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Pd-Catalyzed remote site- and stereo-selective C(alkenyl)–H alkenylation of unactivated cycloalkenes

Chun-Li Mao,[†] Sheng Zhao,[‡] Zhong-Lin Zang,[†] Lin Xiao,[†] Cheng-He Zhou,[†] Yun He,[‡,*] and Gui-Xin Cai[†,*]

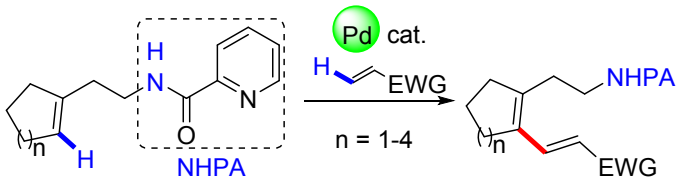
[†]Key Laboratory of Luminescent and Real-Time Analytical Chemistry, Ministry of Education, Institute of Bioorganic & Medicinal Chemistry, School of Chemistry and Chemical Engineering, Southwest University, Chongqing 400715, P. R. China

[‡]Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing, 401331, P. R. China

* E-mails of corresponding author: gxcai@swu.edu.cn; yun.he@cqu.edu.cn.

Keywords: C–C coupling; C(alkenyl)–H activation; palladium catalysis; alkenylation; site- and stereo-selectivity

Remote site- and stereo-selective C(alkenyl) – H activation



- only *E*-selectivity
- general 2 h reaction time
- external ligand free
- removable directing group

Abstract: A palladium-catalyzed alkenylation involving remote δ position C(alkenyl)–H activation of cycloalkenes reacting with electron-deficient alkenes is described. This method features excellent site- and stereoselectivity to efficiently afford only *E*-selective highly substituted 1,3-diene derivatives, extra-ligand-free and good functional group tolerance including estrone and free N–H tryptamine under weakly alkaline conditions. Mechanistic studies suggest that picolinamide as a bidentate directing group enables the formation of unique alkenyl palladacycle intermediates.

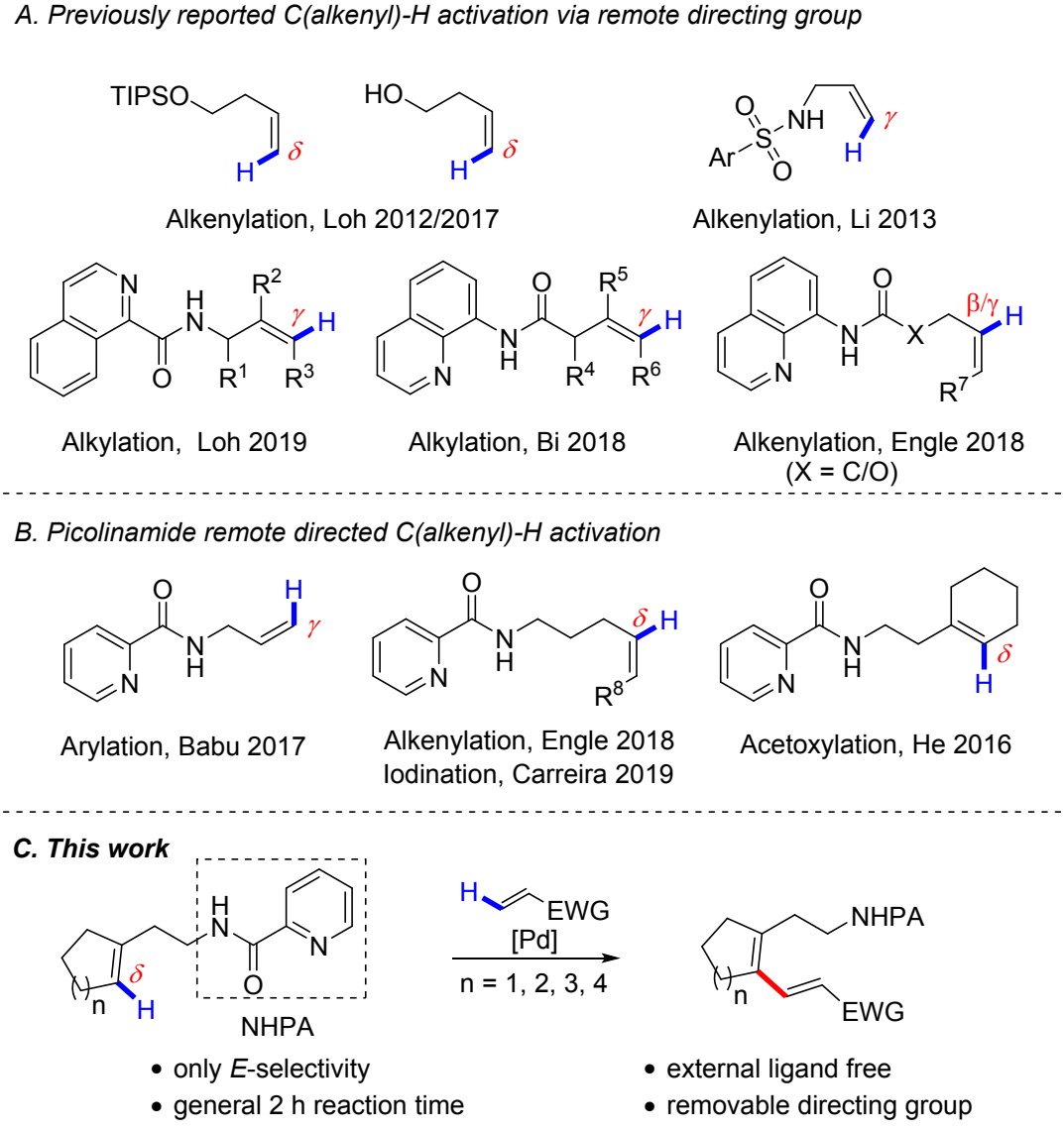
Introduction

Conjugated dienes are extremely valuable molecular skeletons in organic synthesis and represent essential structural motifs in a large class of natural products and bio-active compounds.[1] Strategies for the synthesis of these diene molecules can be generally divided into three categories. First, the reactions of carbonyl alkenylation are classical routes.[2] Second, C–C cross-coupling reactions of activated substrates include Heck reaction,[3] Stille coupling[4] and Negishi coupling.[5] Third, a more direct strategy involving double C(alkenyl)–H bonds activation

has attracted considerable attention from the scientific community.[6] Although the challenges have changed from extra pre-activated steps for starting materials, low atom economy to subsequent issues of adjusting the steric and electronic properties of the alkenes to avoid the homo-coupling reaction, the synthesis of diene is still confronted with two of major challenges — site-selectivity and the low Z/E-selectivity. A novel and highly stereoselective strategy for dealing with site-selective C(alkenyl)–H activation is the introduction of directing groups (DGs).[7,8] This strategy provides easy access to the desired site-selectivity and stereoselectivity via electronic effects and / or chelation and convenience of further functionalization.[9] Ishii,[10a] Glorius,[10b] Nakamura,[10c] and Loh,[10d] etc. have described the strategies for proximal C(alkenyl)–H activation of aliphatic olefins in the presence of monodentate DGs via metal catalysts.[10]

In contrast, fewer examples regarding stereoselective remote directed C(alkenyl)–H activation are reported.[11] Loh[12a,12b] and Li[12c] have demonstrated *δ* or *γ*-C(alkenyl)–H activation and functionalization (Scheme 1 A). Loh[13] and Bi[14] respectively reported alkylation of *γ*-C(alkenyl)–H, and Engle recently published elegant alkenylation of *β* or *γ*-C(alkenyl)–H utilizing different bidentate auxiliaries (Scheme 1 A).[15] Notably, picolinamide (PA) as a removable directing group facilitated remote site-selective functionalization[16] of C(alkenyl)–H bond such as arylation at *γ*-position, alkenylation and iodination at *δ*-position at a distance of three methylenes from PA, as well as acetoxylation at *δ*-position (Scheme 1 B).[17-19] However, only *E*-selective *δ*-C(alkenyl)–H alkenylation of aminoethyl cycloalkenes with PA as a remote bidentate directing group has not been documented. Thus, inspired by the above literature and previous work,[19,20] we report an efficient method for the synthesis of cycle-containing dienes starting from cycloalkenes bearing PA and electron-deficient alkenes to generate corresponding only *E*-products (Scheme 1 C).

Scheme 1. Remote directed C(alkenyl)–H activation and functionalization.

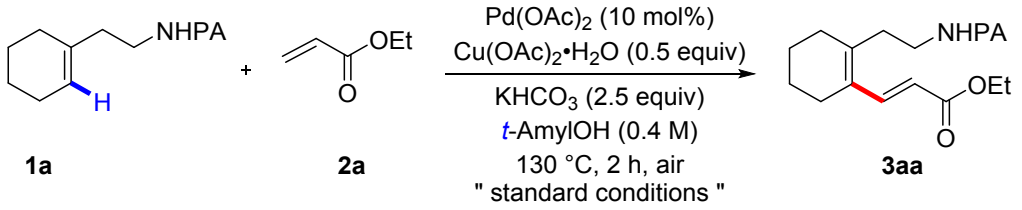


Results and Discussion

We set out to research olefination of δ-C(alkenyl)–H bond of cyclic olefins in Table 1. The model reaction conditions have been established by using **1a** and **2a** as substrates after much trial and error (entry 1). Notably, palladium catalyst is a crucial factor and this reaction did not occur in the absence of $Pd(OAc)_2$ (entry 2). And copper-free conditions led to the moderate yield (entry 3), which demonstrated that $Cu(OAc)_2 \cdot H_2O$ as an oxidant can effectively regenerate Pd(II) catalyst from Pd(0). Moreover, $PhI(OAc)_2$ serving as an oxidant in the Pd(II)/Pd(IV) catalytic cycle great reduced the yield (entry 4), which demonstrated that this reaction differentiating from previous research[19] could prefer a Pd(0)/Pd(II) catalytic cycle. Additionally, removal of base or using acids such as HOAc and PivOH which can boost the palladium catalysis[15,20a] showed unsatisfactory results (entries 5-7). Polar solvent DMSO almost

completely suppressed the desired transformation (entry 8). Further screening reaction conditions including palladium catalysts, oxidants, bases and solvents, as well as reaction temperature has been shown in Supporting Information (SI) Table S1 for more details.

Table 1. Optimization of the reaction conditions[a]



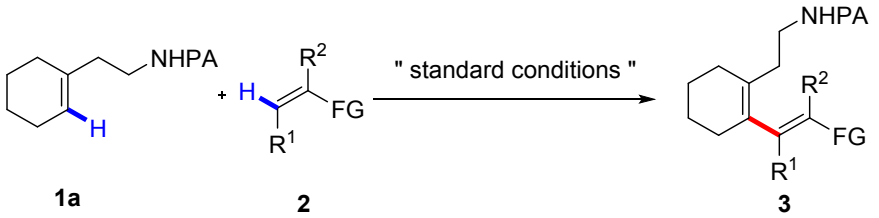
1a **2a** **3aa**

Entry	Variation from standard conditions	Yield[b] (%)
1	None	80
2	Without $Pd(OAc)_2$	0
3	Without $Cu(OAc)_2 \cdot H_2O$	55
4	$PhI(OAc)_2$ instead of $Cu(OAc)_2 \cdot H_2O$	27
5	Without $KHCO_3$	55
6	HOAc instead of $KHCO_3$	55
7	PivOH instead of $KHCO_3$	41
8	DMSO instead of *t*-AmylOH	Trace

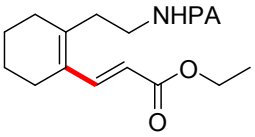
[a] **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), $KHCO_3$ (0.5 mmol), *t*-AmylOH (0.4 M) in a sealed tube under air at 130 °C for 2 h. [b] Isolated yield.

To examine the scope of alkenes, we made **1a** as the coupling partner under the optimal conditions (Scheme 2). Various acrylates can afford the corresponding products (**3aa-3al**) with excellent site-selectivity and stereoselectivity in moderate to good yields. These experimental results showed that the chain length and steric hindrance of ester groups had less effect on the yields of desired products (**3aa-3ak**), and **3aa** was characterized by X-ray crystallography[21]. Owing to the transesterification, *t*-AmylOH was substituted with toluene when **1a** reacted with phenyl acrylate to produce **3al** with 63% isolated yield. Other acrylate derivatives can smoothly transform into corresponding products (**3am-3an**). In addition, the results of **3ao** and **3ap** illustrated that the reaction can be seriously affected by the steric hindrance of double bonds. Unfortunately, the desired products (**3aq-3ar**) cannot be obtained in the treatment of styrene or electron-deficient derivative.

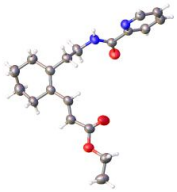
Scheme 2. Scope of alkenes[a]



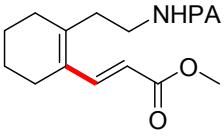
1a **2** **3**



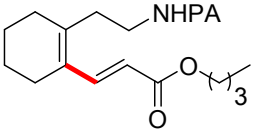
3aa, 80 %



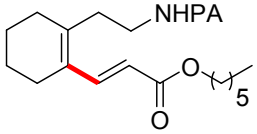
X-ray structure of **3aa**



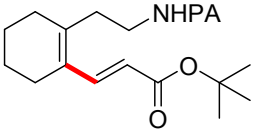
3ab, 76 %



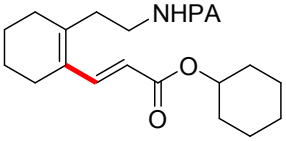
3ac, 75 %



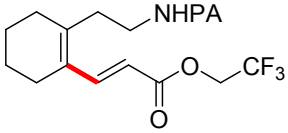
3ad, 72 %



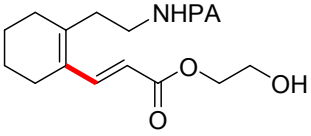
3ae, 70 %



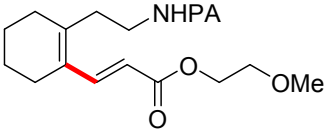
3af, 75 %



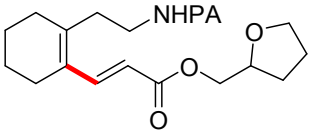
3ag, 64 %



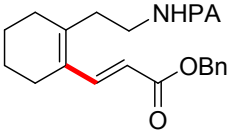
3ah, 48 %



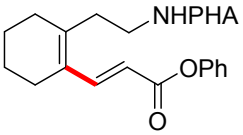
3ai, 70 %



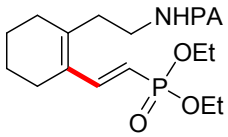
3aj, 70 %



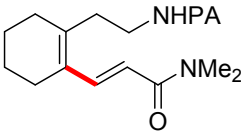
3ak, 73 %



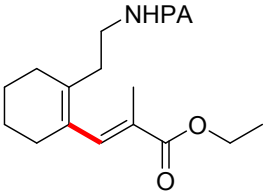
3al, 63 %[b]



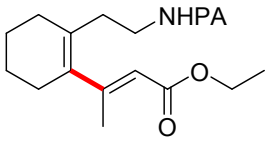
3am, 57 %



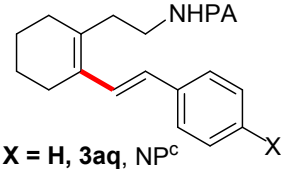
3an, 32 %



3ao, Trace



3ap, NP[c]

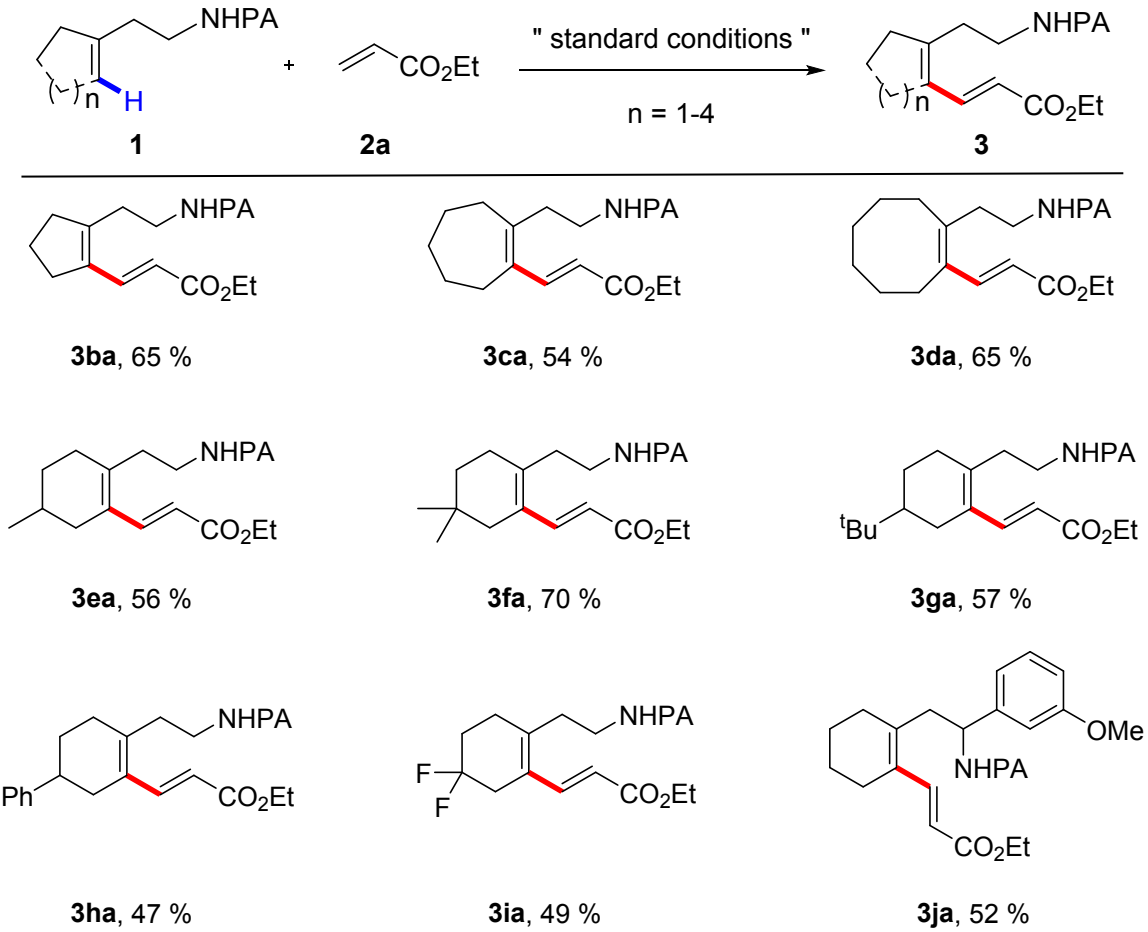


X = H, 3aq, NP[c]
F, 3ar, NP[c]

[a] **1a** (0.2 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), $KHCO_3$ (0.5 mmol), *t*-AmylOH (0.4 M) in a sealed tube under air at 130 °C for 2 h with isolated yields. [b] Using toluene as the solvent. [c] No desired product.

We also explored various cyclic olefins with picolinamide (PA) directing group reacting with **2a** under the optimal conditions with excellent chemoselectivity for relatively stable C(alkenyl)–H of olefins when compared with activated C(allylic)–H of olefins (Scheme 3). It was observed that the ring size of olefins (5-, 7-, 8-membered) has less influence on the reaction to afford corresponding cross-coupling products (**3ba-3da**) In addition, reactions of the substituent groups (such as methyl, dimethyl and tert-butyl groups) on the ring of cyclohexene gave corresponding products (**3ea-3ga**) in moderate and good yields meaning the inapparent steric effect, while desired products (**3ha-3ia**) in lower yields implied a degree of electronic effect. Additionally, the product **3ja** was obtained in 52% yield.

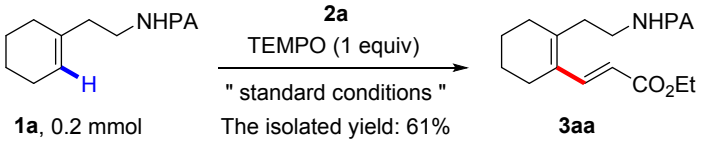
Scheme 3. Scope of olefins with PA directing group [a]



[a] **1** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol), $KHCO_3$ (0.5 mmol), *t*-AmylOH (0.4 M) in a sealed tube under air at 130 °C for 2 h with isolated yields.

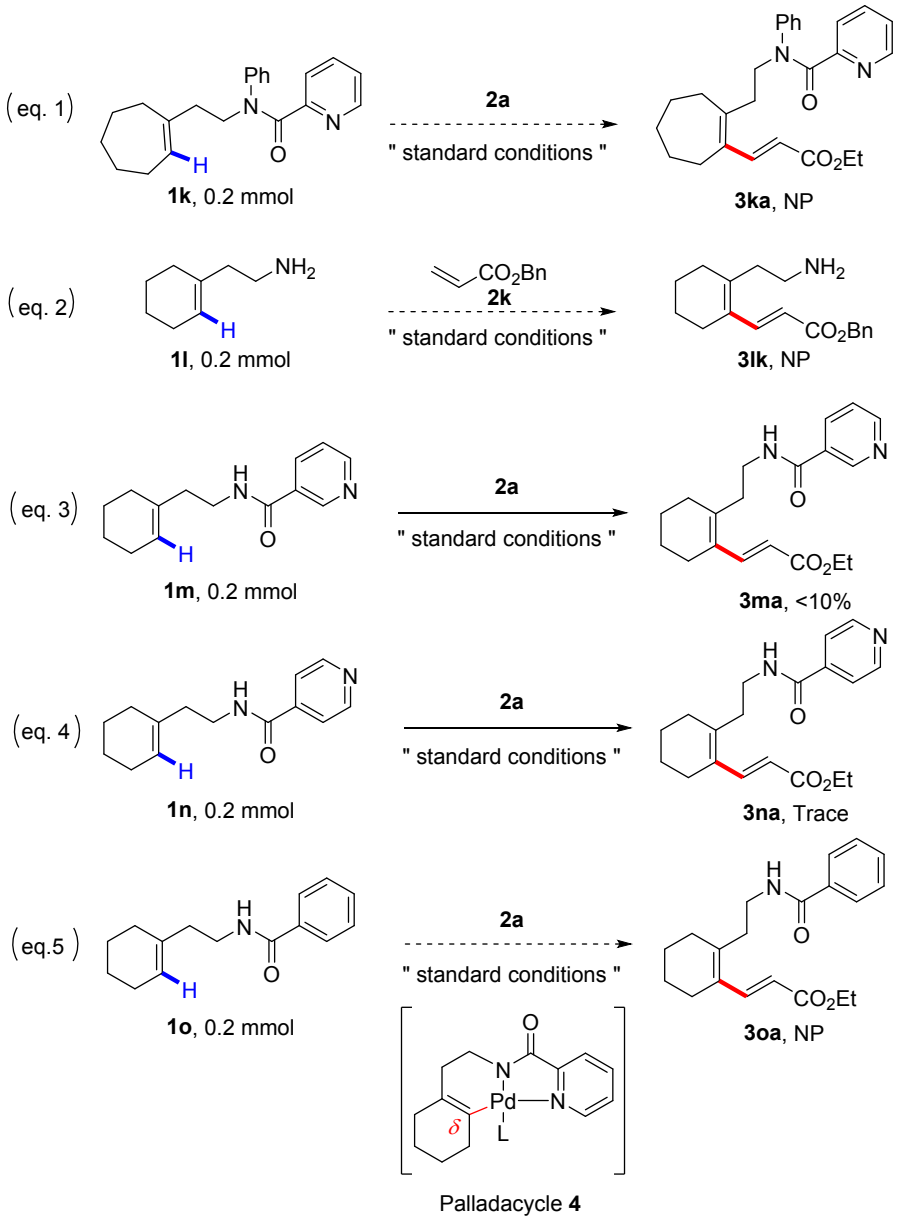
To elucidate the reaction mechanism, relative control experiments were conducted (Schemes 4-7). The addition of TEMPO into the reaction mixture cannot suppress the desired procedure and only led to a slight decline in the yield of **3aa**, which suggested that this reaction do not involve a radical process (Scheme 4).

Scheme 4. Control experiment of radical inhibitor



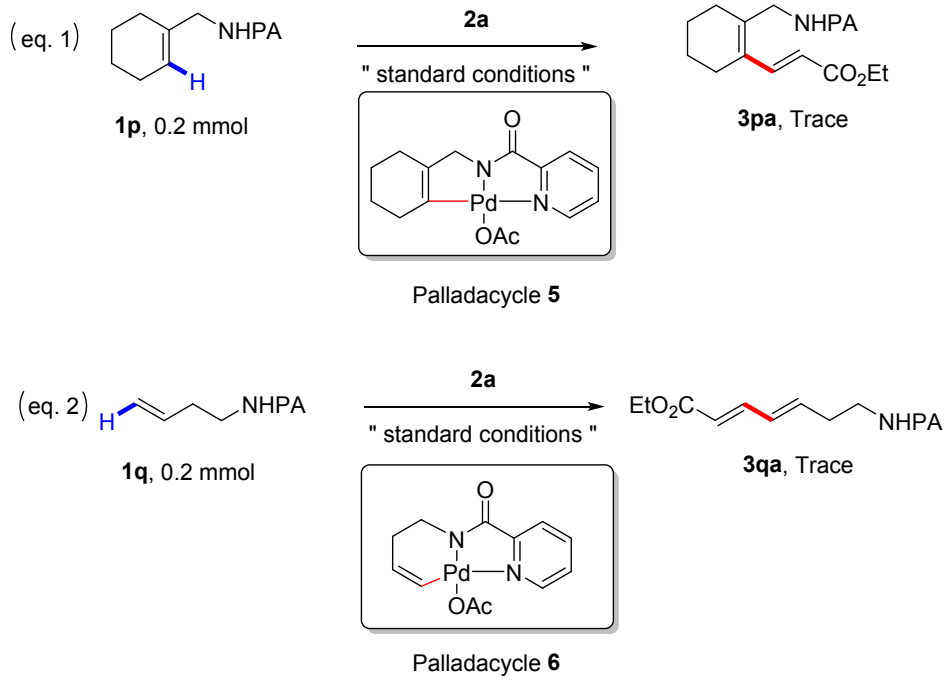
We have conducted a series of control experiments to explore the effect of picolinamide directing group, and experimental results showed that the removal of free N–H bond, the substrate without PA, changing the position of nitrogen on pyridinyl substituent or replacing pyridinyl group with phenyl substituent had negative effects on the reaction outcome (Scheme 5, eq. 1-5). According to above experimental results, we proposed that this transformation could involve palladacycle **4**.

Scheme 5. Effect of picolinamide directing group



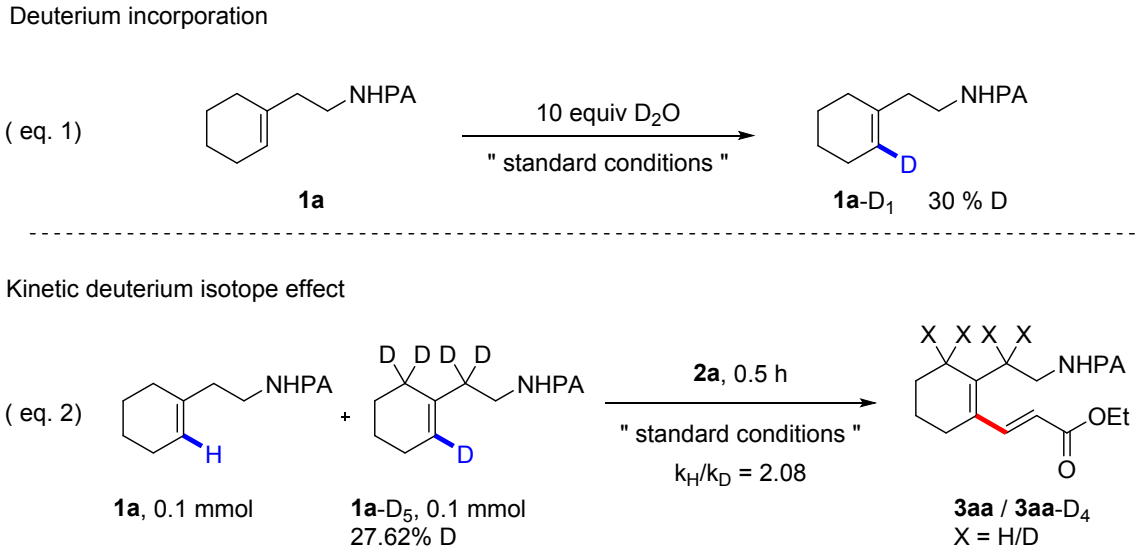
The treatment of **1p** led to a poor performance indicating a highly unstable double 5-membered palladacycle **5** in this system (Scheme 6, eq. 1). Moreover, using acyclic aliphatic olefin **1q** provided the trace amount of product **3qa**, which demonstrated that the rigidity skeleton of cycloalkenes facilitated the formation of palladacycle intermediate **4** in contrast with the palladacycle **6** (Scheme 6, eq. 2).

Scheme 6. Effect of palladacycles



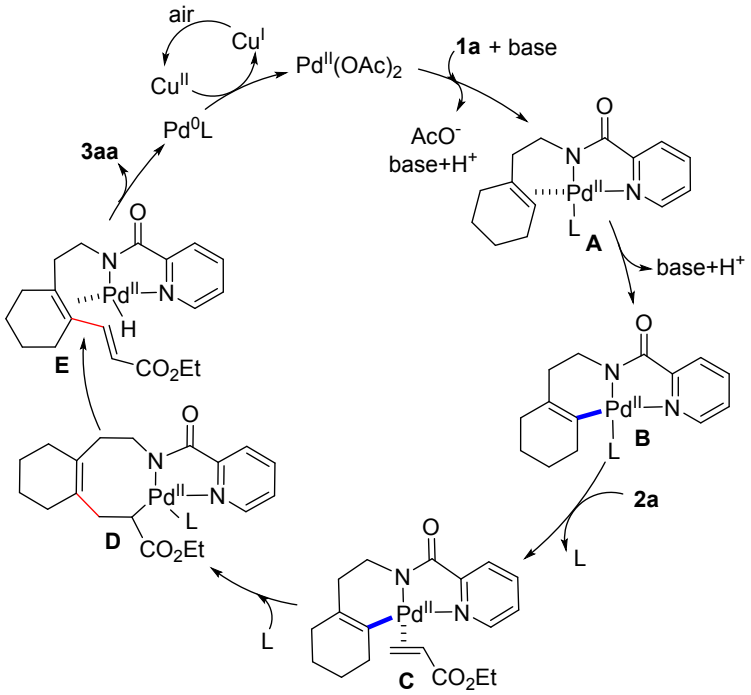
The reaction of **1a** without **2a** was treated with D_2O (10 equiv) and selective deuterium incorporation at the *δ*-C(alkenyl)–H of 1a was observed (30% D), which confirmed reversible formation of palladacycle **4** (Scheme 7, eq. 1). Research on the initial rate constant for the intermolecular competition alkenylation of **1a** and **1a**-D_5, provided a k_H/k_D value of 2.08 (Scheme 7, eq. 2), showing that alkenyl sp^2 C–H cleavage could involve the turnover-limiting step of the reaction and supported a Concerted Metallation Deprotonation (CMD) mechanism.[22b]

Scheme 7. Deuterium labelling experiments



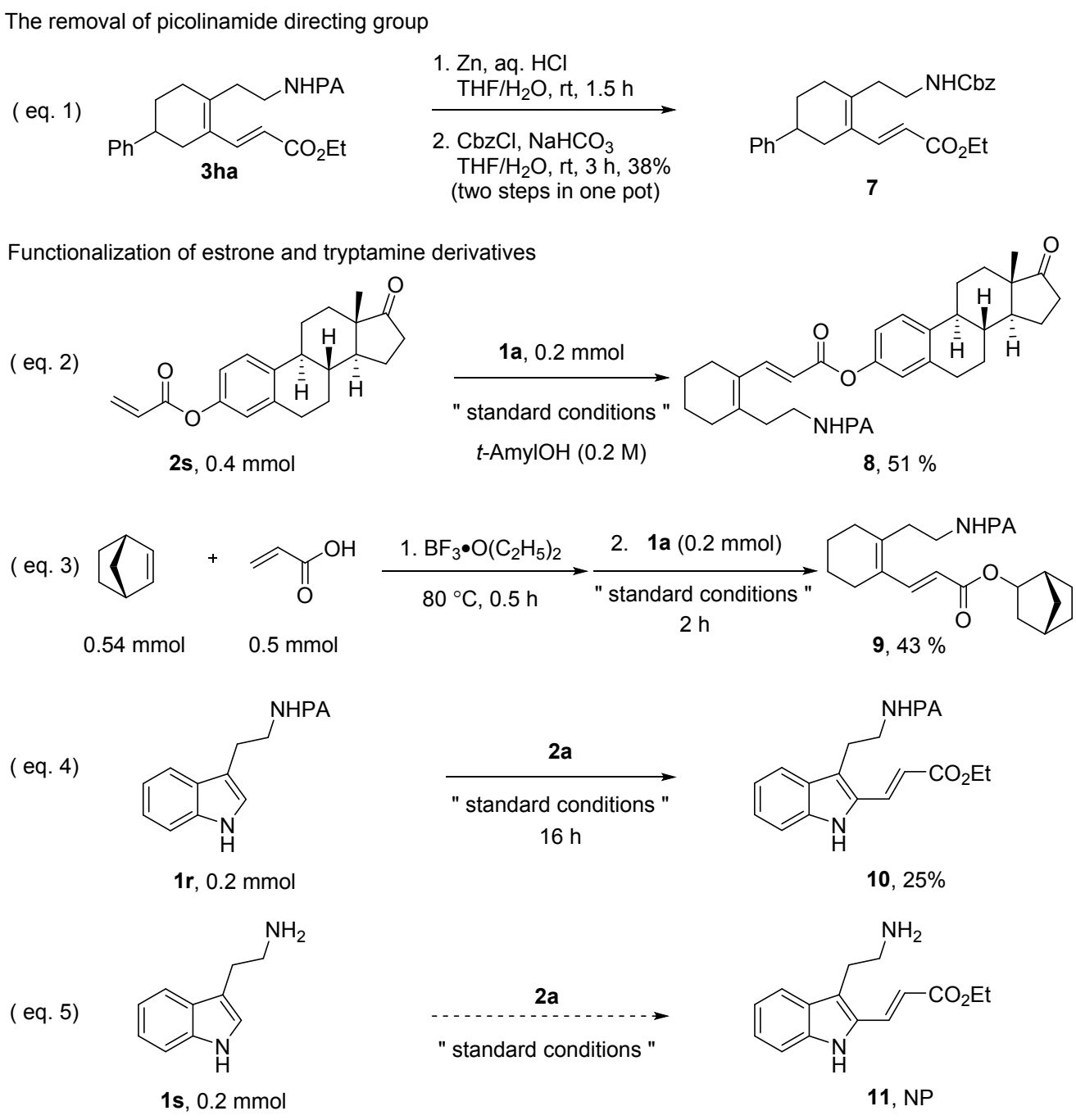
A plausible cycle is illustrated in Scheme 8.[15, 22] Initially, following substrate **1a** coordination to give a π-alkene palladium complex **A**, *δ* C(alkenyl)–H activation occurs to produce the six-membered palladacycle **B**. Ligand exchange of the electron-deficient alkene to generate the intermediate **C**, followed by migratory insertion and coordination to afford the intermediate **D**, *syn β*-H elimination of **D** and reductive elimination of palladium hydride species **E** to release the product **3aa** and oxidation of Pd(0) by $Cu(OAc)_2 \cdot H_2O$ to regenerate Pd(II) catalyst, then closes the Pd(0)/Pd(II) cycle.

Scheme 8. The proposed mechanism



The facile removal of PA made it fairly easy to be utilized as a useful protecting group of terminal NH_2 for further functionalization. For example, **3ha** followed a two-step sequence of PA removal and Cbz protection in one pot (Scheme 9, eq. 1).[16d] Natural product estrone derivative **2s** reacted with **1a** to give the corresponding alkenylated product **8** in 51% isolated yield (Scheme 9, eq. 2). In addition, the one-pot tandem reaction of norbornene can be achieved to afford norbornene derivative **9** with the 43% isolated yield (Scheme 9, eq. 3). Free N–H alkenylated tryptamine derivative **10** was obtained in 25% isolated yield (Scheme 9, eq. 4), while product **11** was not observed (Scheme 9, eq. 5).

Scheme 9. Synthetic applications



Conclusion

In summary, we have developed a palladium-catalyzed *E*-selective cross-coupling of unactivated cycloalkenes and electron-deficient alkenes under weakly alkaline conditions. The picolinamide auxiliary as a remote bidentate directing group enabled highly selective alkenylation of δ C(alkenyl)–H bond via a six-membered palladacycle intermediate involving a Pd(II)/Pd(0) catalytical cycle. Gratifyingly, natural product estrone and free N–H tryptamine derivatives can be tolerated, which can enrich the functional toolkit of natural products.

EXPERIMENTAL SECTION

General Information

Reagents and solvents were purchased from commercial sources (Energy Chemical and J&K) and were used without further purification. All reactions were monitored by TLC with silica gel coated plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a BrukerAvance 600 spectrometer. The chemical shift was given in dimensionless δ values and was frequency referenced relative to TMS in ^{1}H and ^{13}C NMR spectroscopy. Chemical shifts were reported relative to $CDCl_3$ (δ = 7.26 ppm) for ^{1}H NMR and relative to $CDCl_3$ (δ = 77 ppm) for ^{13}C NMR. Peak multiplicities were recorded as follows: s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, and br = broad singlet or a combination of them, J-values were in Hz. And high-resolution mass spectra were obtained from Q-TOF instrument by electrospray ionization (ESI). Melting points were measured on a GongyiYuhua Instrument X-5 digital display micro melting point apparatus and were uncorrected. **1j** and **1k** were directly obtained from He's group.[23, 24]

Synthetic Procedures and Characterization Data.

General Procedure I for preparation of general primary amines (GP I)[23].

Step1: The solution of ketone (1.0 equiv), cyanoacetic acid (1.0 equiv), ammonium acetate (2.0 equiv) in toluene was refluxed at 160 °C (oil bath temperature) for 3h. The mixture was cooled to room temperature, concentrated and monitored by TLC (ethyl acetate: petroleum ether = 1:3). Corresponding nitrile was obtained after purification by flash silica column chromatography.

Step2: An appropriate and dried flask was added $LiAlH_4$ (170 mg, 4.5 mmol) and dry diethyl ether (7 mL) was slowly added. The solution was stirred at 0 °C and then $AlCl_3$ (600 mg, 4.5 mmol) was placed in batches to the solution of $LiAlH_4$ in ether. After stirring 10 min, the solution of prepared nitrile in diethyl ether (2 mL) was dropped at 0 °C to the mixture of $LiAlH_4$ /$AlCl_3$/ether and stirred for 1.5-2 h at room temperature. The reaction was quenched by saturated $NaHCO_3$, adjusted to alkaline until no longer bubbling phenomenon. The filtrate

extracted by ethyl acetate (EA) was dried with anhydrous Na_2SO_4 and concentrated to afford corresponding primary amines. And prepared primary amines were used in the next step without further purification.

General Procedure II for preparation of PA substrates 1 (GP II)[24].

The DCM solution of primary amine (1.0 equiv), picolinic acid (1.1 equiv), [dimethylamino(triazolo[4,5-b]pyridin-3-yloxy)methylidene]-dimethylazanium (HATU, 1.1 equiv), *N*,*N*-Diisopropyl-ethylamine (DIPEA, 3.0 equiv) was stirred overnight at room temperature in nitrogen atmosphere. The reaction was monitored by TLC and quenched with water and stirred at ice-bath for 10 min, extracted twice with DCM, then dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The concentrate was purified by flash silica column chromatography to afford compounds **1**.

***N*-(2-(cyclohex-1-en-1-yl) ethyl) picolinamide (1a)**[24]. **1a** was synthesized following **GP II**. A reaction vessel was charged with 2-(1-cyclohexenyl)ethylamine (1.50 g, 12.0 mmol, 1.0 equiv), 2-picolinic acid (1.62g, 13.2 mmol, 1.1 equiv), HATU (5.011 g, 13.2 mmol, 1.1 equiv), DIPEA (5.9 mL, 35.9 mmol, 3.0 equiv) and DCM (30 mL) to produce **1a** (3.68 g, yield 80%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.4 Hz, 1H), 8.19 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H), 7.85 – 7.82 (m, 1H), 7.42 – 7.38 (m, 1H), 5.54 (s, 1H), 3.55 (q, J = 6.9 Hz, 2H), 2.26 (t, J = 7.0 Hz, 2H), 2.02 – 1.97 (m, 4H), 1.66 – 1.61 (m, 2H), 1.59 – 1.54 (m, 2H).

***N*-(2-(cyclopent-1-en-1-yl) ethyl) picolinamide (1b)** [24]. **1b** was synthesized following **GP II**. A reaction vessel was charged with 2-(cyclopent-1-en-1-yl) ethan-1-amine (186 mg, 1.67 mmol, 1.0 equiv), 2-picolinic acid (209 mg, 1.7 mmol, 1.1 equiv), HATU (646 mg, 1.7 mmol, 1.1 equiv), DIPEA (843 μL, 5.1 mmol, 3.0 equiv) and DCM (5 mL) to produce **1b** (90 mg, yield 42%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:8~1:6). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.3 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.86 – 7.82 (m, 1H), 7.42 – 7.36 (m, 1H), 5.49 (s, 1H), 3.61 (q, J = 6.9 Hz, 2H), 2.42 (t, J = 6.7 Hz, 2H), 2.32 (dt, J = 15.2, 7.0 Hz, 4H), 1.88 (p, J = 7.5 Hz, 2H).

***N*-(2-(cyclohept-1-en-1-yl) ethyl) picolinamide (1c)** [24]. **1c** was synthesized following **GP II**. A reaction vessel was charged with 2-(cyclohept-1-en-1-yl)ethan-1-amine (162 mg, 1.2 mmol, 1.0 equiv), 2-picolinic acid (160 mg, 1.3 mmol, 1.1 equiv), HATU (494 mg, 1.3 mmol, 1.1 equiv), DIPEA (579 μL, 3.5 mmol, 3.0 equiv) and DCM (3 mL) to produce **1c** (113 mg, yield 46%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6~1:5). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.6 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.09 (s, 1H), 7.83 (td, *J* = 7.7, 1.2 Hz, 1H), 7.41 (dd, *J* = 7.2, 5.0 Hz, 1H), 5.70 (t, *J*

= 6.4 Hz, 1H), 3.53 (q, J = 6.8 Hz, 2H), 2.30 (t, *J* = 6.9 Hz, 2H), 2.19 – 2.17 (m, 2H), 2.10 (dd, *J* = 10.9, 6.2 Hz, 2H), 1.74 (dt, *J* = 11.8, 6.0 Hz, 2H), 1.53 – 1.46 (m, 4H).

(*E*)-*N*-(2-(cyclooct-1-en-1-yl) ethyl) picolinamide (1d)[24]. 1d was directly obtained from He's group. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.7 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.09 (s, 1H), 7.83 (td, *J* = 7.7, 1.5 Hz, 1H), 7.42 – 7.37 (m, 1H), 5.49 (t, *J* = 8.1 Hz, 1H), 3.57 (q, 6.9 Hz, 2H), 2.32 (t, *J* = 7.0 Hz, 2H), 2.23 – 2.18 (m, 2H), 2.11 (d, *J* = 7.6 Hz, 2H), 1.54 – 1.46 (m, 8H).

***N*-(2-(4-methylcyclohex-1-en-1-yl) ethyl) picolinamide (1e)**. (1) 4-methylcyclohexanone (801 μL, 7.1 mmol, 1.2 equiv), cyanoacetic acid (510 mg, 6 mmol, 1.0 equiv), NH_4OAc (930 mg, 12 mmol, 2.0 equiv) and toluene (10 mL) were added in a dry 25 mL round bottom flask through the condition of **GP I** (**Step 1**) to obtain the corresponding the nitrile (585 mg, yield 72%, yellow liquid, ethyl acetate: petroleum ether = 1:3, R_f = 0.82) via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6). And then the purified nitrile was disposed according to the way **GP I** (**Step 2**) for 1.5 h to afford the amine (283 mg, yellow liquid). (2) According to **GP II**, a reaction vessel was charged with corresponding amine (283 mg, 2.0 mmol, 1.0 equiv), 2-picolinic acid (270 mg, 2.2 mmol, 1.1 equiv), HATU (837 mg, 2.2 mmol, 1.1 equiv), DIPEA (745 μL, 6.0 mmol, 3.0 equiv) and DCM (5 mL) to produce **1e** via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6): 211 mg; yield 43%; pale-yellow solid; m.p. 43-44 °C, R_f = 0.38 (ethyl acetate: petroleum ether = 1:3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.7 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H), 7.83 (td, J = 7.6, 1.8 Hz, 1H), 7.41 (dd, J = 7.7, 4.7 Hz, 1H), 5.50 (s, 1H), 3.55 (q, J = 6.6 Hz, 2H), 2.27 (t, J = 7.1 Hz, 2H), 2.13 – 1.97 (m, 3H), 1.67 (dd, J = 52.1, 10.3 Hz, 3H), 1.29 – 1.20 (m, 1H), 0.94 (d, J = 5.7 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.1, 150.2, 148.0, 137.2, 134.2, 125.9, 123.0, 122.1, 37.6, 37.4, 33.8, 31.0, 28.2, 28.1, 21.6; HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{21}N_2O$ 245.1648; Found 245.1649.

***N*-(2-(4,4-dimethylcyclohex-1-en-1-yl) ethyl) picolinamide (1f)**. (1) 4,4-dimethylcyclohexanone (500 mg, 4 mmol, 1.0 equiv), cyanoacetic acid (340 mg, 4 mmol, 1.0 equiv), NH_4OAc (616 mg, 8 mmol, 2.0 equiv) and toluene (8 mL) were added in a dry 25 mL round bottom flask through the condition of **GP I** (**Step 1**) to obtain the corresponding nitrile (330 mg, yield 55%, yellow liquid, ethyl acetate: petroleum ether = 1:3, R_f = 0.56) via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6). And then the purified nitrile was disposed according to the way **GP I** (**Step 2**) for 1.5 h to afford the amine (215 mg, colorless liquid). (2) According to **GP II**, a reaction vessel was charged with corresponding amine (215 mg, 1.4 mmol, 1.0 equiv), 2-picolinic acid (190 mg, 1.54 mmol, 1.1 equiv), HATU (586 mg, 1.54 mmol, 1.1 equiv), DIPEA (695 μL,

4.62 mmol, 3.0 equiv) and DCM (4 mL) to produce **1f** via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:7~1:6): 185 mg, yield 51%; pale-yellow solid; m.p. 50-51 °C; R_f = 0.36 (ethyl acetate: petroleum ether = 1:3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (d, J = 4.7 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.05 (s, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (dd, J = 6.9, 5.4 Hz, 1H), 5.46 (s, 1H), 3.56 (q, J = 6.6 Hz, 2H), 2.29 (t, J = 7.1 Hz, 2H), 2.01 (d, J = 6.8 Hz, 2H), 1.80 (dt, J = 4.2, 2.2 Hz, 2H), 1.38 (t, J = 6.4 Hz, 2H), 0.89 (s, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.1, 150.1, 148.0, 137.2, 133.1, 125.9, 122.7, 122.1, 39.3, 37.5, 37.2, 35.6, 28.4, 28.1, 25.9; HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{23}N_2O$ 259.1805; Found 259.1806.

***N*-(2-(4-(*tert*-butyl)cyclohex-1-en-1-yl) ethyl) picolinamide (1g).** (1) 4-*tert*-butylcyclohexanone (1036 μL, 6 mmol, 1.0 equiv), cyanoacetic acid (510 mg, 6 mmol, 1.0 equiv), NH_4OAc (925 mg, 12 mmol, 2.0 equiv) and toluene (10 mL) were added in a dry 25 mL round bottom flask through the condition of **GP I** (**Step 1**) to obtain the corresponding nitrile (766 mg, yield 72%, yellow liquid, ethyl acetate: petroleum ether = 1:3, R_f = 0.72) via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6). And then the purified nitrile was disposed according to the way **GP I** (**Step 2**) for 2 h to afford the amine (517 mg, pale yellow liquid). (2) According to **GP II**, a reaction vessel was charged with corresponding amine (517 mg, 2.9 mmol, 1.0 equiv), 2-picolinic acid (393 mg, 3.2 mmol, 1.1 equiv), HATU (1213 mg, 3.2 mmol, 1.1 equiv), DIPEA (1438 μL, 8.7 mmol, 3.0 equiv) and DCM (8 mL) to produce **1g** via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:7~1:6): 141 mg; yield 17%; yellow solid; m.p. 57-58 °C, R_f = 0.42 (ethyl acetate: petroleum ether = 1:3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.07 (s, 1H), 7.86 – 7.79 (m, 1H), 7.41 (dd, J = 7.7, 4.5 Hz 1H), 5.54 (s, 1H), 3.55 (q, J = 6.7 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 2.06 – 2.00 (m, 3H), 1.86 – 1.75 (m, 2H), 1.27 – 1.14 (m, 2H), 0.86 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.1, 150.2, 148.0, 137.2, 134.4, 125. 9, 123.7, 122.1, 44.0, 37.7, 37.2, 32.2, 29.6, 27.2, 26.9, 24.2; HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{27}N_2O$ 287.2118; Found 287.2121.

***N*-(2-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl) ethyl) picolinamide (1h).** (1) 4-phenylcyclohexanone (1045 mg, 6 mmol, 1.0 equiv), cyanoacetic acid (510 mg, 6 mmol, 1.0 equiv), NH_4OAc (925 mg, 12 mmol, 2.0 equiv) and toluene (10 mL) were added in a dry 25 mL round bottom flask through the condition of **GP I** (**Step 1**) to produce the corresponding nitrile (964 mg, yield 82%, yellow brown liquid, ethyl acetate: petroleum ether = 1:3, R_f = 0.35) via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:3). And then the purified nitrile was disposed according to the way **GP I** (**Step 2**) for 1.5 h to afford the amine (547 mg, yellow liquid). (2) According to **GP II**, a reaction vessel was charged with corresponding amine (547 mg, 2.7 mmol, 1.0 equiv), 2-picolinic acid (366 mg, 2.97 mmol, 1.1 equiv), HATU (1129 mg, 2.97 mmol, 1.1 equiv),

DIPEA (1340 μL, 8.1 mmol, 3.0 equiv) and DCM (7 mL) to obtain **1h** via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:7~1:6): 378 mg; yield 46%; white solid; m.p. 73-74 °C; R_f = 0.26 (ethyl acetate: petroleum ether = 1:3); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, J = 4.3 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.84 (td, J = 7.7, 1.7 Hz 1H), 7.41 (dd, J = 7.6, 4.8 Hz 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.25 – 7.20 (m, 2H), 7.22 – 7.15 (m, 1H), 5.63 (s, 1H), 3.59 (p, J = 6.5 Hz, 2H), 2.80 – 2.73 (m, 1H), 2.36 – 2.27 (m, 3H), 2.26 – 2.13 (m, 2H), 2.10 (d, J = 16.5 Hz, 1H), 1.95 (dq, J = 10.3, 2.6 Hz, 1H), 1.83 – 1.75 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.2, 150.2, 148.1, 147.0, 137.3, 134.6, 128.3, 126.9, 126.0, 126.0, 123.1, 122.2, 39.9, 37.6, 37.4, 33.4, 30.0, 28.7; HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_2O$ 307.1805; Found 307.1804.

***N*-(2-(4,4-difluorocyclohex-1-en-1-yl) ethyl) picolinamide (1i)** [25a]**.** (1) 4,4-difluorocyclohexan-1-one (706 μL, 4 mmol, 1.0 equiv), cyanoacetic acid (340 mg, 4 mmol, 1.0 equiv), NH_4OAc (618 mg, 8 mmol, 2.0 equiv) and toluene (8 mL) were added in a dry 25 mL round bottom flask through the condition of **GP I** (**Step 1**) to obtain the corresponding nitrile (526 mg, yield 84%, colorless liquid, ethyl acetate: petroleum ether = 1:3, R_f = 0.34) via the purification by silica flash column chromatography (ethyl acetate: petroleum ether = 1:3). And then the purified nitrile was disposed according to the way **GP I** (**Step 2**) for 1.5 h to afford the amine (208 mg, yellow liquid). (2) According to **GP II**, a reaction vessel was charged with corresponding amine (208 mg, 1.3 mmol, 1.0 equiv), 2-picolinic acid (176 mg, 1.43 mmol, 1.1 equiv), HATU (543 mg, 1.43 mmol, 1.1 equiv), DIPEA (643 μL, 3.90 mmol, 3.0 equiv) and DCM (4 mL) to obtain **1i** via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5): 207 mg; yield 60%; white solid; m.p. 66-67 °C; R_f = 0.3 (ethyl acetate: petroleum ether = 1:2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 8.19 (d, J = 7.7 Hz, 1H), 8.09 (s, 1H), 7.84 (t, J = 7.1 Hz, 1H), 7.42 (dd, J = 6.2, 5.2 Hz, 1H), 5.39 (s, 1H), 3.58 (q, J = 6.7 Hz, 2H), 2.50 (t, J = 14.2 Hz, 2H), 2.33 (dd, J = 18.1, 11.3 Hz, 4H), 2.08 – 1.98 (m, 2H); ^{19}F NMR (565 MHz, $CDCl_3$) δ -96.78; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.2, 149.9, 148.0, 137.2, 134.3, 126.0, 122.8 (t, $J_{C\text{-}F}$ = 239.7 Hz), 122.0, 118.1(t, $J_{C\text{-}F}$ = 5.2 Hz), 37.4, 36.6, 34.5 (t, $J_{C\text{-}F}$ = 26.4 Hz), 30.3 (t, $J_{C\text{-}F}$ = 24.3 Hz), 26.4 (t, $J_{C\text{-}F}$ = 5.4 Hz); HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}F_2N_2O$ 267.1303; Found 267.1309.

***N*-(2-(cyclohex-1-en-1-yl) ethyl) nicotinamide (1m)**[24]**. 1m** was synthesized following **GP II**. A reaction vessel was charged with 2-(1-cyclohexenyl)ethylamine (280 μL, 2 mmol, 1.0 equiv) and nicotinic acid (271 mg, 2.2 mmol, 1.1 equiv), HATU (836 mg, 2.2 mmol, 1.1 equiv), DIPEA (1034 μL, 6.0 mmol, 3.0 equiv) and DCM (6 mL) in N_2 to produce **1m** (385 mg, yield 84%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.71 (s, 1H),

8.11 (d, J = 7.1 Hz, 1H), 7.39 (s, 1H), 6.55 (s, 1H), 5.53 (s, 1H), 3.56 – 3.48 (m, 2H), 2.28 – 2.22 (m, 2H), 2.03 – 1.93 (m, 4H), 1.69 – 1.53 (m, 4H).

***N*-(2-(cyclohex-1-en-1-yl) ethyl) isonicotinamide (1n)[24]. 1n** was **s**ynthesized following **GP II**. A reaction vessel was charged with 2-(1-cyclohexenyl)ethylamine (140 μL, 1 mmol, 1.0 equiv) and isonicotinic acid (136 mg, 1.1 mmol, 1.1 equiv), HATU (418 mg, 1.1 mmol, 1.1 equiv), DIPEA (517 μL, 3.0 mmol, 3.0 equiv) and DCM (3 mL) in N_2 to obtain **1n** (177 mg, yield 77%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.74 (d, J = 4.5 Hz, 2H), 7.56 (d, J = 4.6 Hz, 2H), 6.20 (s, 1H), 5.55 (s, 1H), 3.54 (q, J = 6.5 Hz, 2H), 2.26 (t, J = 6.4 Hz, 2H), 2.06 – 2.01 (m, 2H), 2.00 – 1.95 (m, 2H), 1.67 – 1.63 (m, 2H), 1.58 (dt, J = 9.0, 5.7 Hz, 2H).

***N*-(2-(cyclohex-1-en-1-yl) ethyl) benzamide (1o). 1o** was synthesized following **GP II**. A reaction vessel was charged with 2-(1-cyclohexenyl)ethylamine (140 μL, 1 mmol, 1.0 equiv) and benzoic acid (134 mg, 1.1 mmol, 1.1 equiv), HATU (418 mg, 1.1 mmol, 1.1 equiv), DIPEA (517 μL, 3.0 mmol, 3.0 equiv) and DCM (3 mL) in N_2 to obtain **1o** (58 mg, yield 35%) as colorless oil via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.2 Hz, 1H), 7.43 (t, J = 7.4 Hz, 2H), 6.12 (s, 1H), 5.55 (s, 1H), 3.53 (q, J = 6.5 Hz, 2H), 2.25 (t, J = 5.9 Hz, 2H), 2.00 (d, J = 27.9 Hz, 4H), 1.66 – 1.55 (m, 4H). ^{1}H NMR of **1o** is consistent with the previous report.[25b]

***N*-(cyclohex-1-en-1-yl methyl) picolinamide (1p).** (1) To a 15 mL tube was added cyclohexanone (207 μL, 2 mmol), ethylenediamine (7 μL, 0.1 mmol), nitromethane (1.5 mL) and the resulting was refluxed in a preheated oil bath at 110 °C for 7 h, using TLC to monitor the reaction (ethyl acetate: petroleum ether = 1:3). The reaction was cooled to room temperature and evaporated under reduced pressure to get the crude compound 1-(2-nitroethyl)cyclohex-1-ene without further purification. Then 1-(2-nitroethyl)cyclohex-1-ene was treated with zinc powder (0.7 g) and acetic acid (2 mL) at room temperature for 1-3 h, and the mixture was filtered with diatomaceous earth, adjusted pH value by saturated $NaHCO_3$ solution and extracted with EA to afford cyclohex-1-en-1-ylmethanamine (116 mg, the crude product) without further purification. (2) According to the **GP II**, the prepared cyclohex-1-en-1-ylmethanamine (116 mg, 1 mmol, 1 equiv), 2-picolinic acid (135 mg, 1.1 mmol, 1.1 equiv), HATU (418 mg, 1.1 mmol, 1.1 equiv), DIPEA (517 μL, 3.1 mmol, 3.0 equiv) and DCM (3 mL) were added in the 25 mL reaction flask in N_2 to obtain **1p** (23 mg, yield 11%, as yellow oil) via the purification by flash silica column chromatography (ethyl acetate: petroleum ether =1:7~ 1:6). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.55 (d, J = 4.6 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H), 7.85 (td, J = 7.7, 1.6 Hz, 1H), 7.45

– 7.39 (m, 1H), 5.66 (s, 1H), 3.97 (d, J = 6.0 Hz, 2H), 2.04 – 1.99 (m, 4H), 1.67 – 1.61 (m, 2H), 1.58 (td, J = 5.8, 3.5 Hz, 2H). ^{1}H NMR of **1p** is consistent with the previous report.[24]

***N*-(but-3-en-1-yl)picolinamide (1q)**[26]. (1) To the solution of 4-bromo-1-buten (1015 μL, 10 mmol), Potassium phtalimide (2315 mg, 12.5 mmol), TBAB (160 mg, 0.5 mmol) in MeCN (16 mL) was refluxed in a preheated oil bath at 90 °C for 5h. The mixture was filtered to remove an excess of potassium salts and MeCN was evaporated under reduced pressure. And then it was extracted by Et_2O and brine twice (4 mL × 2), dried over K_2CO_3 and concentrated to afford *N*-(3-butenyl) phthalimide (1.939 g, yield 96 %). (2) *N*-(3-butenyl) phthalimide was dissolved in EtOH (32 mL) and hydrazine hydrate (972 μL) was added. The mixture was refluxed in a preheated oil bath at for 1 h (90 °C). Next, 2N NaOH (50 mL) was put into the system and evaporated the solution, extracted by EA twice. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give but-3-en-1-amine (558 mg, yield 80%) without further purification. (3) The mixture of but-3-en-1-amine (558 mg), triethylamine (1648 μL, 11.85 mmol) and DMAP (96 mg, 0.79 mmol) was charged into a 50 mL flask containing 20 mL DCM. Sequentially, picolinoyl chloride which is synthesized via 2-picolinic acid (1476 mg, 12 mmol, 1.0 equiv), oxalyl chloride (1270 μL, 15 mmol, 1.25 equiv), DMF (1.5 mL) and DCM (30 mL) in the reaction flask (100 mL) for 24 h at room temperature was added dropwise under the ice bath. The reaction was room temperature and stirred for 28 h. When the system was finished, it was quenched with water, extracted by DCM, washed with brine and purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:8) to get **1q** (34 mg, yield 3%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.0 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.10 (s, 1H), 7.84 (td, J = 7.7, 1.6 Hz, 1H), 7.41 (dd, J = 6.4, 4.8 Hz, 1H), 5.86 (ddt, J = 13.6, 10.1, 6.8 Hz, 1H), 5.16 (dd, J = 17.1, 1.4 Hz, 1H), 5.11 (d, J = 10.2 Hz, 1H), 3.56 (q, J = 6.7 Hz, 2H), 2.40 (q, J = 6.8 Hz, 2H). ^{1}H NMR of **1q** is consistent with the previous report[27].

***N*-(2-(1*H*-indol-3-yl) ethyl) picolinamide (1r). 1r** was synthesized following **GP II**. A reaction vessel was charged with tryptamine (160 mg, 1.0 mmol, 1.0 equiv), 2-picolinic acid (136 mg, 1.1 mmol, 1.1 equiv), HATU (418 mg, 1.1 mmol, 1.1 equiv), DIPEA (517 μL, 3.0 mmol, 3.0 equiv) and DCM (3 mL) in N_2 to obtain **1r** (179 mg, yield 68%) as white solid via the purification by flash silica column chromatography (ethyl acetate: petroleum ether = 1:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, J = 4.7 Hz, 1H), 8.21 (d, J = 7.9 Hz, 2H), 8.13 (s, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.17 – 7.07 (m, 2H), 3.83 (q, J = 6.8 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H). ^{1}H NMR of **1r** is consistent with the previous report[28].

(8*R*,9*S*,13*S*,14*S*)- 13-Methyl- 17-oxo- 7,8,9,11,12,13,14,15, 16,17-decahydro-6*H*-cyclopenta [a] phenanthren-3-yl acrylate (2s)[29]**.** Estrone (1352 mg, 5 mmol), acrylic acid (340 μL, 5 mmol), DCC (1288 mg,

6.25 mmol) were dissolved by DCM (20 mL). Next, DMAP (60 mg, 0.5 mmol) was added and stirred at RT for 24 h under an atmosphere of argon, filtered to remove of excess of estrone and the filtrate was evaporated under reduced pressure and purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6) to get the desired product **2s** (334 mg, yield 21%, white solid). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.93 – 6.82 (m, 2H), 6.59 (d, *J* = 17.3 Hz, 1H), 6.31 (dd, *J* = 17.3, 10.5 Hz, 1H), 6.00 (d, *J* = 10.4 Hz, 1H), 2.97 – 2.87 (m, 2H), 2.51 (dd, *J* = 19.0, 8.7 Hz, 1H), 2.44 – 2.38 (m, 1H), 2.30 (t, *J* = 8.8 Hz, 1H), 2.19 – 1.94 (m, 4H), 1.64 – 1.46 (m, 6H), 0.91 (s, 3H). ^{1}H NMR of **2s** is consistent with the previous report[30a].

General Procedure of Synthesis of Products 3. (Note: All the non-solid PA substrates are dissolved in the solvent and then added to the reaction system.)

Ethyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl) acrylate (3aa). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **3aa** (53 mg, yield 80%, pale yellow solid, m.p. 82-83 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.6 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.83 (dd, J = 7.7, 1.5 Hz, 1H), 7.80 (d, J = 15.8 Hz, 1H), 7.44 – 7.34 (m, 1H), 5.77 (d, J = 15.6 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.57 (q, J = 6.8 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.30 – 2.25 (m, 2H), 2.20 – 2.13 (m, 2H), 1.72 – 1.57 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 164.2, 149.9, 147.9, 143.5, 141.9, 137.2, 129.5, 125.9, 122.1, 115.8, 60.0, 38.4, 33.7, 31.6, 25.4, 22.4, 22.3, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_3$ 329.1860; Found 329.1859.

Methyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en -1-yl)acrylate (3ab). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and methyl acrylate **2b** (36 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4) to afford **3ab** (48 mg, yield 76%, pale yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 3.7 Hz, 1H), 8.18 (d, J = 7.7 Hz, 1H), 8.14 (s, 1H), 7.85 – 7.81 (m, 1H), 7.79 (d, J = 15.6 Hz, 1H),

7.42 – 7.38 (m, 1H), 5.77 (d, J = 15.6 Hz, 1H), 3.68 (s, 3H), 3.57 (q, J = 6.8 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H), 2.31 – 2.24 (m, 2H), 2.18 – 2.13 (m, 2H), 1.70 – 1.62 (m, 4H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 168.1, 164.3, 149.9, 148.0, 143.8, 142.2, 137.2, 129.5, 126.0, 122.1, 115.3, 51.31, 38.4, 33.8, 31.7, 25.4, 22.5, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}N_2O_3$ 315.1703; Found 315.1701.

Butyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl) acrylate (3ac). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and butyl acrylate **2c** (57 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4) to afford **3ac** (53 mg, yield 75%, pale yellow solid, m.p. 83-84 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.83 (dd, J = 7.7, 1.6 Hz, 1H), 7.80 (d, J = 15.7 Hz, 1H), 7.42 – 7.38 (m, 1H), 5.78 (d, J = 15.6 Hz, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.57 (q, J = 6.7 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.31 – 2.24 (m, 2H), 2.21 – 2.14 (m, 2H), 1.69 – 1.59 (m, 6H), 1.43 – 1.34 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 164.2, 149.9, 148.0, 143.5, 141.9, 137.2, 129.5, 126.0, 122.1, 115.8, 64.0, 38.4, 33.8, 31.6, 30.8, 25.4, 22.5, 22.3, 19.2, 13.7; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{29}N_2O_3$ 357.2173; Found 357.2171.

Hexyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl) acrylate (3ad). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and hexyl acrylate **2d** (70 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5) to afford **3ad** (55 mg, yield 72%, pale yellow solid, m.p. 84-85 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.6 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 8.13 (s, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.80 (d, J = 15.5 Hz, 1H), 7.40 (dd, J = 7.4, 4.8 Hz, 1H), 5.78 (d, J = 15.5 Hz, 1H), 4.08 (t, J = 6.8 Hz, 2H), 3.57 (q, J = 6.8 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.28 (t, J = 5.8 Hz, 2H), 2.17 (d, J = 5.6 Hz, 2H), 1.66 – 1.62 (m, 4H), 1.40 – 1.24 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 164.2, 149.9, 148.0, 143.5, 141.9, 137.2, 129.5, 126.0, 122.1, 115.8, 64.3, 38.5, 33.8, 31.7, 31.5, 28.7, 25.6, 25.4, 22.5, 22.5, 22.3, 14.0; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}N_2O_3$ 385.2486; Found 385.2486.

***tert*-Butyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl)acrylate (3ae).** The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and *tert*-butyl acrylate **2e** (58 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5) to afford **3ae** (50 mg, yield 70%, pale yellow solid, m.p. 94-95 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 4.2 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.84 – 7.81 (m, 1H), 7.73 (d, J = 15.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 5.72 (d, J = 15.5 Hz, 1H), 3.56 (q, J = 6.8 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.27 (t, J = 5.0 Hz, 2H), 2.17 – 2.13 (m, 2H), 1.68 – 1.61 (m, 4H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.2, 164.2, 149.9, 148.0, 142.8, 141.0, 137.2, 129.5, 126.0, 122.1, 117.6, 79.9, 38.5, 33.7, 31.6, 28.2, 25.5, 22.5, 22.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{29}N_2O_3$ 357.2173; Found 357.2176.

Cyclohexyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl)acrylate (3af). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and cyclohexyl acrylate **2f** (63 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5) to afford **3af** (57 mg, yield 75%, yellow solid, m.p. 70-71 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.3 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.83 (d, J = 7.7 Hz, 1H), 7.80 (d, J = 15.7 Hz, 1H), 7.43 – 7.38 (m, 1H), 5.78 (d, J = 15.5 Hz, 1H), 4.78 (td, J = 8.8, 4.2 Hz, 1H), 3.57 (q, J = 6.9 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.29 – 2.26 (m, 2H), 2.19 – 2.15 (m, 2H), 1.87 – 1.60 (m, 10H), 1.45 – 1.34 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.2, 164.2, 149.9, 148.0, 143.3, 141.6, 137.2, 129.6, 126.0, 122.1, 116.4, 72.2, 38.5, 33.7, 31.7, 31.6, 25.5, 23.8, 22.5, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{31}N_2O_3$ 383.2329; Found 383.2335.

2,2,2-Trifluoroethyl (*E*)-3-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ag). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and 2,2,2-trifluoroethyl acrylate **2g** (51 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air

atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:6) to afford **3ag** (49 mg, yield 64%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.7 Hz, 1H), 8.17 (d, J = 7.5 Hz, 1H), 8.13 (s, 1H), 7.90 (d, J = 15.5 Hz, 1H), 7.83 (t, J = 6.8 Hz, 1H), 7.43 – 7.35 (m, 1H), 5.80 (d, J = 15.5 Hz, 1H), 4.47 (q, J = 8.4 Hz, 2H), 3.58 (q, J = 6.5 Hz, 2H), 2.63 (t, J = 6.4 Hz, 2H), 2.33 – 2.27 (m, 2H), 2.19 – 2.13 (m, 2H), 1.70 – 1.61 (m, 4H); ^{19}F NMR (565 MHz, $CDCl_3$) δ -73.72. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.9, 164.3, 149.9, 147.9, 145.8, 144.4, 137.2, 129.5, 126.0, 123.2 (q, $J_{C\text{-}F}$ = 277.3 Hz), 122.1, 113.2, 60.1 (q, $J_{C\text{-}F}$ = 36.4 Hz), 38.4, 33.9, 31.8, 25.4, 22.4, 22.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}F_3N_2O_3$ 383.1577; Found 383.1580.

2-Hydroxyethyl (*E*)-3-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ah). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and 2-hydroxyethyl acrylate **2h** (42 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:1) to afford **3ah** (33 mg, yield 48%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 4.0 Hz, 1H), 8.35 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 15.6 Hz, 1H), 7.86 (t, J = 7.6 Hz, 1H), 7.45 – 7.39 (m, 1H), 5.77 (d, J = 15.6 Hz, 1H), 4.76 (s, 1H), 4.28 – 4.24 (m, 2H), 3.93 (s, 2H), 3.48 (q, J = 6.9 Hz, 2H), 2.66 – 2.58 (m, 2H), 2.28 – 2.22 (m, 2H), 2.19 – 2.14 (m, 2H), 1.71 – 1.60 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 165.3, 149.5, 148.1, 143.2, 142.6, 137.5, 129.9, 126.3, 122.3, 115.6, 66.6, 61.0, 39.4, 33.9, 32.0, 25.0, 22.5, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}N_2O_4$ 345.1809; Found 345.1812.

2-Methoxyethyl (*E*)-3-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ai). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and 2-methoxyethyl acrylate **2i** (52 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:2) to afford **3ai** (50 mg, yield 70%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 3.7 Hz, 1H), 8.20 – 8.10 (m, 2H), 7.87 – 7.79 (m, 2H), 7.40 (dd, J = 7.7, 4.6 Hz, 1H),

5.84 (d, J = 15.5 Hz, 1H), 4.26 (t, J = 4.8 Hz, 2H), 3.62 (t, J = 4.8 Hz, 2H), 3.56 (q, J = 7.0 Hz, 2H), 3.40 (s, 3H), 2.62 (t, J = 7.4 Hz, 2H), 2.30 – 2.25 (m, 2H), 2.17 – 2.13 (m, 2H), 1.68 – 1.60 (m, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.7, 164.2, 149.9, 148.0, 143.9, 142.4, 137.2, 129.5, 126.0, 122.1, 115.3, 70.6, 63.2, 59.0, 38.5, 33.8, 31.7, 25.4, 22.4, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_2O_4$ 359.1965; Found 359.1968.

(Tetrahydrofuran-2-yl) methyl (*E*)-3-(2-(2-(picolinamido) ethyl)cyclohex-1-en-1-yl)acrylate (3aj). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and (tetrahydrofuran-2-yl)methyl acrylate **2j** (59 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:1) to afford **3aj** (54 mg, yield 70%, yellow solid, m.p. 64-65 °C). ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.9 Hz, 1H), 8.19 – 8.11 (m, 2H), 7.87 – 7.77 (m, 2H), 7.40 (t, d, J = 5.9 Hz, 1H), 5.84 (d, J = 15.5 Hz, 1H), 4.20 – 4.12 (m, 2H), 4.04 (dd, J = 10.9, 6.4 Hz, 1H), 3.90 (dd, J = 7.0, 6.3 Hz, 1H), 3.80 (q, J = 7.2, Hz, 1H), 3.58 – 3.53 (m, 2H), 2.61 (t, J = 6.6 Hz, 2H), 2.31 – 2.24 (m, 2H), 2.18 – 2.12 (m, 2H), 2.00 (p, J = 6.4 Hz, 1H), 1.94 – 1.87 (m, 2H), 1.64 (t, J = 7.0 Hz, 5H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.6, 164.2, 149.8, 148.0, 143.9, 142.4, 137.2, 129.5, 126.0, 122.1, 115.4, 76.6, 68.4, 66.2, 38.5, 33.7, 31.6, 28.0, 25.7, 25.4, 22.4, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{29}N_2O_4$ 385.2122; Found 385.2123.

Benzyl (*E*)-3-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ak). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and benzyl acrylate **2k** (60 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4) to afford **3ak** (57 mg, yield 73%, yellow solid, m.p. 92-93 °C). ^1H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 4.2 Hz, 1H), 8.15 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.86 (d, J = 15.6 Hz, 1H), 7.80 (td, J = 7.7, 1.6 Hz, 1H), 7.39 – 7.34 (m, 5H), 7.33 – 7.30 (m, 1H), 5.82 (d, J = 15.5 Hz, 1H), 5.15 (s, 2H), 3.56 (q, J = 6.7 Hz, 2H), 2.62 (t, J = 7.3 Hz, 2H), 2.31 – 2.26 (m, 2H), 2.18 – 2.12 (m, 2H), 1.67 – 1.62 (m, 4H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.5, 164.3, 149.9, 148.0, 144.1, 142.5, 137.2, 136.4, 129.6, 128.5, 128.1, 128.0,

126.0, 122.1, 115.3, 65.9, 38.4, 33.8, 31.7, 25.4, 22.4, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{27}N_2O_3$ 391.2016; Found 391.2017.

Phenyl (*E*)-3-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3al). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and phenyl acrylate **2l** (55 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in toluene (0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4) to afford **3al** (47 mg, yield 63%, yellow solid, m.p. 90-91 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.4 Hz, 1H), 8.16 (d, J = 7.8 Hz, 2H), 7.98 (d, J = 15.5 Hz, 1H), 7.80 (td, J = 7.7, 1.5 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.21 (t, J = 7.4 Hz, 1H), 7.09 – 7.06 (m, 2H), 5.95 (d, J = 15.5 Hz, 1H), 3.59 (q, J = 6.8 Hz, 2H), 2.65 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 5.5 Hz, 2H), 2.26 – 2.20 (m, 2H), 1.73 – 1.63 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.1, 164.3, 151.0, 149.8, 148.0, 145.1, 143.8, 137.3, 129.7, 129.2, 126.1, 125.5, 122.2, 121.6, 114.8, 38.5, 33.9, 31.8, 25.4, 22.4, 22.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}N_2O_3$ 377.1860; Found 377.1861.

Diethyl (*E*)-(2-(2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)vinyl)phosphonate (3am). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl) picolinamide **1a** (46 mg, 0.2 mmol) and diethyl vinylphosphonate **2m** (61 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate) to afford **3am** (45 mg, yield 57%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, J = 4.8 Hz, 1H), 8.18 (d, J = 8.9 Hz, 2H), 7.84 (t, J = 7.8 Hz, 1H), 7.63 (dd, J = 22.8, 17.3 Hz, 1H), 7.41 (t, J = 6.1 Hz, 1H), 5.59 (t, J = 18.1 Hz, 1H), 4.12 – 3.95 (m, 4H), 3.56 (q, J = 7.1 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 2.30 – 2.26 (m, 2H), 2.17 – 2.13 (m, 2H), 1.69 – 1.60 (m, 4H), 1.31 (t, J = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.1, 149.7, 147.9, 145.5 (d, $J_{C\text{-}P}$ = 7.2 Hz), 142.7, 137.1, 129.5 (d, $J_{C\text{-}P}$ = 22.6 Hz), 125.9, 121.9, 110.9 (d, $J_{C\text{-}P}$ = 191.9 Hz), 61.4 (d, $J_{C\text{-}P}$ = 5.5 Hz), 38.3, 33.4, 31.3, 25.0, 22.3, 22.2, 16.2 (d, $J_{C\text{-}P}$ = 6.2 Hz); HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{30}N_2O_4P$ 393.1938; Found 393.1939.

(*E*)-*N*-(2-(2-(3-(dimethylamino)-3-oxoprop-1-en-1-yl) cyclohex-1-en-1-yl)ethyl)picolinamide (3an). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)ethyl) picolinamide **1a** (46 mg, 0.2 mmol) and *N*,*N*-dimethylacrylamide **2n** (41 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg,

0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:1) to afford **3an** (21 mg, yield 32%, yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, J = 4.2 Hz, 1H), 8.21 – 8.15 (m, 2H), 7.86 – 7.81 (m, 1H), 7.79 (d, J = 15.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 6.22 (d, J = 15.0 Hz, 1H), 3.55 (q, J = 7.0 Hz, 2H), 3.06 (s, 3H), 3.02 (s, 3H), 2.63 (t, J = 7.6 Hz, 2H), 2.30 – 2.26 (m, 2H), 2.23 –2.17 (m, 2H), 1.71 – 1.60 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 164.2, 150.0, 148.0, 141.9, 139.8, 137.1, 129.4, 125.9, 122.1, 114.7, 38.7, 37.3, 35.8, 33.8, 31.6, 25.7, 22.6, 22.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{26}N_3O_2$ 328.2020; Found 328.2018.

Ethyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclopent-1-en-1-yl) acrylate (3ba). The reaction was carried out using *N*-(2-(cyclopent-1-en-1-yl)ethyl)picolinamide **1b** (43 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **3ba** (41 mg, yield 65%, pale yellow solid, m.p. 71-72 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.2 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.09 (s, 1H), 7.83 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 15.5 Hz, 1H), 7.42 – 7.38 (m, 1H), 5.71 (d, J = 15.5 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.60 (q, J = 6.8 Hz, 2H), 2.68 (t, J = 7.0 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.50 (t, J = 7.1 Hz, 2H), 1.94 – 1.87 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.5, 164.2, 149.9, 149.0, 148.0, 137.5, 137.2, 135.3, 126.0, 122.1, 118.0, 60.1, 37.8, 37.5, 32.6, 29.2, 21.6, 14.3; HRMS (ESI-TOF) m/z: Calcd for $[M + Na]^+$ $C_{18}H_{22}N_2O_3Na$ 337.1523; Found 337.1522.

Ethyl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohept-1-en-1-yl) acrylate (3ca). The reaction was carried out using *N*-(2-(cyclohept-1-en-1-yl)ethyl)picolinamide **1c** (49 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **3ca** (37 mg, yield 54%, pale yellow solid, m.p. 76-77 °C). ^{1}H NMR

(600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.1 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.12 (s, 1H), 7.82 (t, J = 7.7 Hz, 1H), 7.75 (d, J = 15.5 Hz, 1H), 7.43 – 7.36 (m, 1H), 5.83 (d, J = 15.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.57 (q, J = 6.9 Hz, 2H), 2.67 (t, J = 7.2 Hz, 2H), 2.47 – 2.44 (m, 2H), 2.41 – 2.36 (m, 2H), 1.80 – 1.76 (m, 2H), 1.56 – 1.51 (m, 2H), 1.49 – 1.42 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 164.2, 149.9, 148.9, 148.0, 142.3, 137.2, 136.7, 126.0, 122.0, 116.1, 60.1, 37.9, 35.6, 35.0, 32.0, 28.5, 26.1, 25.9, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{27}N_2O_3$ 343.2016; Found 343.2018.

Ethyl (*E*)-3-((*Z*)-2-(2-(picolinamido)ethyl) cyclooct-1-en-1-yl)acrylate (3da). The reaction was carried out using (*E*)-*N*-(2-(cyclooct-1-en-1-yl)ethyl)picolinamide **1d** (52 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **3da** (46 mg, yield 65%, pale yellow solid, m.p. 86-87 °C). ^1H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.7 Hz, 1H), 8.18 (d, J = 7.9 Hz, 2H), 7.83 (t, J = 7.7 Hz, 1H), 7.74 (d, J = 15.6 Hz, 1H), 7.40 (dd, J = 7.7, 4.7 Hz, 1H), 5.86 (d, J = 15.6 Hz, 1H), 4.15 (q, J =7.1 Hz, 2H), 3.58 (q, J = 6.8 Hz, 2H), 2.67 (t, J = 7.4 Hz, 2H), 2.45 (dt, J = 28.4, 6.2 Hz 4H), 1.65 (p, J = 6.0 Hz, 2H), 1.59 – 1.52 (m, 2H), 1.50 – 1.38 (m, 4H), 1.27 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.8, 164.2, 149.9, 148.0, 146.7, 141.4, 137.2, 133.1, 126.0, 122.1, 116.6, 60.1, 38.5, 33.5, 33.1, 29.7, 28.9, 26.9, 26.5, 26.4, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{29}N_2O_3$ 357.2173; Found 357.2174.

Ethyl (*E*)-3-(5-methyl-2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ea). The reaction was carried out using *N*-(2-(4-methylcyclohex-1-en-1-yl)ethyl) picolinamide **1e** (49 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **3ea** (38 mg, yield 56%, pale yellow solid, m.p. 70-71 °C). ^1H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.2 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.83 (td, J = 7.7, 1.4 Hz, 1H), 7.79 (d, J = 15.6 Hz, 1H), 7.43 – 7.38 (m, 1H), 5.79 (d, J = 15.5 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.63 – 3.50 (m, 2H), 2.70 – 2.54 (m, 2H), 2.35 – 2.25 (m, 3H), 1.81 – 1.58 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.00 (d, J = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.7, 164.2, 149.9, 147.9, 143.1, 141.8,

137.1, 129.1, 125.9, 122.0, 115.8, 60.0, 38.4, 34.0, 33.4, 31.7, 30.5, 28.3, 21.7, 14.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{20}H_{27}N_2O_3$ 343.2022; Found 343.2027.

Ethyl (*E*)-3-(5,5-dimethyl-2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (**3fa**). The reaction was carried out using *N*-(2-(4,4-dimethylcyclohex-1-en-1-yl)ethyl) picolinamide **1f** (52 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5~1:4) to afford **3fa** (50 mg, yield 70%, pale yellow solid, m.p. 79-80 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.0 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.13 (s, 1H), 7.82 (td, *J* = 9.2, 4.7 Hz, 2H), 7.42 – 7.36 (m, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.58 (q, J = 6.8 Hz,, 2H), 2.64 (t, *J* = 7.1 Hz, 2H), 2.31 (t, *J* = 6.5 Hz, 2H), 1.94 (s, 2H), 1.41 (t, *J* = 6.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.92 (s, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.6, 164.1, 149.8, 147.9, 142.0, 142.0, 137.1, 128.5, 125.9, 122.0, 115.8, 60.0, 39.3, 38.4, 34.9, 33.2, 29.4, 28.6, 28.1, 14.2; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{21}H_{29}N_2O_3$ 357.2173; Found 357.2172.

Ethyl (*E*)-3-(5-(*tert*-butyl)-2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (**3ga**). The reaction was carried out using *N*-(2-(4-(tert-butyl)cyclohex-1-en-1-yl)ethyl) picolinamide **1g** (57 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5~1:4) to afford **3ga** (44 mg, yield 57%, pale yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.7 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H), 8.13 (s, 1H), 7.85 – 7.77 (m, 2H), 7.40 (dd, *J* = 7.5, 4.7 Hz, 1H), 5.82 (d, *J* = 15.4 Hz, 1H), 4.21 – 4.12 (m, 2H), 3.65 – 3.49 (m, 2H), 2.72 – 2.55 (m, 2H), 2.41 – 2.20 (m, 3H), 1.94 – 1.79 (m, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.15 (qd, *J* = 12.2, 5.1 Hz, 1H), 0.91 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 164.2, 149.9, 148.0, 143.5, 142.1, 137.2, 129.6, 126.0, 122.1, 115.6, 60.1, 43.9, 38.4, 33.4, 33.1, 32.3, 27.2, 27.1, 23.8, 14.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{23}H_{33}N_2O_3$ 385.2486; Found 385.2485.

Ethyl (*E*)-3-(4-(2-(picolinamido)ethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl) acrylate (**3ha**). The reaction was carried out using *N*-(2-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)ethyl)picolinamide **1h** (61 mg, 0.2 mmol) and

ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5~1:4) to afford **3ha** (38 mg, yield 47%, pale yellow solid, m.p. 100-101 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.0 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 2H), 7.82 (dd, *J* = 11.7, 3.7 Hz, 2H), 7.42 – 7.38 (m, 1H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.22 (dd, *J* = 13.5, 7.1 Hz, 3H), 5.77 (d, *J* = 15.6 Hz, 1H), 4.13 (q, *J* = 7.0 Hz, 2H), 3.61 (ddq, *J* = 34.0, 13.6, 6.8 Hz, 2H), 2.83 (d, *J* = 10.2 Hz, 1H), 2.77 – 2.70 (m, 1H), 2.67 – 2.59 (m, 1H), 2.55 – 2.44 (m, 3H), 2.32 – 2.19 (m, 1H), 2.00 (d, *J* = 12.1 Hz, 1H), 1.79 (qd, *J* = 12.1, 5.7 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.5, 164.2, 149.9, 148.0, 146.1, 143.0, 141.4, 137.2, 129.3, 128.4, 126.8, 126.2, 126.0, 122.1, 116.2, 60.0, 39.7, 38.4, 33.7, 33.5, 32.0, 29.2, 14.2; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}N_2O_3$ 405.2173; Found 405.2172.

Ethyl (*E*)-3-(5,5-difluoro-2-(2-(picolinamido)ethyl) cyclohex-1-en-1-yl)acrylate (3ia). The reaction was carried out using *N*-(2-(4,4-difluorocyclohex-1-en-1-yl)ethyl)picolinamide **1i** (53 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:8~1:2) to afford **3ia** (36 mg, yield 49%, pale yellow oil). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.3 Hz, 1H), 8.16 (d, J = 7.8 Hz, 2H), 7.86 – 7.80 (m, 1H), 7.73 (d, J = 15.6 Hz, 1H), 7.41 (dd, J = 6.9, 5.3 Hz, 1H), 5.70 (d, J = 15.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.59 (q, J = 6.8 Hz, 2H), 2.68 – 2.61 (m, 4H), 2.57 (t, J = 6.0 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{19}F NMR (565 MHz, $CDCl_3$) δ -95.81; ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.0, 164.4, 149.7, 148.0, 141.6, 140.3, 137.3, 126.1, 125.4 (t, J_{C-F} = 5.3 Hz), 122.5 (t, J_{C-F} = 239.0 Hz), 122.1, 117.1, 60.3, 38.1, 34.9 (t, J_{C-F} = 27.5 Hz), 33.1, 30.1 (t, J_{C-F} = 24.3 Hz), 29.6(t, J_{C-F} = 5.4 Hz), 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}F_2N_2O_3$ 365.1671; Found 365.1671.

Ethyl (*E*)-3-(2-(2-(3-methoxyphenyl)-2-(picolinamido) ethyl)cyclohex-1-en-1-yl)acrylate (3ja). The reaction was carried out using *N*-(2-(cyclohex-1-en-1-yl)-1-(3-methoxyphenyl)ethyl)picolinamide **1j** (67 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2·H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL)

under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:5~1:4) to afford **3ja** (45 mg, yield 52%, pale yellow solid, m.p. 99-100 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, J = 4.8 Hz, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.39 (dd, J = 7.6,4.7 Hz 1H), 7.29 – 7.20 (m, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.90 (s, 1H), 6.78 (dd, J = 8.2, 2.6 Hz, 1H), 5.67 (d, J = 15.5 Hz, 1H), 5.28 (q, J = 7.8 Hz, 1H), 4.23 – 4.16 (m, 2H), 3.80 (s, 3H), 3.02 (dd, J = 13.5, 8.1 Hz, 1H), 2.75 (dd, J = 13.6, 6.9 Hz, 1H), 2.19 (t, J =5.4 Hz, 2H), 2.07 (s, 2H), 1.60 – 1.54 (m, 4H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.7, 163.5, 159.9, 149.8, 148.0, 143.1, 142.4, 142.0, 137.2, 130.3, 129.7, 126.0, 122.1, 118.8, 115.7, 112.9, 112.4, 60.0, 55.2, 52.9, 40.9, 31.9, 25.5, 22.4, 22.2, 14.4; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{31}N_2O_4$ 435.2278; Found 435.2281.

General procedure of facile removal of PA group to generate ethyl (*E*)-3-(4-(2-(((benzyloxy)carbonyl)amino)ethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)acrylate (7). Ethyl (*E*)-3-(4-(2-(picolinamido) ethyl) -1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl) acrylate (**3ha**) (40 mg, 0.1 mmol) was dissolved in THF/H_2O (2:1, 1.5 mL), and aq. HCl (245 μL, 12 N) was added into a 10 mL reaction bottle. Then Zinc powder (98 mg, 1.5 mmol) was added in batches and the mixture was stirred at RT for 1.5 h. Afterward, $NaHCO_3$ was added to adjust the pH to 7~8 and CbzCl (22 μL, 0.15 mmol) were added and the resulting mixture was stirred at RT for another 3 hours and quenched with water. The mixture was extracted with DCM (2 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:12~1:11) to afford ethyl (*E*)-3-(4-(2-(((benzyloxy)carbonyl)amino)ethyl)-1,2,5,6-tetrahydro-[1,1'-biphenyl]-3-yl)acrylate **7** (17 mg, yield 38%, white solid, m.p. 94-95 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 15.6 Hz, 1H), 7.36 – 7.28 (m, 7H), 7.21 (d, *J* = 7.8 Hz, 3H), 5.82 (d, *J* = 15.5 Hz, 1H), 5.09 (s, 2H), 4.88 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.38 – 3.28 (m, 2H), 2.79 (s, 1H), 2.59 (dt, *J* = 12.9, 6.6 Hz, 1H), 2.54 – 2.46 (m, 2H), 2.36 (t, *J* = 20.9 Hz, 2H), 2.25 – 2.18 (m, 1H), 1.97 (d, *J* = 10.6 Hz, 1H), 1.75 (ddd, *J* = 16.5, 11.9, 5.6 Hz, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.8, 156.3, 146.1, 143.0, 141.5, 136.6, 129.4, 128.5, 128.1, 126.8, 126.3, 116.3, 66.7, 60.2, 39.9, 39.7, 33.8, 31.9, 29.2, 14.3; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{32}NO_4$ 434.2326; Found 434.2326.

Synthesis of (8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a] phenanthren-3-yl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl) acrylate (8). The reaction was carried

out using *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol) and (8*R*,9*S*,13*S*,14*S*)-13-Methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-3-yl acrylate **2s** (127 mg, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.2 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:8~1:2) to afford **8** (56 mg, yield 51%, pale yellow solid, m.p. 198-199 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (d, J = 4.0 Hz, 1H), 8.19 – 8.11 (m, 2H), 7.96 (d, J = 15.5 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.40 (dd, J = 6.5, 4.9 Hz, 1H), 7.27 (d, J = 9.6 Hz, 1H), 6.87 – 6.83 (m, 1H), 6.80 (s, 1H), 5.95 (d, J = 15.5 Hz, 1H), 3.59 (q, J = 6.8 Hz, 2H), 2.94 – 2.88 (m, 2H), 2.65 (t, J = 7.0 Hz, 2H), 2.51 (dd, J = 19.0, 8.7 Hz, 1H), 2.43 – 2.37 (m, 1H), 2.32 – 2.28 (m, 2H), 2.25 – 2.21 (m, 2H), 2.19 – 1.94 (m, 5H), 1.70 – 1.45 (m, 10H), 0.92 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 220.6, 166.3, 164.2, 149.8, 148.8, 148.0, 145.0, 143.6, 137.7, 137.2, 137.0, 129.6, 126.2, 126.0, 122.1, 121.6, 118.8, 114.9, 50.5, 47.9, 44.1, 38.4, 38.0, 35.8, 33.8, 31.7, 31.6, 29.4, 26.4, 25.7, 25.4, 22.4, 22.3, 21.6, 13.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{40}N_2O_4Na$, 575.2880; Found 575.2881.

Synthesis of (1*S*,4*R*)-bicyclo[2.2.1]heptan-2-yl (*E*)-3-(2-(2-(picolinamido)ethyl)cyclohex-1-en-1-yl)acrylate (9) (two steps in one pot)**:** The acrylate system was synthesized following the reference[30b]. (1) A mixture of norbornene (51 mg, 0.54 mmol), acrylic acid (34 μL, 0.5 mmol) and $BF_3 \cdot O(C_2H_5)_2$ (2 μL, 0.016 mmol) was heated at 80 °C for 0.5 h in a sealed tube (25 mL) and then cooled down to room temperature, quenched by two drops of water to give the acrylate system. (2) And then *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (20 mg, 0.1 mmol) and 2-methyl-2-butanol (*t*-AmylOH, 0.5 mL) were added the acrylate system. The mixture was heated under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. And the reaction was monitored by TLC and cooled to RT. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:3) to afford **9** (34 mg, yield 43%, white solid, m.p. 110-111 °C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.8 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.12 (s, 1H), 7.83 (t, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 15.5 Hz, 1H), 7.40 (dd, *J* = 7.5, 4.8 Hz, 1H), 5.75 (d, *J* = 15.5 Hz, 1H), 4.61 (d, *J* = 7.0 Hz, 1H), 3.56 (q, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.3 Hz, 2H), 2.28 (q, *J* = 5.4, 4.9 Hz, 4H), 2.16 (d, *J* = 5.5 Hz, 2H), 1.76 – 1.70 (m, 2H), 1.64 (t, *J* = 6.6 Hz, 3H), 1.55 – 1.49 (m, 2H), 1.46 – 1.40 (m, 2H), 1.16 – 1.08 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.4, 164.2, 149.9, 148.0, 143.3, 141.6, 137.2, 129.5, 126.0, 122.1, 116.3, 77.3, 41.5,

39.7, 38.4, 35.4, 35.3, 33.8, 31.6, 28.2, 25.5, 24.4, 22.5, 22.3; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{24}H_{31}N_2O_3$ 395.2329; Found 395.2329.

Synthesis of ethyl (*E*)-3-(3-(2-(picolinamido)ethyl)-1*H*-indol-2-yl) acrylate (10): The reaction was carried out using *N*-(2-(1*H*-indol-3-yl)ethyl)picolinamide **1r** (53 mg, 0.2 mmol) and ethyl acrylate **2a** (44 μL, 0.4 mmol) in the presence of $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (*t*-AmylOH, 0.4 M) in a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 16 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography (ethyl acetate: petroleum ether = 1:4~1:3) to afford **10** (18 mg, 25%, yellow solid, m.p. 151-152°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46 (d, J = 4.8 Hz, 1H), 8.42 (s, 1H), 8.21 (d, J = 7.8 Hz, 2H), 7.83 (td, J = 7.6, 1.7 Hz, 1H), 7.74 (d, J = 15.9 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.38 (dd, J = 7.6, 4.8 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.15 (d, J = 15.9 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.75 (q, J = 6.8 Hz, 2H), 3.23 (t, J = 7.1 Hz, 2H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.0, 164.5, 149.8, 148.0, 137.6, 137.2, 131.8, 130.7, 128.3, 126.0, 125.1, 122.1, 120.2, 119.9, 119.4, 114.9, 111.2, 60.5, 40.4, 24.6, 14.3; HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{21}N_3O_3Na$ 386.1475; Found 386.1475.

Deuterium labelling experiments

General procedure of deuterium incorporation. The mixture of *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide **1a** (46 mg, 0.2 mmol), D_2O (36 μL, 2.0 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (0.5 mL) was added to a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 2 h. Then the solvent was evaporated. The crude product was purified by flash silica column chromatography to afford **1a**/**1a**-D1 (36 mg), for which a deuterium content of 30% was determined by ^{1}H NMR spectroscopy.

General procedure of kinetic deuterium isotope experiment. Firstly, cyclohexanone-D_4 was obtained according to the reported literature[31]. Then **1a**-D_5 was synthesized following **GP I** and **GP II** (Figure S3). Finally, *N*-(2-(cyclohex-1-en-1-yl)ethyl)picolinamide (**1a**: 23 mg, 0.1 mmol and **1a**-D_5: 23 mg, 0.1 mmol), ethyl acrylate **2a** (44 μL, 0.4 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), $KHCO_3$ (50 mg, 0.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mg, 0.1 mmol) in 2-methyl-2-butanol (0.5 mL) were added to a sealed tube (25 mL) under air atmosphere at 130 °C via a heating mantle with magnetic stirrer for 0.5 h. And the reaction was monitored by TLC and cooled to room temperature. Then the solvent was evaporated. The crude product was purified by flash silica column

chromatography to afford **3aa** / **3aa-**D_4 (44 mg, 67%), for which a deuterium content of 7.14% was determined by ^{1}H NMR spectroscopy. The k_H/k_D was calculated according to the literature[19,31b].

Associated Content

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Optimization Details (PDF)

Deuterium Labelling Experiments (PDF)

X-ray Crystallography of Compound **3aa** (CCDC 1906866) (CIF)

Copies of ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra of all of the synthesized compounds (PDF)

Author Information

Notes

The authors declare no competing financial interest.

Corresponding Author: *E-mail: gxcai@swu.edu.cn; yun.he@cqu.edu.cn.

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