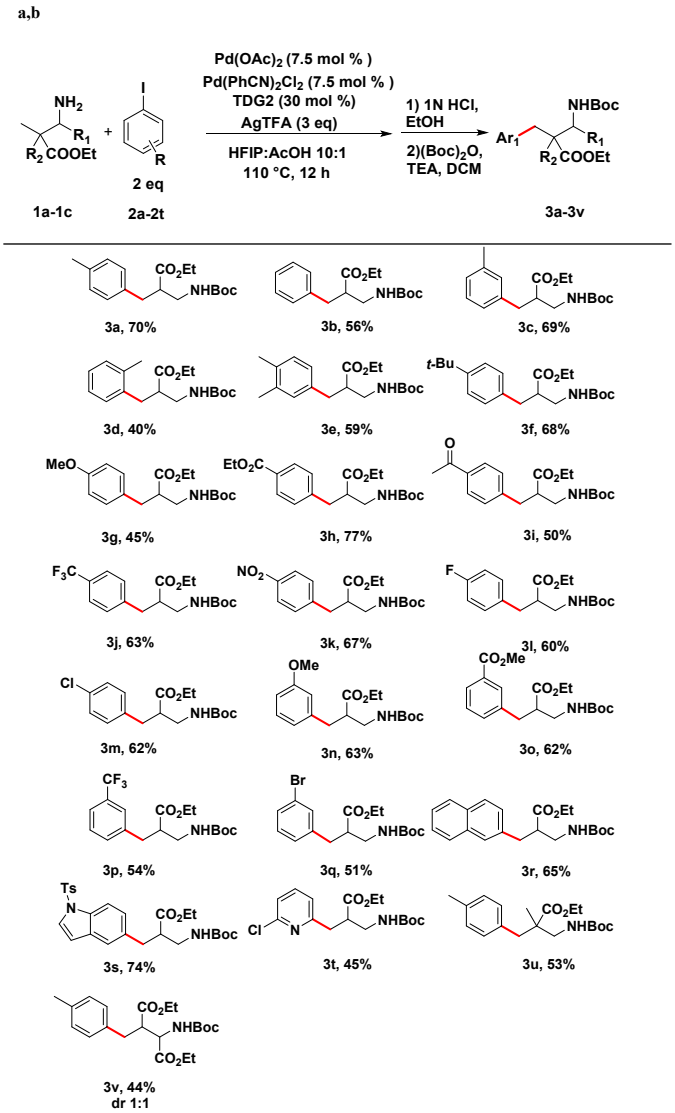
Entry	Pd	TDG	Ag salt	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	TDG1	AgTFA	HFIP:AcOH 10:1	10
2	$Pd(OAc)_2$	TDG2	AgTFA	HFIP:AcOH 10:1	48
3	$Pd(OAc)_2$	TDG3	AgTFA	HFIP:AcOH 10:1	<5
4	$Pd(OAc)_2$	TDG4	AgTFA	HFIP:AcOH 10:1	<5
5	$Pd(OAc)_2$	TDG5	AgTFA	HFIP:AcOH 10:1	<5
6	$Pd(OAc)_2$	TDG6	AgTFA	HFIP:AcOH 10:1	<5
7	$Pd(OAc)_2$	TDG7	AgTFA	HFIP:AcOH 10:1	14
8	$Pd(OAc)_2$	TDG2	Ag_2CO_3	HFIP:AcOH 10:1	7
9	$Pd(OAc)_2$	TDG2	$AgSbF_6$	HFIP:AcOH 10:1	16
10	$Pd(OAc)_2$	TDG2	AgOAc	HFIP:AcOH 10:1	21
11	$Pd(OAc)_2$	TDG2	-	HFIP:AcOH 10:1	NR
12	$Pd(OAc)_2$	TDG2	AgTFA	HFIP	16
13	$Pd(OAc)_2$	TDG2	AgTFA	AcOH	32
14	$Pd(OAc)_2$	TDG2	AgTFA	TFA	29
15	$Pd(TFA)_2$	TDG2	AgTFA	HFIP:AcOH 10:1	11
16	$Pd(PhCN)_2Cl_2$	TDG2	AgTFA	HFIP:AcOH 10:1	47
17	$Pd_2(dba)_3$	TDG2	AgTFA	HFIP:AcOH 10:1	16
18[c]	$Pd(OAc)_2$, $Pd(TFA)_2$	TDG2	AgTFA	HFIP:AcOH 10:1	57

19[c]	$Pd(OAc)_2$, $Pd_2(dba)_3$	TDG2	AgTFA	HFIP:AcOH 10:1	55
20[c]	$Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$	TDG2	AgTFA	HFIP:AcOH 10:1	73 (70[d])
21[c, e]	$Pd(OAc)_2$, $Pd(PhCN)_2C_{l2}$	TDG2	AgTFA	HFIP:AcOH 10:1	59
22[c, f]	$Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$	TDG2	AgTFA	HFIP:AcOH 10:1	42
23[c, g]	$Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$	TDG2	AgTFA	HFIP:AcOH 10:1	51
24[c]	$Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$	TDG2	AgTFA	HFIP:TFA 10:1	54

[a] Reactions were performed using **1a** (0.3 mmol, 1 equiv.), **2a** (0.6 mmol, 2 equiv.), Pd catalyst (15 mol %), silver salt (0.9 mmol, 3 equiv.), **TDG** (30 mol %), solvent (2 mL). [b] ^{1}HNMR yield, used 1,3,5-trimethoxybenzene as an internal standard. [c] $Pd(OAc)_2$ (7.5 mol %) and another Pd catalyst (7.5 mol %) were used. [d] Isolated yield. [e] 2 equiv. of H_2O was additional added. [f] 10 equiv. of H_2O was additional added. [g] the reaction was performed under argon.

Under optimal conditions, we next investigated the reaction of ethyl 3-amino-2-methylpropanoate **1a** with a variety of iodides **2a-2t** (Table 2). Boc protection of the amino esters was performed in order to ease of separation and purification. Unsubstituted iodobenzene (**2b**) and various other methyl substituted aryl iodides (**2c** and **2d**) were firstly introduced to give the desired γ-aryl substituted β^2-amino esters. Except *o*-methyl substituted which was poorly tolerated due to steric effects, methyl substituted in other positions and phenyl substituted aryl iodides gave moderate to good yields (**3a**–**3e**, 40-70%). Aryl iodides bearing electron-donating groups (*t*-Bu and OMe), electron-withdrawing group (COOEt, CH_3CO, CF_3, and NO_2), and the halogens (F and Cl) at the *para*-position of the phenyl ring produced the desired products in moderate to good yields (**3f–3m**, 45−77%). Moreover, *meta*-substituted aryl iodides with important functional groups including OMe, COOMe, CF_3, and Br gave the products in moderate yields (**3n–3q**, 51−63%). A naphthalene iodide was also well-tolerated and gave **3r** in 65% yield. Various heteroaryl iodides such as indole and pyridine provided the desired products in 74% and 45% yield, respectively (**3s** and **3t**). Next，more β^2-amino esters **1b-1e** as substrate underwent arylation with 4-iodotoluene **2a** under optimal conditions. Ethyl 3-amino-2,2-dimethylpropanoate **1b** reacted with 4-iodotoluene to obtain the product in 53% yield (**3u**). Once again, similar α-amino esters provided a 44% yield of the isomer product (**3v**). Regrettably, only trace arylation product was detected when using γ- substituted β^2-amino esters- ethyl 2-(aminomethyl)-4-methylpentanoate (**1d**) and ethyl 3-amino-2-benzylpropanoate (**1e**) as substrates.

Table 2. γ-C(sp^3)-H Arylation of Free β^2-Amino Esters

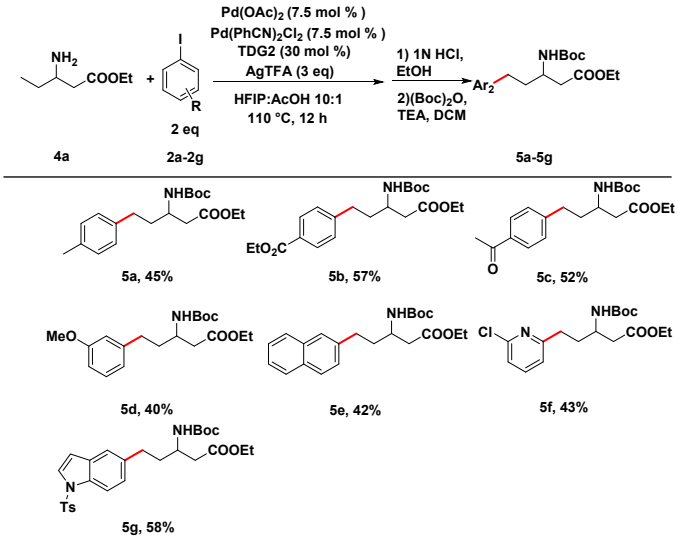


[a] Reactions conditions: **1a** (0.3 mmol, 1 equiv.), **2** (0.6 mmol, 2 equiv.), $Pd(OAc)_2$ (7.5 mol %), $Pd(PhCN)_2Cl_2$ (7.5 mol %), AgTFA (0.9 mmol, 3 equiv.), **TDG2** (30 mol %), HFIP : AcOH 10 : 1 (2 mL). [b] Isolated yield.

Using ethyl 3-aminopentanoate **4a** as the substrate, we carried out the scope study on aryl iodides **2a-2g** (Table 3). Unfortunately, *p*-methyl iodobenzene underwent arylation of β^3-amino esters to provide the lower yield in this case (**5a**, 45%). However, a slightly increased or parallel yield were obtained when electron-withdrawing groups COOEt and CH_3CO were introduced at the *para*-position of the aryl iodides, the yields were 57% and 52%, respectively (**5b** and **5c**). Aryl iodides with *meta*-electron-donating groups behaved similarly (**5d**, 40%). It is noteworthy that naphthalene and heteroaryl iodides were also tolerated, affording the desired products in moderate yields (**5e-5g**, 42%-58%).

Table 3. γ-C(sp^3)-H Arylation of Free β^3-Amino Esters

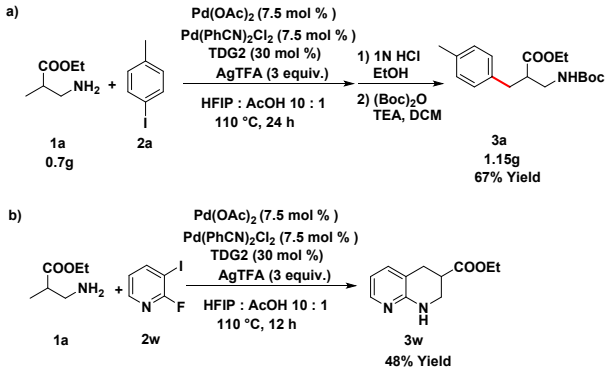
a,b



[a] Reactions conditions: **4a** (0.3 mmol, 1 equiv.), **2** (0.6 mmol, 2 equiv.), $Pd(OAc)_2$ (7.5 mol %), $Pd(PhCN)_2Cl_2$ (7.5 mol %), AgTFA (0.9 mmol, 3 equiv.), **TDG2** (30 mol %), HFIP : AcOH 10 : 1 (2 mL). [b] Isolated yield.

To explore the synthetic utility of this reaction, gram-scale synthesis of ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-methylbenzyl)propanoate **3a** was promoted, which obtained in 67% yield under optimal condition (**Scheme 3a)**. The C−H arylation of **1a** with 2-fluoro-3-iodopyridine **2w** affording the corresponding product **3w** in 48% yield by one-pot fashion revealed that an application of this strategy to the synthesis of bioactive fragment in pharmaceutical research (**Scheme 3b)**.[14]

Scheme 3. Gram-Scale Synthesis of Compound 3a and Synthetic Applications



CONCLUSIONS

In summary, we developed the combination of double Pd(II)-catalyzed directed γ-C(sp^3)–H arylation of free β^2-amino esters and β^3-amino esters with aryl iodides as coupling parteners employing a commercially available catalytic transient directing group. This new approach features high efficiency, broad functional tolerance, and wild reaction conditions, which provided a variety of unnatural β-amino acids by site-selective C–H functionalization of β-amino esters. Free β^2-amino esters and β^3-amino esters are shown to react with a diverse range of simple aryl and heteroaryl iodide reagents.

EXPERIMENTAL SECTION

General Information Unless otherwise specified, the reagents were purchased from commercial sources, and used without further purification. All products were characterized byNMR and HRMS spectra. ^{1}H and ^{13}C NMR spectra were recorded on a 400, 500 or 600 MHz instrument. The chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublets (dd), triplet of doublets(td), doublet of triplets(dt) and broad (br). Highresolution mass spectra (HRMS) were measured on a Micromass Ultra Q-TOF spectrometer. Analytical thin-layer chromatography (TLC) was performed on HSGF 254 (0.2-0.3 mm thickness). Column chromatography was performed on silica gel (300-400 mesh) using petroleum ether/ethyl acetate or dichoromethane/methanol. All of the heating reactions are carried out in oil bath.

General procedures for 1a-1e and 4a. To a solution of β-amino acid (1.0 equiv.) in EtOH was added $SOCl_2$ (1.5 equiv.) dropwise at 0 °C. The resulting mixture was heated to 90 °C for 6 h. After the solution was cooled and concentrated in vacuo. Then the crude residue was diluted with DCM (40 mL) and treated with ammonia hydroxide (25-28% w/w, 10 mL),stirred at room temperature for 2 h. The layers were separated and the aqueous layer were washed with DCM (2 x 30 mL) , and the organic layers were combined. The organic solution was washed by brine, dried over anhydrous sodium sulphate (Na_2SO_4) and concentrated to give the desired β-amino ester as pale-yellow oil which was used without further purification.

General procedures for 3a-3v and 5a-5g. A tube was charged with $Pd(OAc)_2$ (6.4 mg, 7.5 mol %), $Pd(PhCN)_2Cl_2$ (11.0 mg, 7.5 mol %), AgTFA (252.6 mg, 1.14 mmol), transient directing group (TDG2, 14.1 mg, 30 mol %), 4-iodotoluene (**2a**, 166 mg, 0.76 mmol) and HFIP : AcOH 10 : 1 (2 mL), followed by the free β^2-amino ester (**1a**, 50 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 30 minutes before heating to 110 °C for 12 hours. After that, the reaction mixture was cooled to room temperature and the solvent was filtered through a celite pad and washed with DCM. The solution was concentrated under vacuum. Then EtOH (2 mL) and HCl (2 *N*, 1 mL) were added to the residue, and the mixture was stirred at room temperature for 3 h. The solvent was filtered through a celite pad, washed with EtOH and concentrated under vacuum. The mixture was subsequently dissolved with DCM (4 mL) and TEA (15 equiv.) and Boc_2O (4.0 equiv.) were added. And then the brown solution was stirred at room temperature for 8 hours. DCM was added and the organic layer was extracted, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using petroleum

ether/ ethyl acetate (10:1) to afford the product **3a** as a colorless oil (yield: 70 %).

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-methylbenzyl)propanoate (3a). Colorless oil (86 mg, 70 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 4.84 (d, *J* = 6.6 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.40 – 3.33 (m, 1H), 3.25 (dt, *J* = 13.9, 6.9 Hz, 1H), 2.95 – 2.84 (m, 2H), 2.77 (dt, *J* = 12.2, 5.5 Hz, 1H), 2.30 (s, 3H), 1.42 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 174.3, 155.8, 136.0, 135.2, 129.2, 128.8, 79.3, 60.6, 47.4, 41.5, 35.5, 28.4, 21.0, 14.1. HRMS (ESI) calculated for $C_{18}H_{28}NO_4$ $[M+H]^+$: 322.2013; found: 322.2014.

Ethyl 2-benzyl-3-((*tert*-butoxycarbonyl)amino)propanoate (3b). Colorless oil (66 mg, 56 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.20 – 7.16 (m, 2H), 4.87 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.39 (s, 1H), 3.29 (d, *J* = 6.6 Hz, 1H), 3.03 – 2.89 (m, 2H), 2.83 (d, *J* = 8.4 Hz, 1H), 1.44 (s, 9H), 1.18 (t, *J* = 7.0 Hz, 3H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 174.2, 138.3, 128.9, 128.4, 126.5, 79.3, 60.6, 47.3, 41.6, 35.9, 28.4, 14.1. HRMS (ESI) calculated for $C_{17}H_{26}NO_4$ $[M+H]^+$: 308.1856; found: 308.1855.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(3-methylbenzyl)propanoate (3c). Colorless oil (84 mg, 69 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (t, *J* = 7.5 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.98 – 6.94 (m, 2H), 4.87 (d, *J* = 6.4 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.40 – 3.31 (m, 1H), 3.29 – 3.22 (m, 1H), 2.93 – 2.85 (m, 2H), 2.80 – 2.74 (m, 1H), 2.31 (s, 3H), 1.42 (s, 9H), 1.19 – 1.16 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 174.3, 155.8, 138.2, 138.0, 129.7, 128.4, 127.3, 125.9, 79.3, 60.6, 47.4, 41.6, 35.9, 28.4, 21.4, 14.1. HRMS (ESI) calculated for $C_{18}H_{28}NO_4$ $[M+H]^+$: 322.2013; found: 322.2015.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(2-methylbenzyl) propanoate (3d). Colorless oil (49 mg, 40 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.16 – 7.09 (m, 4H), 4.86 (s, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.41 – 3.29 (m, 2H), 2.97 – 2.86 (m, 2H), 2.78 (dd, *J* = 13.1, 6.1 Hz, 1H), 2.32 (s, 3H), 1.42 (s, 9H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 174.5, 155.7, 136.6, 136.1, 130.4, 129.5, 126.7, 126.0, 79.3, 60.6, 46.0, 41.7, 33.2, 28.3, 19.4, 14.1. HRMS (ESI) calculated for $C_{18}H_{27}NNaO_4$ $[M+Na]^+$: 344.1832; found: 344.1843.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(3,4-dimethylbenzyl)propanoate (3e). Colorless oil (75 mg, 59 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 6.88 (dd, *J* = 7.7, 2.0 Hz, 1H), 4.86 (d, *J* = 6.5 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.39 – 3.32 (m, 1H), 3.28 – 3.21 (m, 1H), 2.88 (d, *J* = 10.6 Hz, 2H), 2.73 (q, *J* = 9.8 Hz, 1H), 2.21 (d, *J* = 3.8 Hz, 6H), 1.42 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 157.2, 138.0, 137.1, 136.1, 131.7, 131.2, 127.68, 80.8, 62.1, 48.9, 43.0, 37.0, 29.8, 21.2, 20.8, 15.6. HRMS (ESI) calculated for $C_{19}H_{30}NO_4$ $[M+H]^+$: 336.2169; found: 336.2174.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-(*tert*-butyl)benzyl) propanoate (3f). Colorless oil (94 mg, 68 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 2H), 4.87 (s, 1H), 4.16 – 4.04 (m, 2H), 3.37 (dt, *J* = 16.6, 4.7 Hz, 1H), 3.31 – 3.21 (m, 1H), 2.90 (d, *J* = 9.4 Hz, 2H), 2.78 (q, *J* = 10.0 Hz, 1H), 1.42 (s, 8H), 1.29 (s, 9H), 1.16 (dt, *J* = 9.7, 8.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 174.4, 155.8, 149.4, 135.2, 128.6, 125.4, 79.3, 60.6, 47.3, 41.6, 35.5, 34.4, 31.4, 28.4, 14.1. HRMS (ESI) calculated for $C_{21}H_{34}NO_4$ $[M+H]^+$: 364.2482; found: 364.2493.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-methoxybenzyl)propanoate (3g). Colorless oil (58 mg, 45% yield, purified by silica gel chromatography using PE/EA 15:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.3 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 2H), 4.85 (d, *J* = 6.5 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.77 (d, *J* = 1.2 Hz, 3H), 3.35 (dt, *J* = 11.3, 4.9 Hz, 1H), 3.29 – 3.20 (m, 1H), 2.87 (q, *J* = 7.9 Hz, 2H), 2.78 – 2.70 (m, 1H), 1.42 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.9, 157.8, 155.3, 129.9, 129.4, 113.4, 78.9, 60.2, 54.8, 47.1, 41.1, 34.6, 27.9, 13.7. HRMS (ESI) calculated for $C_{18}H_{28}NO_5$ $[M+H]^+$: 338.1962; found: 338.1963.

Ethyl 4-(2-(((*tert*-butoxycarbonyl)amino)methyl)-3-ethoxy-3-oxopropyl)benzoate (3h). Colorless oil (111 mg, 77 % yield, purified by silica gel chromatography using PE/EA 15:1–5:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.19 (m, 2H), 4.90 (d, *J* = 6.5 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.09 (qd, *J* = 7.2, 2.2 Hz, 2H), 3.38 (dt, *J* = 11.6, 5.4 Hz, 1H), 3.28 (dt, *J* = 14.0, 7.0 Hz, 1H), 2.97 (ddd, *J* = 23.0, 14.2, 9.0 Hz, 2H), 2.87 (dd, *J* = 12.9, 5.9 Hz, 1H), 1.43 (s, 9H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.9, 166.5, 155.8, 143.7, 129.8, 128.9, 79.5, 60.9, 60.8, 47.1, 41.7, 35.8, 28.3, 14.3, 14.1. HRMS (ESI) calculated for $C_{20}H_{30}NO_6$ $[M+H]^+$: 380.2068; found: 380.2067.

Ethyl 2-(4-acetylbenzyl)-3-((*tert*-butoxycarbonyl)amino)propanoate (3i). Colorless oil (66 mg, 50 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.89 (s, 1H), 4.12 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.39 (s, 1H), 3.30 (dt, *J* = 14.0, 6.8 Hz, 1H), 3.03 (dd, *J* = 12.8, 7.6 Hz, 1H), 3.00 – 2.86 (m, 2H), 2.60 (s, 3H), 1.46 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 196.7, 172.8, 154.8, 143.1, 134.7, 128.1, 127.6, 78.5, 59.8, 46.0, 40.6, 34.8, 27.3, 25.6, 13.1. HRMS (ESI) calculated for $C_{19}H_{27}NNaO_5$ $[M+Na]^+$: 372.1781; found: 372.1780.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-(trifluoromethyl)benzyl)propanoate (3j). White solid (90 mg, 63 % yield,

purified by silica gel chromatography using PE/EA 20:1–6:1), m.p.:51-53 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.89 (t, *J* = 6.4 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.38 (dt, *J* = 13.9, 5.5 Hz, 1H), 3.29 (dt, *J* = 13.9, 7.0 Hz, 1H), 3.02 – 2.83 (m, 3H), 1.43 (s, 9H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.8, 155.8, 142.6, 129.3, 128.9 (d, *J* = 32.4 Hz), 125.4 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 271.8 Hz), 79.6, 60.8, 47.1, 41.6, 35.6, 28.3, 14.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.5. HRMS (ESI) calculated for $C_{18}H_{24}F_3NNaO_4$ $[M+Na]^+$: 398.1550; found: 398.1542.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-nitrobenzyl)propanoate (3k). Light yellow solid (90 mg, 67 % yield, Purified by silica gel chromatography using PE/EA 20:1–6:1), m.p.: 62-63 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.11 (m, 2H), 7.42 – 7.33 (m, 2H), 4.95 (t, *J* = 6.1 Hz, 1H), 4.10 (qq, *J* = 7.5, 3.7 Hz, 2H), 3.45 – 3.36 (m, 1H), 3.32 (q, *J* = 6.9 Hz, 1H), 3.05 (dd, *J* = 12.9, 7.6 Hz, 1H), 2.94 (td, *J* = 14.2, 12.8, 5.9 Hz, 2H), 1.44 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, CDCl3) δ 173.5, 155.8, 146.7, 146.3, 129.8, 123.7, 79.6, 60.9, 46.9, 41.6, 35.4, 28.3, 14.1. HRMS (ESI) calculated for $C_{17}H_{24}N_2NaO_6$ $[M+Na]^+$: 375.1527; found: 375.1531.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-fluorobenzyl)propanoate (3l). Colorless oil (74 mg, 60 % yield, Purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 2H), 7.41 – 7.33 (m, 2H), 4.93 (d, *J* = 6.7 Hz, 1H), 4.10 (qd, *J* = 7.2, 3.8 Hz, 2H), 3.39 (dt, *J* = 13.7, 5.4 Hz, 1H), 3.31 (dt, *J* = 13.9, 6.8 Hz, 1H), 3.05 (dd, *J* = 12.9, 7.6 Hz, 1H), 3.01 – 2.89 (m, 2H), 1.44 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.6, 162.2, 157.8 (d, *J* = 616.3 Hz), 155.3, 133.6 (d, *J* = 3.2 Hz), 129.9 (d, *J* = 7.9 Hz), 114.8 (d, *J* = 21.4 Hz), 79.0, 60.3, 47.0, 41.1, 34.6, 27.9, 13.7. ^{19}F NMR (470 MHz, CDCl3) δ -116.6. HRMS (ESI) calculated for $C_{17}H_{24}FNNaO_4$ $[M+Na]^+$: 348.1582; found: 348.1574.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(4-chlorobenzyl)propanoate (3m). Colorless oil (81 mg, 62 % yield, Purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.22 (m, 2H), 7.12 – 7.08 (m, 2H), 4.86 (s, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.41 – 3.31 (m, 1H), 3.25 (dt, *J* = 14.1, 7.3 Hz, 1H), 2.88 (h, *J* = 7.7 Hz, 2H), 2.81 – 2.71 (m, 1H), 1.42 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 173.5, 155.3, 136.4, 131.9, 129.8, 128.1, 79.0, 60.3, 46.8, 41.1, 34.7, 27.9, 13.7. HRMS (ESI) calculated for $C_{17}H_{24}ClNNaO_4$ $[M+Na]^+$: 364.1286; found: 364.1290.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(3-methoxybenzyl)propanoate (3n). Colorless oil (81 mg, 63 % yield, Purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.9 Hz, 1H), 6.75 (ddd, *J* = 8.4, 3.3, 1.7 Hz, 2H), 6.72 – 6.70 (m, 1H), 4.88 (d, *J* = 6.5 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 3.43 – 3.33 (m, 1H), 3.28 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.92 (d, *J* = 10.7 Hz, 2H), 2.79 (d, *J* = 7.4 Hz, 1H), 1.42 (s, 9H), 1.19 (t, *J* = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 174.3, 159.7, 155.8, 139.9, 129.5, 121.3, 114.6, 112.0, 79.4, 60.7, 55.1, 47.3, 41.6, 35.9, 28.4, 14.1. HRMS (ESI) calculated for $C_{18}H_{28}NO_5$ $[M+H]^+$: 338.1962; found: 338.1961.

Methyl 3-(2-(((*tert*-butoxycarbonyl)amino)methyl)-3-ethoxy-3-oxopropyl)benzoate (3o). Colorless oil (86 mg, 62 % yield, Purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (dt, *J* = 7.2, 1.7 Hz, 1H), 7.86 (t, *J* = 1.7 Hz, 1H), 7.39 – 7.34 (m, 2H), 4.91 (d, *J* = 6.5 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.91 (s, 3H), 3.38 (d, *J* = 5.8 Hz, 1H), 3.28 (dt, *J* = 14.0, 6.6 Hz, 1H), 3.03 – 2.84 (m, 3H), 1.43 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 173.9, 167.0, 155.8, 138.8, 133.6, 130.3, 130.0, 128.6, 127.9, 79.5, 60.8, 52.1, 47.3, 41.6, 35.6, 28.4, 14.1. HRMS (ESI) calculated for $C_{19}H_{28}NO_6$ $[M+H]^+$: 366.1911; found: 366.1904.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)benzyl)propanoate (3p). White solid (77 mg, 54 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1), m.p.:52-55 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 1H), 7.44 – 7.35 (m, 3H), 4.89 (d, *J* = 6.4 Hz, 1H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.45 – 3.36 (m, 1H), 3.30 (dt, *J* = 13.8, 6.8 Hz, 1H), 3.07 – 2.79 (m, 3H), 1.43 (s, 8H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.8, 155.8, 139.4, 132.4, 130.8 (d, *J* = 31.9 Hz), 128.9, 125.6 (d, *J* = 4.2 Hz), 124.1 (q, *J* = 272.1 Hz), 123.5 (d, *J* = 3.7 Hz), 79.6, 60.8, 47.3, 41.7, 35.6, 28.3, 14.0. ^{19}F NMR (470 MHz, CDCl3) δ -62.6. HRMS (ESI) calculated for $C_{18}H_{24}F_3NNaO_4$ $[M+Na]^+$: 398.1550; found: 398.1539.

Ethyl 2-(3-bromobenzyl)-3-((*tert*-butoxycarbonyl)amino)propanoate (3q). Pale yellow oil (75 mg, 51 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 12.6 Hz, 2H), 7.14 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 4.92 (t, *J* = 6.4 Hz, 1H), 4.10 (tt, *J* = 9.9, 5.1 Hz, 2H), 3.43 – 3.16 (m, 2H), 2.89 (d, *J* = 8.9 Hz, 2H), 2.80 (t, *J* = 8.7 Hz, 1H), 1.43 (s, 9H), 1.18 (t, *J* = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.4, 155.3, 140.3, 131.5, 129.6, 129.2, 127.1, 122.0, 79.0, 60.3, 46.8, 41.2, 35.0, 27.9, 13.7 HRMS (ESI) calculated for $C_{17}H_{24}BrNNaO_4$ $[M+Na]^+$: 408.0781; found: 408.0773.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-(naphthalen-2-ylmethyl)propanoate (3r). Colorless oil (89 mg, 65 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 – 7.72 (m, 3H), 7.61 (d, *J* = 1.9 Hz, 1H), 7.43 (pd, *J* = 6.9, 1.5 Hz, 2H), 7.30 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.91 (t, *J* = 6.4 Hz, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 3.46 – 3.37 (m, 1H), 3.31 (dt, *J* = 14.1, 7.3 Hz, 1H), 3.10 (dd, *J* = 12.9, 7.3 Hz, 1H), 2.99 (ddt, *J* = 19.5, 12.8, 7.0 Hz, 2H), 1.42 (s, 9H), 1.12 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 174.3, 155.8, 135.9, 133.5, 132.3, 128.2, 127.6, 127.6, 127.4, 127.2, 126.0, 125.5, 79.4, 60.7, 47.4, 41.8, 36.1, 28.4, 14.1. HRMS (ESI) calculated for $C_{21}H_{28}NO_4$ $[M+H]^+$: 358.2013; found: 358.2003 .

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-((1-tosyl-1*H*-indol-5-y

l)methyl)propanoate (3s). White solid (141 mg, 74 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1), m.p.: 41-43 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.52 (d, *J* = 3.7 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 2H), 7.11 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.57 (d, *J* = 3.7 Hz, 1H), 4.86 (t, *J* = 6.4 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 2H), 3.36 (dt, *J* = 12.0, 5.2 Hz, 1H), 3.25 (dt, *J* = 14.1, 7.2 Hz, 1H), 2.98 (dd, *J* = 12.9, 7.3 Hz, 1H), 2.94 – 2.82 (m, 2H), 2.33 (s, 3H), 1.42 (s, 9H), 1.07 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 173.8, 155.4, 144.4, 134.9, 133.2, 133.0, 130.6, 129.4, 126.4, 126.2, 125.2, 121.0, 113.0, 108.4, 79.0, 60.2, 47.2, 41.2, 35.3, 27.9, 21.1, 13.6. HRMS (ESI) calculated for $C_{26}H_{32}N_2NaO_6S$ $[M+Na]^+$: 523.1873; found: 523.1871.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-((6-chloropyridin-2-yl)methyl)propanoate (3t). Colorless oil (59 mg, 45 % yield, purified by silica gel chromatography using PE/EA 10:1–4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.07 (m, 1H), 4.98 (s, 1H), 4.12 (qd, *J* = 7.1, 2.3 Hz, 2H), 3.41 – 3.33 (m, 2H), 3.17 – 3.11 (m, 2H), 2.97 (q, *J* = 5.7, 5.1 Hz, 1H), 1.42 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 173.7, 159.6, 155.8, 150.7, 139.0, 122.1, 79.3, 60.8, 45.1, 41.2, 36.9, 28.3, 14.1. HRMS (ESI) calculated for $C_{16}H_{24}ClN_2O_4$ $[M+H]^+$: 343.1419; found: 343.1412 .

Ethyl 3-((*tert*-butoxycarbonyl)amino)-2-methyl-2-(4-methylbenzyl)propanoate (3u). Colorless oil (61 mg, 53 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.7 Hz, 2H), 6.99 – 6.94 (m, 2H), 4.89 (s, 1H), 4.13 (qd, *J* = 7.2, 2.9 Hz, 2H), 3.30 (dd, *J* = 13.7, 5.5 Hz, 1H), 3.27 – 3.20 (m, 1H), 2.88 – 2.79 (m, 2H), 2.30 (s, 3H), 1.43 (d, *J* = 2.0 Hz, 9H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.15 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 175.7, 155.7, 135.8, 133.0, 129.5, 128.4, 78.7, 60.3, 47.9, 46.4, 42.3, 27.9, 20.6, 19.8, 13.9. HRMS (ESI) calculated for $C_{19}H_{30}NO_4$ $[M+H]^+$: 336.2169; found: 336.2172.

Diethyl 2-((*tert*-butoxycarbonyl)amino)-3-(4-methylbenzyl)succinate (3v). Colorless oil (isomer-1 23 mg, isomer-2 20 mg, 44 % yield, purified by silica gel chromatography using PE/EA 20:1–6:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.10 (s, 4H), 5.56 (d, *J* = 9.9 Hz, 1H), 4.41 (dd, *J* = 9.9, 3.8 Hz, 1H), 4.23 – 4.06 (m, 4H), 3.30 (td, *J* = 7.6, 3.7 Hz, 1H), 3.04 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.80 (dd, *J* = 13.9, 8.2 Hz, 1H), 2.31 (s, 3H), 1.48 (s, 9H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.6, 170.9, 155.4, 135.8, 134.5, 128.8, 128.5, 79.5, 61.0, 60.6, 53.2, 48.2, 33.9, 27.9, 20.6, 13.6, 13.2. ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.08 (s, 4H), 5.29 (d, *J* = 8.9 Hz, 1H), 4.62 (dd, *J* = 8.6, 5.2 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 4.14 – 3.99 (m, 2H), 3.15 (s, 1H), 3.06 (dd, *J* = 13.8, 9.3 Hz, 1H), 2.79 (dd, *J* = 14.0, 5.9 Hz, 1H), 2.30 (s, 3H), 1.44 (s, 9H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.0, 170.7, 155.1, 136.1, 135.3, 129.1, 128.9, 80.1, 61.72, 61.0, 54.6, 50.1, 33.5, 28.3, 21.0, 14.2, 14.0. HRMS (ESI) calculated for $C_{21}H_{32}NO_6$ $[M+H]^+$: 394.2224; found: 394.2227.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-5-(p-tolyl)pentanoate (5a). White solid (66 mg, 45 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1), m.p.: 71-73 °C; ^{1}H NMR (500 MHz, $CDCl_3$ δ 7.10 (s, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.01 (d, *J* = 8.9 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.99 (d, *J* = 14.2 Hz, 1H), 2.73 – 2.47 (m, 4H), 2.32 (d, *J* = 14.3 Hz, 3H), 1.90 – 1.76 (m, 2H), 1.47 (s, 8H), 1.28 (d, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.7, 155.4, 138.4, 135.4, 129.1, 128.2, 79.3, 60.6, 47.5, 39.4, 36.6, 32.1, 28.4, 21.0, 14.2. HRMS (ESI) calculated for $C_{19}H_{29}NNaO_4$ $[M+Na]^+$: 358.1989; found: 358.1989.

Ethyl 4-(3-((*tert*-butoxycarbonyl)amino)-5-ethoxy-5-oxopentyl)benzoate (5b). Colorless oil (77 mg, 57 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 2H), 7.28 – 7.24 (m, 2H), 5.05 (d, *J* = 9.4 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.98 (s, 1H), 2.86 – 2.65 (m, 2H), 2.54 (td, *J* = 15.6, 13.9, 5.4 Hz, 2H), 1.99 – 1.78 (m, 2H), 1.47 (s, 9H), 1.40 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 171.1, 166.1, 154.9, 146.4, 129.3, 127.9, 78.9, 60.3, 60.1, 46.9, 38.9, 35.6, 32.2, 27.9, 13.9, 13.7. HRMS (ESI) calculated for $C_{21}H_{32}NO_6$ $[M+H]^+$: 394.2224; found: 394.2222.

Ethyl 5-(4-acetylphenyl)-3-((*tert*-butoxycarbonyl)amino)pentanoate (5c). Colorless oil (65 mg, 52 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 – 7.83 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.06 (d, *J* = 9.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.98 (p, *J* = 6.5, 4.6 Hz, 1H), 2.75 (dddd, *J* = 30.3, 13.9, 10.8, 6.3 Hz, 2H), 2.59 (s, 3H), 2.54 (td, *J* = 17.1, 15.6, 5.3 Hz, 2H), 1.95 – 1.78 (m, 2H), 1.46 (s, 9H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 197.8, 171.5, 155.3, 147.3, 135.1, 128.6, 128.6, 79.4, 60.6, 47.2, 39.3, 36.0, 32.6, 28.3, 26.6, 14.1. HRMS (ESI) calculated for $C_{20}H_{30}NO_5$ $[M+H]^+$: 364.2118; found: 364.2114.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-5-(3-methoxyphenyl)pentanoate (5d). White solid (48 mg, 40 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1), m.p.: 70-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.19 (m, 1H), 6.80 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.77 – 6.74 (m, 2H), 5.02 (d, *J* = 8.6 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 3.99 (q, *J* = 13.9, 10.0 Hz, 1H), 3.82 (s, 3H), 2.76 – 2.62 (m, 2H), 2.55 (dt, *J* = 15.6, 7.6 Hz, 2H), 1.91 – 1.80 (m, 2H), 1.47 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.04, 161.12, 156.79, 144.58, 130.82, 122.17, 115.55, 112.75, 80.70, 78.69, 61.97, 48.89, 40.80, 37.79, 34.07, 29.82, 15.61. ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 197.8, 171.5, 155.3, 147.3, 135.1, 128.6, 128.5, 79.4, 60.6, 47.2, 39.3, 36.0, 32.6, 28.3, 26.5, 14.1. HRMS (ESI) calculated for $C_{19}H_{30}NO_5$ $[M+H]^+$: 352.2118; found: 352.2120

Ethyl 3-((*tert*-butoxycarbonyl)amino)-5-(naphthalen-2-yl)pentanoate (5e). White solid (54 mg, 42 % yield, purified by silica gel chromatography using PE/EA 12:1–4:1), m.p.: 78-80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.65 (d, *J* = 1.7 Hz, 1H),

7.46 (dqd, J = 8.1, 6.9, 1.5 Hz, 2H), 7.35 (dd, J = 8.4, 1.7 Hz, 1H), 5.14 – 5.02 (m, 1H), 4.16 (q, J = 7.2 Hz, 2H), 4.04 (q, J = 14.8, 12.4 Hz, 1H), 2.97 – 2.80 (m, 2H), 2.58 (q, J = 10.7, 8.6 Hz, 2H), 2.05 – 1.91 (m, 1H), 1.49 (s, 8H), 1.27 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.1, 156.8, 140.5, 135.1, 133.5, 129.4, 129.0, 128.9, 128.6, 127.8, 127.4, 126.6, 80.7, 62.0, 49.0, 40.8, 37.8, 34.2, 29.8, 15.6. HRMS (ESI) calculated for $C_{22}H_{30}NO_4$ $[M+H]^+$: 372.2169; found: 372.2166.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-5-(6-chloropyridin-2-yl) pentanoate (5f). White solid (47 mg, 43 % yield, purified by silica gel chromatography using PE/EA 10:1–3:1), m.p.: 90-92 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (t, J = 7.7 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 5.09 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.97 (s, 1H), 2.93 – 2.75 (m, 2H), 2.54 (dd, J = 5.7, 1.9 Hz, 2H), 2.00 – 1.90 (m, 2H), 1.44 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 171.5, 162.3, 155.4, 150.8, 139.1, 121.7, 79.3, 60.6, 47.4, 39.6, 34.6, 28.4, 14.2. HRMS (ESI) calculated for $C_{17}H_{26}ClN_2O_4$ $[M+H]^+$: 357.1576; found: 357.1571.

Ethyl 3-((*tert*-butoxycarbonyl)amino)-5-(1-tosyl-1*H*-indol-5-yl)pentanoate (5g). White solid (103 mg, 58 % yield, purified by silica gel chromatography using PE/EA 10:1–3:1), m.p.: 43-45 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.80 – 7.74 (m, 2H), 7.54 (d, J = 3.7 Hz, 1H), 7.34 (d, J = 1.6 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.15 (dd, J = 8.5, 1.7 Hz, 1H), 6.60 (dd, J = 3.7, 0.8 Hz, 1H), 5.02 (d, J = 9.3 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.99 (d, J = 7.0 Hz, 1H), 2.82 – 2.66 (m, 2H), 2.60 – 2.48 (m, 2H), 2.36 (s, 3H), 1.93 – 1.79 (m, 2H), 1.46 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (125MHz, $CDCl_3$) δ 171.6, 155.4, 144.8, 136.7, 135.4, 133.4, 131.0, 129.9, 126.8, 126.5, 125.3, 120.7, 113.4, 108.9, 79.3, 60.6, 47.4, 39.4, 36.9, 32.4, 28.4, 21.6, 14.2. HRMS (ESI) calculated for $C_{27}H_{35}N_2O_6S$ $[M+H]^+$: 515.2210; found: 515.2210.

Gram-scale synthesis of compound 3a. A tube was charged with $Pd(OAc)_2$ (89.9 mg, 7.5 mol %), $Pd(PhCN)_2Cl_2$ (153.5 mg, 7.5 mol %), AgTFA (3.54 g, 16.0 mmol), transient directing group (TDG2, 197.1 mg, 30 mol %), 4-iodotoluene (**2a**, 2.33 g, 10.7 mmol) and HFIP : AcOH 10 : 1 (30 mL), followed by the free β-amino ester (**1a**, 0.7 g, 5.3 mmol). The reaction mixture was stirred at room temperature for 30 minutes before heating to 110 °C for 24 hours. After that, the reaction mixture was cooled to room temperature and the solvent was filtered through a celite pad and washed with DCM. The solutions were concentrated under vacuum. Then EtOH (50 mL) and HCl (2 *N*, 15 mL) were added to the residue and the mixture was stirred at room temperature for 3 h. The solvent was filtered through a celite pad, washed with EtOH and concentrated under vacuum. The mixture was subsequently dissolved with DCM (80 mL) and TEA (15 equiv.) and Boc_2O (4.0 equiv.) were added. And then the brown solution was stirred at room temperature for 8 hours. DCM was added and the organic layer was extracted, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using petroleum ether/ ethyl acetate (10:1) to afford the product **3a** as a colorless oil (1.15 g yield: 67 %).

General procedure for compound 3w. A tube was charged with $Pd(OAc)_2$ (6.4 mg, 7.5 mol %), $Pd(PhCN)_2Cl_2$ (11.0 mg, 7.5 mol %), AgTFA (252.6 mg, 1.14 mmol), transient directing group (TDG2, 14.1 mg, 30 mol%), 2-fluoro-3-iodopyridine (**2w**, 170 mg, 0.76 mmol) and HFIP : AcOH 10:1 (2 mL), followed by the free β^2-amino ester (**1a**, 50 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 30 minutes before heating to 110 °C for 12 hours. After that, the reaction mixture was cooled to room temperature and the solvent was filtered through a celite pad and washed with DCM. The solution was concentrated under vacuum. Then EtOH (2 mL) and HCl (2 *N*, 1 mL) were added to the residue and the mixture was stirred at room temperature for 3 h. The solvent was filtered through a celite pad, washed with EtOH and concentrated under vacuum. DCM was added and the organic layer was extracted, washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography using DCM/ MeOH (10:1) to afford the product **3w** as a white solid (yield: 48 %).

Ethyl 1,2,3,4-tetrahydro-1,8-naphthyridine-3-carboxylate (3w). White solid (38 mg, 48 % yield, purified by silica gel chromatography using DCM/MeOH 20:1–10:1), m.p.: 57-59 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.28 (dp, J = 7.3, 1.1 Hz, 1H), 6.57 (dd, J = 7.2, 5.2 Hz, 1H), 5.67 (s, 1H), 4.19 (qd, J = 7.1, 1.2 Hz, 2H), 3.69 (dt, J = 12.0, 3.7 Hz, 1H), 3.54 (ddd, J = 12.0, 9.0, 1.4 Hz, 1H), 3.00 (d, J = 7.3 Hz, 2H), 2.93 – 2.86 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.5, 154.3, 142.8, 137.8, 115.8, 112.7, 61.1, 42.9, 37.0, 28.9, 14.1. HRMS (ESI) calculated for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: 207.1128; found: 207.1122 .

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.
Copies of ^1H NMR, ^{13}C $\{^1H\}$ NMR, and ^{19}F NMR Spectra spectra for all compounds.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: hliu@simm.ac.cn (H. L.).
*E-mail: jwang@simm.ac.cn (J. W.).

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (81620108027, 21632008, and 21877118) and supported by grants from Science and Technology Commission of Shanghai Municipality (17431903100 and 18431907100).

REFERENCES

(1) (a) Berks, A. H., Preparations of two pivotal intermediates for the synthesis of 1-beta-methyl carbapenem antibiotics. *Tetrahedron.* **1996,** *52*, 331-375; (b) Lelais, G.; Seebach, D., beta(2)-amino acids - Syntheses, occurrence in natural products, and components of beta-peptides. *Biopolymers.* **2004,** *76*, 206-243; (c) Magriotis, P. A., Recent progress in the enantioselective synthesis of beta-lactams: Development of the first catalytic approaches. *Angew. Chem. Int. Ed.* **2001,** *40*, 4377-4379; (d) Mikami, K.; Fustero, S.; Sanchez-Rosello, M.; Acena, J. L.; Soloshonok, V.; Sorochinsky, A., Synthesis of Fluorinated beta-Amino Acids. *Synthesis-Stuttgart.* **2011**, 3045-3079; (e) Seebach, D.; Beck, A. K.; Capone, S.; Deniau, G.; Groselj, U.; Zass, E., Enantioselective Preparation of beta(2)-Amino Acid Derivatives for beta-Peptide Synthesis. *Synthesis-Stuttgart.* **2009**, 1-32.

(2) (a) Fang, X. J.; Jackstell, R.; Beller, M., Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes. *Angew. Chem. Int. Ed.* **2013,** *52*, 14089-14093; (b) Fleischer, I.; Jennerjahn, R.; Cozzula, D.; Jackstell, R.; Franke, R.; Beller, M., A Unique Palladium Catalyst for Efficient and Selective Alkoxycarbonylation of Olefins with Formates. *Chemsuschem.* **2013,** *6*, 417-420; (c) Lukaszuk, A.; Demaegdt, H.; Szemenyei, E.; Toth, G.; Tymecka, D.; Misicka, A.; Karoyan, P.; Vanderheyden, P.; Vauquelin, G.; Tourwe, D., beta-homo-amino acid scan of angiotensin IV. *J. Med. Chem.* **2008,** *51*, 2291-2296; (d) Pavlov, N.; Gilles, P.; Didierjean, C.; Wenger, E.; Naydenova, E.; Martinez, J.; Calmes, M., Asymmetric Synthesis of beta(2)-Tryptophan Analogues via Friedel-Crafts Alkylation of Indoles with a Chiral Nitroacrylate. *J. Org. Chem.* **2011,** *76*, 6116-6124.

(3) (a) Lin, D. Z.; Lv, L.; Wang, J.; Ding, X.; Jiang, H. L.; Liu, H., Preparation of alpha-Alkyl-beta-Amino Acids via beta-Alanine Ni(II) Complex. *J. Org. Chem.* **2011,** *76*, 6649-6656; (b) Moumne, R.; Lavielle, S.; Karoyan, P., Efficient synthesis of beta(2)-amino acid by homologation of alpha-amino acids involving the Reformatsky reaction and Mannich-type imminium electrophile. *J. Org. Chem.* **2006,** *71*, 3332-3334; (c) Weiner, B.; Szymanski, W.; Janssen, D. B.; Minnaard, A. J.; Feringa, B. L., Recent advances in the catalytic asymmetric synthesis of beta-amino acids. *Chem. Soc. Rev.* **2010,** *39*, 1656-1691.

(4) (a) Stevenazzi, A.; Marchini, M.; Sandrone, G.; Vergani, B.; Lattanzio, M., Amino acidic scaffolds bearing unnatural side chains: An old idea generates new and versatile tools for the life sciences. *Biorg. Med. Chem. Lett.* **2014,** *24*, 5349-5356; (b) Brennfuhrer, A.; Neumann, H.; Beller, M., Palladium-Catalyzed Carbonylation Reactions of Alkenes and Alkynes. *Chemcatchem.* **2009,** *1*, 28-41; (c) Godard, C.; Munoz, B. K.; Ruiz, A.; Claver, C., Pd-catalysed asymmetric mono- and bis-alkoxycarbonylation of vinylarenes. *Dalton Transactions.* **2008**, 853-860; (d) Kiss, G., Palladium-catalyzed Reppe carbonylation. *Chem. Rev.* **2001,** *101*, 3435-3456; (e) Qiang, L. Q.; Guo, S. J.; Jie, D.; Tao, M. P., Research of the Method for Position Detection of the Rotor in the Interior Permanent Magnet Synchronous Motor. *Proceedings of the 4th International Conference on Mechatronics, Materials, Chemistry and Computer Engineering 2015 (Icmmcce 2015).* **2015,** *39*, 1370-1374.

(5) (a) Ano, Y.; Tobisu, M.; Chatani, N., Palladium-Catalyzed Direct Ethynylation of C(sp(3))-H Bonds in Aliphatic Carboxylic Acid Derivatives. *JACS.* **2011,** *133*, 12984-12986; (b) Chen, G.; Shigenari, T.; Jain, P.; Zhang, Z. P.; Jin, Z.; He, J.; Li, S. H.; Mapelli, C.; Miller, M. M.; Poss, M. A.; Scola, P. M.; Yeung, K. S.; Yu, J. Q., Ligand-Enabled beta-C-H Arylation of alpha-Amino Acids Using a Simple and Practical Auxiliary. *JACS.* **2015,** *137*, 3338-3351; (c) Chowdhury, S.; Vaishnav, R.; Panwar, N.; Haq, W., Regioselective beta-Csp(3)-Arylation of beta-Alanine: An Approach for the Exclusive Synthesis of Diverse beta-Aryl-beta-amino Acids. *J. Org. Chem.* **2019,** *84*, 2512-2522; (d) Liu, L.; Liu, Y. H.; Shi, B. F., Synthesis of amino acids and peptides with bulky side chains via ligand-enabled carboxylate-directed gamma-C(sp(3))-H arylation. *Chemical Science.* **2020,** *11*, 290-294; (e) Tran, L. D.; Daugulis, O., Nonnatural Amino Acid Synthesis by Using Carbon-Hydrogen Bond Functionalization Methodology. *Angew. Chem. Int. Ed.* **2012,** *51*, 5188-5191; (f) Zhao, L.; Basle, O.; Li, C. J., Site-specific C-functionalization of free-(NH) peptides and glycine derivatives via direct C-H bond functionalization. *Proc. Natl. Acad. Sci. U. S. A.* **2009,** *106*, 4106-4111; (g) Dolui, P.; Das, J.; Chandrashekar, H. B.; Anjana, S. S.; Maiti, D., Ligand-Enabled Pd-II-Catalyzed Iterative gamma-C(sp3)-H Arylation of Free Aliphatic Acid. *Angew. Chem. Int. Ed.* **2019,** *58*, 13773-13777.

(6) (a) Guin, S.; Dolui, P.; Zhang, X. L.; Paul, S.; Singh, V. K.; Pradhan, S.; Chandrashekar, H. B.; Anjana, S. S.; Paton, R. S.; Maiti, D., Iterative Arylation of Amino Acids and Aliphatic Amines via delta-C(sp(3))-H Activation: Experimental and Computational Exploration. *Angew. Chem. Int. Ed.* **2019,** *58*, 5633-5638; (b) Landge, V. G.; Parveen, A.; Nandakumar, A.; Balaraman, E., Pd(II)-Catalyzed gamma-C(sp(3))-H alkynylation of amides: selective functionalization of R chains of amides (RC)-C-1(O)NHR. *Chem. Commun.* **2018,** *54*, 7483-7486; (c) Pramanick, P. K.; Zhou, Z. B.; Hou, Z. L.; Yao, B., Free Amino Group-Directed gamma-C(sp(3))-H Arylation of alpha-Amino Esters with Diaryliodonium Triflates by Palladium Catalysis. *J. Org. Chem.* **2019,** *84*, 5684-5694.

(7) (a) Han, J.; Zheng, Y. X.; Wang, C.; Zhu, Y.; Huang, Z. B.; Shi, D. Q.; Zeng, R. S.; Zhao, Y. S., Pd-Catalyzed Coupling of gamma-C(sp(3))-H Bonds of Oxalyl Amide-Protected Amino Acids with Heteroaryl and Aryl Iodides. *J. Org. Chem.* **2016,** *81*, 5681-5689; (b) Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C., Palladium-catalyzed N-(2-pyridyl)sulfonyl-directed C(sp(3))-H gamma-arylation of amino acid derivatives. *Chemical Science.* **2013,** *4*, 175-179; (c) Chan, K. S. L.; Wasa, M.; Chu, L.; Laforteza, B. N.; Miura, M.; Yu, J. Q., Ligand-enabled cross-coupling of C(sp(3))-H bonds

with arylboron reagents via Pd(II)/Pd(o) catalysis. *Nat. Chem.* **2014,** *6*, 146-150; (d) Zhang, L. S.; Chen, G. H.; Wang, X.; Guo, Q. Y.; Zhang, X. S.; Pan, F.; Chen, K.; Shi, Z. J., Direct Borylation of Primary C-H Bonds in Functionalized Molecules by Palladium Catalysis. *Angew. Chem. Int. Ed.* **2014,** *53*, 3899-3903; (e) Noisier, A. F. M.; Brimble, M. A., C-H Functionalization in the Synthesis of Amino Acids and Peptides. *Chem. Rev.* **2014,** *114*, 8775-8806; (f) Saint-Denis, T. G.; Zhu, R. Y.; Chen, G.; Wu, Q. F.; Yu, J. Q., Enantioselective C(sp(3))-H bond activation by chiral transition metal catalysts. *Science.* **2018,** *359*, 759-772.

(8) (a) Zhang, F. L.; Hong, K.; Li, T. J.; Park, H.; Yu, J. Q., Functionalization of C(sp(3))-H bonds using a transient directing group. *Science.* **2016,** *351*, 252-256; (b) Gandeepan, P.; Ackermann, L., Transient Directing Groups for Transformative C-H Activation by Synergistic Metal Catalysis. *Chem.* **2018,** *4*, 199-222; (c) Hong, K.; Park, H.; Yu, J. Q., Methylene C(sp(3))-H Arylation of Aliphatic Ketones Using a Transient Directing Group. *Acs Catalysis.* **2017,** *7*, 6938-6941; (d) Yang, K.; Li, Q.; Liu, Y. B.; Li, G. G.; Ge, H. B., Catalytic C-H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand. *JACS.* **2016,** *138*, 12775-12778; (e) Modak, A.; Maiti, D., Metal catalyzed defunctionalization reactions. *Org. Biomol. Chem.* **2016,** *14*, 21-35; (f) Zhao, Q.; Poisson, T.; Pannecoucke, X.; Besset, T., The Transient Directing Group Strategy: A New Trend in Transition-Metal-Catalyzed C-H Bond Functionalization. *Synthesis-Stuttgart.* **2017,** *49*, 4808-4826; (g) Gandeepan, P.; Ackermann, L., Transient Directing Groups for Transformative C–H Activation by Synergistic Metal Catalysis. *Chem.* **2018,** *4*, 199-222; (h) St John-Campbell, S.; White, A. J. P.; Bull, J. A., Methylene C(sp(3))-H beta,beta'-Diarylation of Cyclohexanecarbaldehydes Promoted by a Transient Directing Group and Pyridone Ligand. *Org. Lett.* **2020,** *22*, 1807-1812; (i) Thrimurtulu, N.; Dey, A.; Singh, A.; Pal, K.; Maiti, D.; Volla, C. M. R., Palladium Catalyzed Regioselective C4 - Arylation and Olefination of Indoles and Azaindoles. *Adv. Synth. Catal.* **2019,** *361*, 1441-1446.

(9) (a) Xu, Y.; Young, M. C.; Wang, C. P.; Magness, D. M.; Dong, G. B., Catalytic C(sp(3))-H Arylation of Free Primary Amines with an exo Directing Group Generated In Situ. *Angew. Chem. Int. Ed.* **2016,** *55*, 9084-9087; (b) Yada, A.; Liao, W. Q.; Sato, Y.; Murakami, M., Buttressing Salicylaldehydes: A Multipurpose Directing Group for C(sp(3))-H Bond Activation. *Angew. Chem. Int. Ed.* **2017,** *56*, 1073-1076; (c) Wu, Y. W.; Chen, Y. Q.; Liu, T.; Eastgate, M. D.; Yu, J. Q., Pd-Catalyzed gamma-C(sp(3))-H Arylation of Free Amines Using a Transient Directing Group. *JACS.* **2016,** *138*, 14554-14557; (d) Chen, Y. Q.; Wang, Z.; Wu, Y. W.; Wisniewski, S. R.; Qiao, J. X.; Ewing, W. R.; Eastgate, M. D.; Yu, J. Q., Overcoming the Limitations of gamma- and delta-C-H Arylation of Amines through Ligand Development. *JACS.* **2018,** *140*, 17884-17894; (e) Liu, Y. B.; Ge, H. B., Site-selective C-H arylation of primary aliphatic amines enabled by a catalytic transient directing group. *Nat. Chem.* **2017,** *9*, 26-32; (f) St John-Campbell, S.; Ou, A. K.; Bull, J. A., Palladium-Catalyzed C(sp(3))-H Arylation of Primary Amines Using a Catalytic Alkyl Acetal to Form a Transient Directing Group. *Chemistry-a European Journal.* **2018,** *24*, 17838-17843; (g) Lin, H.; Wang, C.; Bannister, T. D.; Kamenecka, T. M., Site-Selective gamma-C(sp(3))-H and gamma-C(sp(2))-H Arylation of Free Amino Esters Promoted by a Catalytic Transient Directing Group. *Chemistry-a European Journal.* **2018,** *24*, 9535-9541; (h) Tan, W.; Wang, C. H.; Jiang, X. F., Visible-Light-Mediated C(sp(3))-H Thiocarbonylation for Thiolactam Preparation with Potassium Sulfide. *Chin. J. Chem* . **2019,** *37*, 1234-1238.

(10) (a) Wang, S. N.; Nian, Y.; Zhou, S. B.; Wang, J.; Liu, H., Chemical Resolution of C,N-Unprotected alpha-Substituted beta-Amino Acids Using Stable and Recyclable Proline-Derived Chiral Ligands. *J. Org. Chem.* **2018,** *83*, 9870-9878; (b) Zhou, S. B.; Wang, S. N.; Wang, J.; Nian, Y.; Peng, P. F.; Soloshonok, V. A.; Liu, H., Configurationally Stable (S)- and (R)--Methylproline-Derived Ligands for the Direct Chemical Resolution of Free Unprotected (3)-Amino Acids. *Eur. J. Org. Chem.* **2018**, 1821-1832.

(11) (a) Chen, Z.-S.; Huang, L.-Z.; Jeon, H. J.; Xuan, Z.; Lee, S.-g., Cooperative Pd(0)/Rh(II) Dual Catalysis: Interceptive Capturing of π-Allyl Pd(II) Complexes with α-Imino Rh(II) Carbenoids. *ACS Catalysis.* **2016,** *6*, 4914-4919; (b) Ibrahim, M. Y. S.; Denmark, S. E., Palladium/Rhodium Cooperative Catalysis for the Production of Aryl Aldehydes and Their Deuterated Analogues Using the Water-Gas Shift Reaction. *Angew. Chem. Int. Ed. Engl.* **2018,** *57*, 10362-10367; (c) Maity, R.; Mekic, A.; van der Meer, M.; Verma, A.; Sarkar, B., Triply cyclometalated trinuclear iridium(III) and trinuclear palladium(II) complexes with a tri-mesoionic carbene ligand. *Chem. Commun. (Camb.).* **2015,** *51*, 15106-9; (d) Miyamura, H.; Isshiki, S.; Min, H.; Kobayashi, S., Lewis acid-driven reaction pathways in synergistic cooperative catalysis over gold/palladium bimetallic nanoparticles for hydrogen autotransfer reaction between amide and alcohol. *Chinese Journal of Catalysis.* **2016,** *37*, 1662-1668; (e) Seth, K.; Purohit, P.; Chakraborti, A. K., Cooperative catalysis by palladium-nickel binary nanocluster for Suzuki-Miyaura reaction of ortho-heterocycle-tethered sterically hindered aryl bromides. *Org. Lett.* **2014,** *16*, 2334-7; (f) Smith, K. B.; Brown, M. K., Regioselective Arylboration of Isoprene and Its Derivatives by Pd/Cu Cooperative Catalysis. *J. Am. Chem. Soc.* **2017,** *139*, 7721-7724; (g) Xiang, K.; Tong, P.; Yan, B.; Long, L.; Zhao, C.; Zhang, Y.; Li, Y., Synthesis of Benzannulated [6,6]-Spiroketals by a One-Pot Carbonylative Sonogashira Coupling/Double Annulation Reaction. *Org. Lett.* **2019,** *21*, 412-416.

(12) (a) Ansari, N. H.; Dacko, C. A.; Akhmedov, N. G.; Soderberg, B. C., Double Palladium Catalyzed Reductive Cyclizations. Synthesis of 2,2'-, 2,3'-, and 3,3'-Bi-1H-indoles, Indolo[3,2-b]indoles, and Indolo[2,3-b]indoles. *J. Org. Chem.* **2016,** *81*, 9337-9349; (b) Ariafard, A.; Hyland, C. J.; Canty, A. J.; Sharma, M.; Yates, B. F., Theoretical investigation into the

mechanism of reductive elimination from bimetallic palladium complexes. *Inorg. Chem.* **2011,** *50*, 6449-57; (c) Loones, K. T.; Maes, B. U.; Dommisse, R. A.; Lemiere, G. L., The first tandem double palladium-catalyzed aminations: synthesis of dipyrido[1,2-a:3',2'-d]imidazole and its benzo- and aza-analogues. *Chem. Commun. (Camb.).* **2004**, 2466-7; (d) Normand, A. T.; Nechaev, M. S.; Cavell, K. J., Mechanisms in the reaction of palladium(II)-pi-allyl complexes with aryl halides: evidence for NHC exchange between two palladium complexes. *Chemistry (Easton).* **2009,** *15*, 7063-73; (e) Stambuli, J. P.; Buhl, M.; Hartwig, J. F., Synthesis, characterization, and reactivity of monomeric, arylpalladium halide complexes with a hindered phosphine as the only dative ligand. *JACS.* **2002,** *124*, 9346-9347; (f) Surawatanawong, P.; Hall, M. B., Theoretical Study of Alternative Pathways for the Heck Reaction through Dipalladium and "Ligand-Free" Palladium Intermediates. *Organometallics*. **2008,** *27*, 6222-6232.

(13) Xie, H.; Fan, T.; Lei, Q.; Fang, W., New progress in theoretical studies on palladium-catalyzed C−C bond-forming reaction mechanisms. *Science China Chemistry*. **2016,** *59*, 1432-1447.

(14) Wang, J. B.; Breslin, M. J.; Coleman, P. J.; Duggan, M. E.; Hunt, C. A.; Hutchinson, J. H.; Leu, C. T.; Rodan, S. B.; Rodan, G. A.; Duong, L. T.; Hartman, G. D., Non-peptide alpha(v)beta(3) antagonists. Part 7: 3-Substituted tetrahydro-[1,8]naphthyridine derivatives. *Biorg. Med. Chem. Lett.* **2004,** *14*, 1049-1052.