Synthesis Z.-Y. Gu et al. Special Topic

Intermolecular C–H Amidation of Alkenes with Carbon Monoxide and Azides via Tandem Palladium Catalysis

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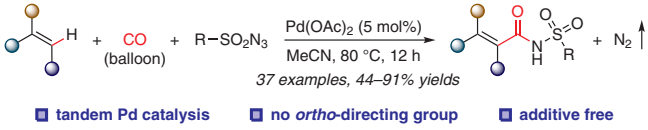
Published as part of the Special Topic *Bond Activation – in Honor of Prof. Shinji Murai*

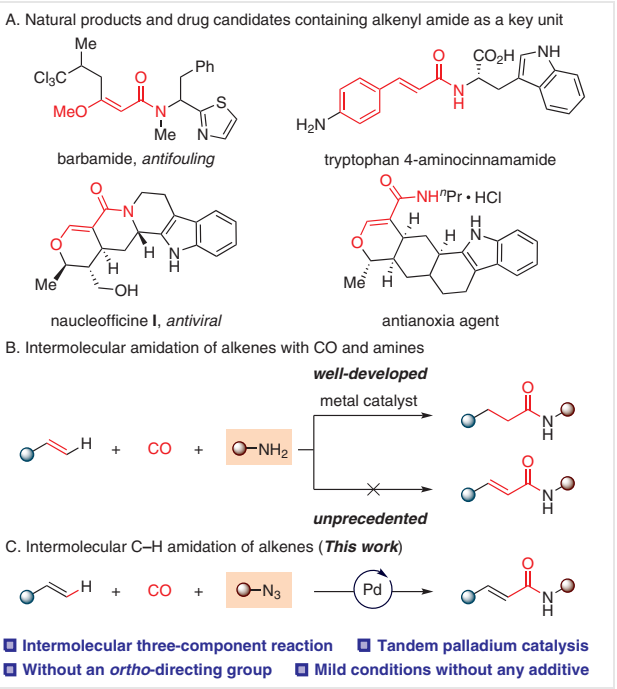


Received: 07.02.2021
Accepted after revision: 26.02.2021
Published online: 26.02.2021
DOI: 10.1055/a-1401-4486; Art ID: ss-2021-f0053-st

Abstract An atom- and step-economic intermolecular multi-component palladium-catalyzed C–H amidation of alkenes with carbon monoxide and organic azides has been developed for the synthesis of alkenyl amides. The reaction proceeds efficiently without an *ortho*-directing group on the alkene substrates. Nontoxic dinitrogen is generated as the sole by-product. Computational studies and control experiments have revealed that the reaction takes place via an unexpected mechanism by tandem palladium catalysis.

Key words C–H carbonylation, amidation, palladium, alkene, amides

The amide motif is undoubtedly one of the most important structural units in nature. It not only plays an essential role in life as the backbone of proteins but also presents in numerous marketed drugs and materials.[1] Among them, the alkenyl amides are widely found in natural products and pharmaceuticals (Scheme 1A).[2] In addition, alkenyl amides are also reliable and versatile synthetic intermediates for the synthesis of a variety of useful chemicals, such as amines, isonitriles, ketones, and heterocycles.[3] Conventional route for the preparation of alkenyl amides relies on condensation of carboxylic acids and amines in the presence of a stoichiometric 'coupling' reagent.[4] However, the production of large quantities of waste is the major concern in this traditional amide synthesis.[5] Therefore, the development of catalytic, atom-economic, and efficient methods to produce alkenyl amides are of great significance and rewarding.



Scheme 1 Intermolecular C–H amidation of alkenes

To overcome the low atom economy in traditional alkenyl amide synthesis, catalytic condensation of the alkenyl carboxylic acids and amines has been developed using boronic acid as a catalyst.[6] Recently, many strategies have been developed for the catalytic synthesis of alkenyl amides using other easily accessed raw materials other than carboxylic acids, such as hydroaminocarbonylation of alkynes

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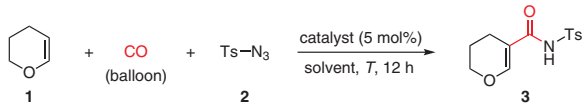
with carbon monoxide (CO) and amines.[7] Use of inexpensive and abundant CO gas for catalytic carbonylation is one of the most straightforward and powerful strategies to prepare carbonyl compounds.[8] Aminocarbonylation of alkenyl halides (pseudohalide) or alkenyl organometallic reagents is another well-established methods for the synthesis of alkenyl amides.[9] Obviously, direct C–H carbonylation of alkenes to produce alkenyl amides is much attractive and atom-economic due to utilization of simple olefin as the substrate. However, all of the reported C–H aminocarbonylation of alkenes needed substrates bearing an NH functionality as an intramolecuar *ortho*-directing group.[10] Transition-metal-catalyzed intermolecular aminocarbonylation of alkenes with free amines generally produced the corresponding alkyl amides, which has been well developed (Scheme 1B).[11] Intermolecular C–H aminocarbonylation of alkenes with free amines to produce alkenyl amides has not been reported yet.[12]

Transition-metal-catalyzed C–N bond-forming reactions via a metal-nitrene intermediate is a powerful method to prepare various N-containing chemicals.[13] Readily available organic azides are one class of convenient nitrene precursors, which expel N_2 as the sole byproduct in the nitrene transfer reactions.[14] Catalytic carbonylation of azides has been utilized for the synthesis of ureas and carbamates, avoiding direct utilization of air- and moisture-sensitive isocyanate compounds.[15] We recently reported a convenient approach for Rh-catalyzed C–H amidation of electron-rich (hetero)arenes with CO and azides to produce aryl amides.[16] This finding inspired us that C–H amidation of alkenes might be achieved with CO and azides via suitable metal catalysis. We now report a Pd-catalyzed multi-component intermolecular C–H amidation of alkenes with organic azides under 1 atm of CO (Scheme 1C). This method has the advantages of synthetic simplicity, high efficiency, atom- and step-economy, thus providing cost-efficient and straightforward access to valuable alkenyl amides under mild additive-free conditions.

Given the important role and wide presence of oxygen heterocycles in pharmaceutical industry,[17] we began by investigating the C–H amidation of dihydropyran (DHP, **1**) with CO (balloon pressure) and *p*-toluenesulfonyl azide (**2**) in the presence of various metal catalysts. Both Pd(II) and Pd(0) can catalyze this reaction. The desired amidation product **3** was obtained in 78% yield with 5 mol% $Pd(OAc)_2$ as the catalyst in MeCN at 80 °C (Table 1, entry 1). The use of Pd(0) catalysts, $Pd_2(dba)_3$, or $Pd(PPh_3)_4$ were less effective (entries 2, 3). No olefin aziridination product was observed in the reaction.[18] Moderate efficiency was observed when $[Rh(cod)Cl]_2$ was used as the catalyst (entry 4). The yield of **3** was increased to 90% when the amount of **2** was increased to 1.5 equivalents (entry 7). A slightly lower yield (81%) was obtained when the reaction temperature was decreased to 60 °C (entry 8). Lower yields were obtained when other solvents were tested, such as toluene and THF (entries 10, 11). The acetonitrile as solvent may serve as a good coordinative ligand for palladium catalyst. Control experiment showed that no reaction occurred without Pd catalyst, demonstrating the essential role of the Pd catalyst in promoting the reaction (entry 12).

Table 1 Catalytic C–H Amidation of Alkene[a]



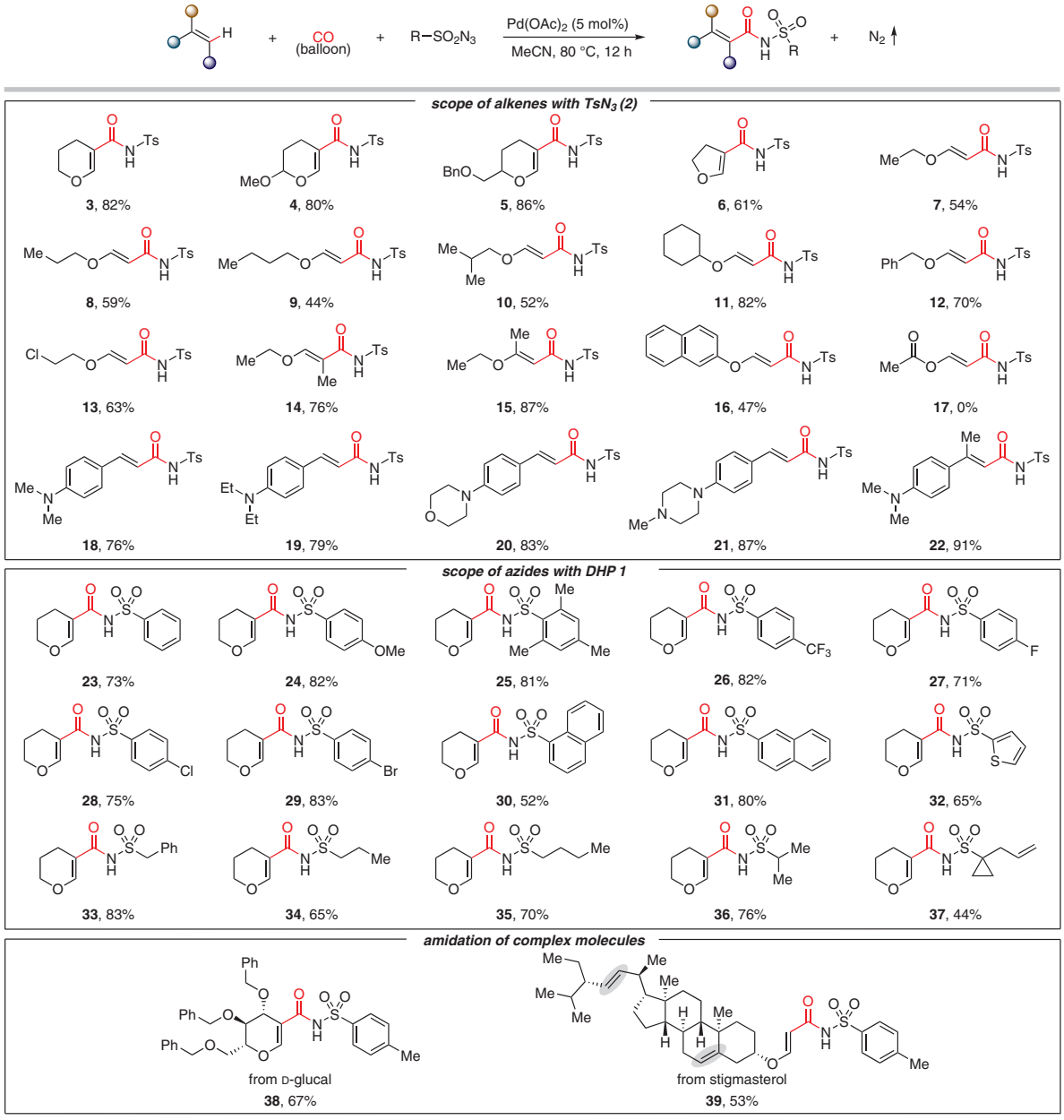
Entry	Catalyst	Solvent	Temp (°C)	Yield (%)[b]
1	$Pd(OAc)_2$	MeCN	80	78
2	$Pd_2(dba)_3$	MeCN	80	48
3	$Pd(PPh_3)_4$	MeCN	80	44
4	$[Rh(cod)Cl]_2$	MeCN	80	55
5	$Cu(OAc)_2$	MeCN	80	trace
6	$Co_2(CO)_8$	MeCN	80	trace
7[c]	**$Pd(OAc)_2$**	**MeCN**	**80**	**90**
8[c]	$Pd(OAc)_2$	MeCN	60	81
9[c]	$Pd(OAc)_2$	MeCN	25	12
10[c]	$Pd(OAc)_2$	toluene	80	trace
11[c]	$Pd(OAc)_2$	THF	80	19
12[c]	–	MeCN	80	0

[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CO (balloon), catalyst (5 mol%), MeCN (3 mL), 12 h.
[b] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.
[c] With 0.75 mmol of **2**.

With the optimal reaction conditions in hand, we first investigated a wide range of alkenes in this C–H amidation reaction under 1 atm of CO (Scheme 2). Overall, good to excellent yields of acrylamides were obtained. It was gratifying to observe that 2-methoxy-DHP and 2-[(benzyloxy)methyl]-DHP exhibited good reactivity producing the corresponding products **4** and **5** in 80% and 86% yield, respectively. Amidation of 2,3-dihydrofuran also occurred smoothly affording the desired product **6** in 61% yield. A variety of linear alkoxyethenes, such as ethoxy-, propoxy-, butoxy-, isobutoxy-, cyclohexoxy-, and benzyloxyethene displayed moderate to good reactivity, furnishing the corresponding products **7**–**12** in 44–82% yields. Remarkably, amidation of (2-chloroethoxy)ethene produced chlorine-containing acrylamide derivative **13** in 63% yield, which could be easily functionalized for further transformation. It should be noted that amidation of an *E*/*Z* mixture of 1-ethoxy-1-propene gave *E*-alkenyl amide **14** in 76% yield as a single stereoisomeric product. Excellent yield of (*E*)-**15** was obtained as the sole stereoisomeric product in the amidation of 1,1-disubstituted olefin (2-ethoxy-1-propene). The aryloxyethene can also be used as a substrate, delivering

the desired product **16** in moderate yield. However, no reaction occurred with vinyl acetate, which might due to its property of electron deficiency (→ **17**, 0%). Notably, this C–H amidation reaction is not restricted to vinyl ester substrates, as stryene derivatives are also amenable to the reaction. We found that electron-rich styrenes displayed good reactivity in this reaction. For example, a variety of styrenes bearing amino group all worked very well, and the corresponding C–H amidation products **18**–**22** were isolated in 76–91% yields. Unfortunately, no reaction occurred when simple aliphatic unactivated olefins, styrenes with electron-withdrawing groups, dienes, and simple cycloalkenes were used under current conditions

We then investigated the scope of organic azides in the amidation of DHP (**1**). It was found that arylsulfonyl azides with both electron-donating group (Me, OMe), electron-withdrawing group (CF_3), or halogen substituents on the benzene ring showed good reactivity, leading to the desired products **24**–**29** in 71–83% yield. The reaction of naphthylsulfonyl and heteroarylsulfonyl azides occurred smoothly

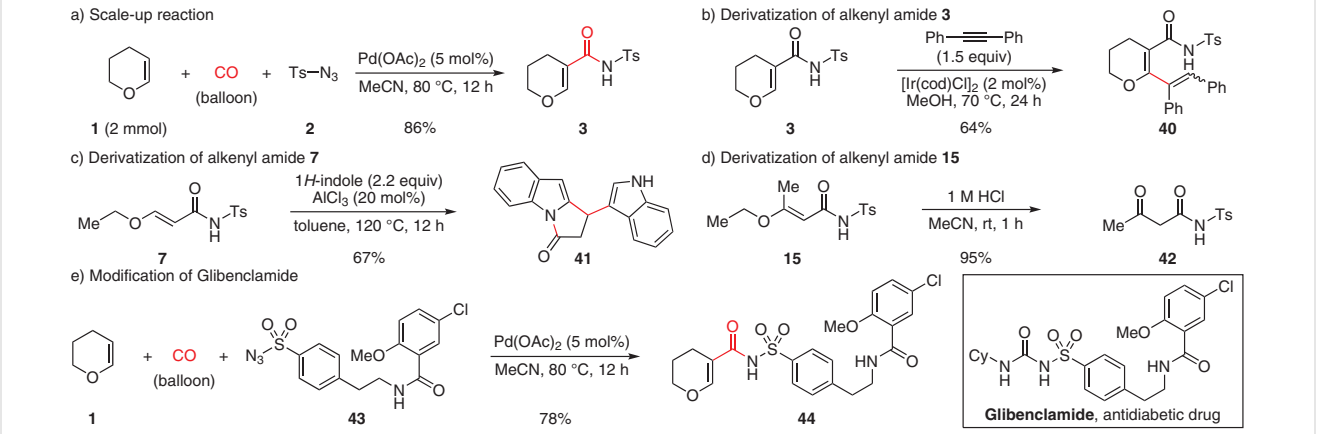


Scheme 2 Scope of C–H amidation of alkenes. *Reagents and conditions*: alkene (0.5 mmol), azide (0.75 mmol), CO (balloon), $Pd(OAc)_2$ (5 mol%), MeCN (3 mL), 80 °C, 12 h. Isolated yields are shown.

(→ **30**–**32**). Furthermore, the alkylsulfonyl azides also exhibited good reactivity in this transformation (→ **33**–**37**). Unfortunately, no reaction occurred with azidobenzene or (azidomethyl)benzene as the substrate under the standard conditions. Finally, late stage C–H amidation of olefin-containing complex molecules was carried out. Amidation of 3,4,6-tri-*O*-benzyl-D-glucal occurred smoothly generating the corresponding amide **38** in 67% yield. And selective C–H amidation of vinyl ester derived from natural stigmasterol produced the target product **39** in moderate yield, without touching the other two double bonds in the molecule.

To demonstrate the synthetic utility of this method, a scale-up reaction for C–H amidation of DHP (**1**) was carried out. The desired product **3** was obtained in 86% yield (Scheme 3a). Then, Ir-catalyzed alkenylation of **3** with alkyne occurred smoothly generating functionalized 1,3-diene **40** in good yield (Scheme 3b). Indole-containing heterocycles are widely present in pharmaceutical compounds and biologically active molecules.[19] We found that reaction of alkenyl amide **7** with 1*H*-indole produced polycyclic indole derivative **41** in good yield using $AlCl_3$ as a Lewis acid catalyst via transamidation and double addition reactions (Scheme 3c). The product **15** could be easily converted to β-ketoamides **42** in excellent yield under acidic conditions at room temperature (Scheme 3d). Antidiabetic Glibenclamide is a sulfonamide-containing small molecular drug, one of the top 200 most prescribed medication in US in2016.[20] Amidation of DHP (**1**) with sulfonyl azide **43** produced the analogue **44** of Glibenclamide in 78% yield under the standard conditions (Scheme 3e).

Computational studies were carried out to gain a mechanistic insight into this reaction (see SI for detailed computational details). When $Pd(OAc)_2$ is considered as an active catalyst, the formation of the intermediate of isocyanate is evaluated via two possible mechanistic pathways. The first pathway is the Pd(II)-catalyzed denitrogenation of TsN_3 via **TS1a** to afford the palladium nitrene species (*path a*, Figure S1 in Supporting Information). Subsequently, the generated **INT2a** can bind with CO to afford the isocyanate intermediate. The second pathway is that CO might coordinate with Pd(II) and undergo migratory insertion with TsN_3 via **TS1b** followed by N_2 dissociation to generate the isocyanate intermediate (*path b*). Computational results show that both of the Pd(II)-catalyzed pathways have substantially high activation barriers (larger than 30 kcal/mol, Figure S1). In addition, one may suggest that CO could reduce the Pd(II) catalyst to Pd(0). When Pd(0) species is employed to catalyze the reaction, the aforementioned pathways are also considered. It is interesting to find that the activation barrier catalyzed by Pd(0) is significantly lowered than that catalyzed by Pd(II) (Figure 1). Thus, computational results imply that it is more feasible for Pd(0) species to promote the reaction to form the isocyanate intermediate. We found that activation barrier of Pd(0)-catalyzed migratory insertion with TsN_3 to generate the isocyanate intermediate (**Ts1b′**, *path b*, Figure 1) is much lower than that of Pd(0)-catalyzed denitrogenation of TsN_3 (**Ts1a′**, *path a*, Figure 1). Afterward, the substrate ethoxyethene (**1′**) could undergo migratory insertion with the formed isocyanate intermediate at the Pd(0) site. Two possible regioselectivities are considered and the corresponding transition states are shown as **TS3a′** and **TS3b′**, respectively. The predicted activation barriers indicate that the insertion of the terminal carbon of **1′** with C atom of the isocyanate group is more favorable to occur. This result could be rationalized by HOMO analysis of **1′** that the electron density of alkene moiety is more localized at the terminal carbon due to the presence of O connected with the alkenyl group (Figure 2). Similar character is also found in the HOMO of **1**. Therefore, the formation of **INT4′** is more ready to occur. The subsequent β-H elimination could follow to produce **INT6′**. Finally, the reductive elimination of **INT6′** could proceed to furnish the final product. It should be noted that the formation of a β-lactam intermediate is detected between DHP (**1**) and sulfonyl isocyanate in the absence of Pd catalyst, which can be further transformed into alkenyl amides under high temperature.[21]



Scheme 3 Synthetic applications

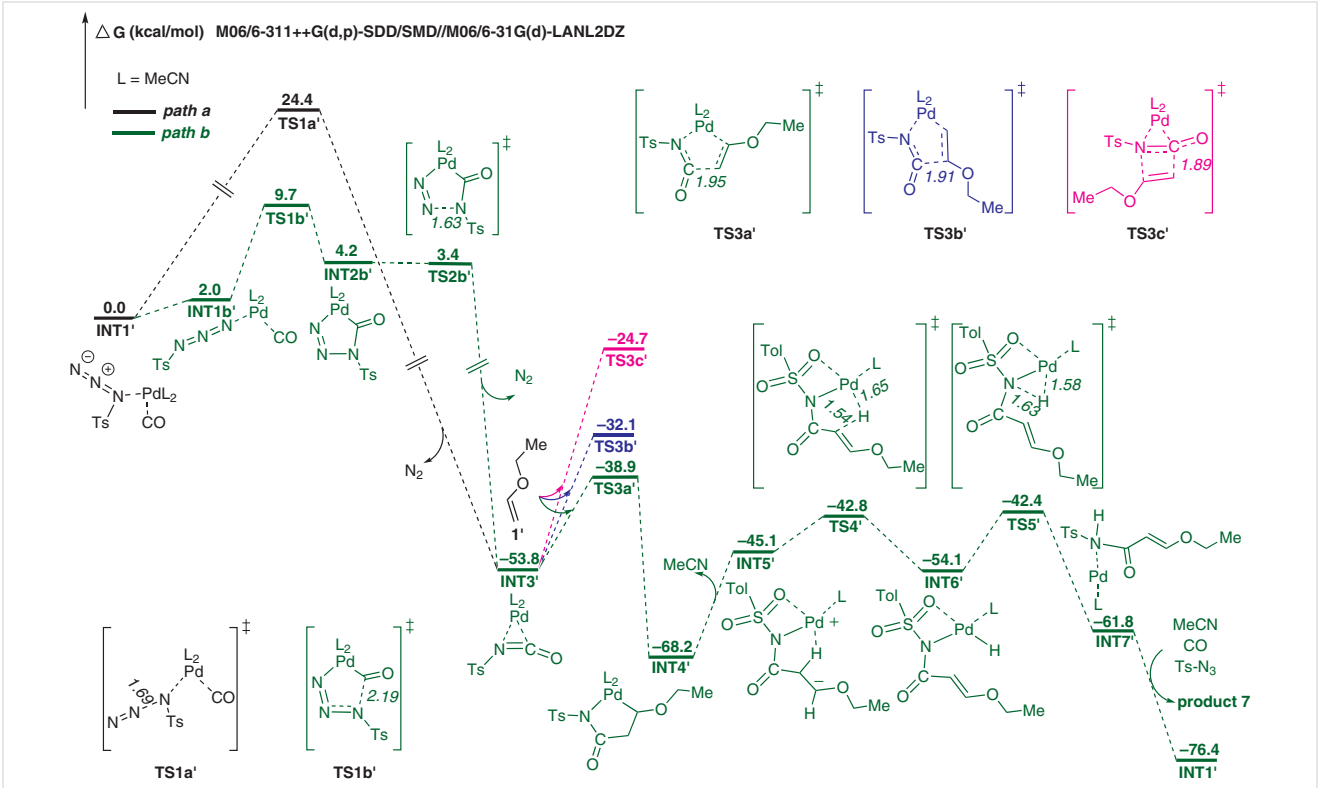


Figure 1 Energy profiles for the Pd(0)-catalyzed C–H amidation of alkenes with CO and TsN_3 (bond lengths are shown in Å)

However, the activation barriers is much higher than that of Pd-catalyzed process (Figure 2, **TS3c′** and Figure S3 in Supporting Information).[22] Nevertheless, the formation of β-lactam intermediate is not necessary in the presence of Pd catalyst according to the computational studies.[23]

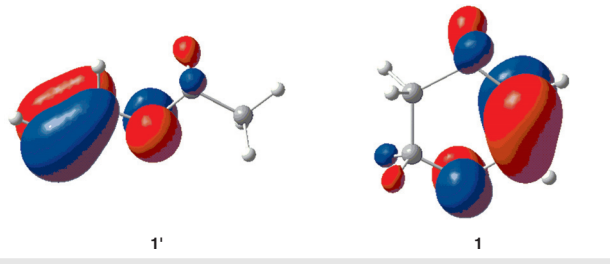
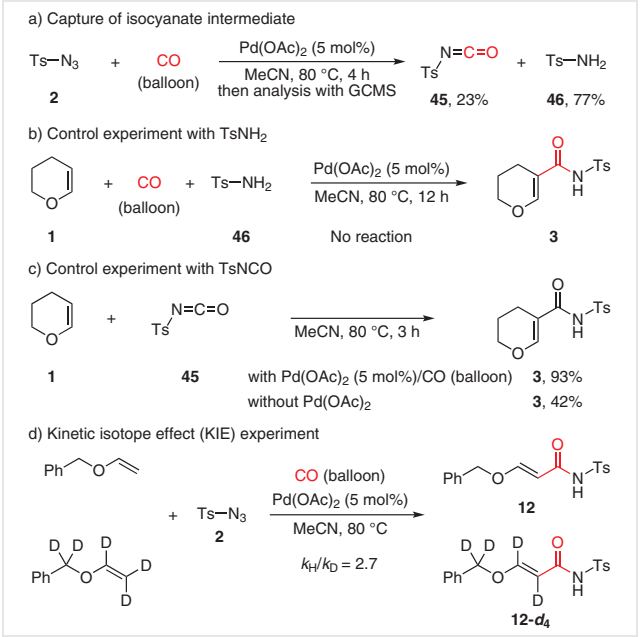


Figure 2 Highest occupied molecular orbitals (HOMO) for alkene **1′** and **1**

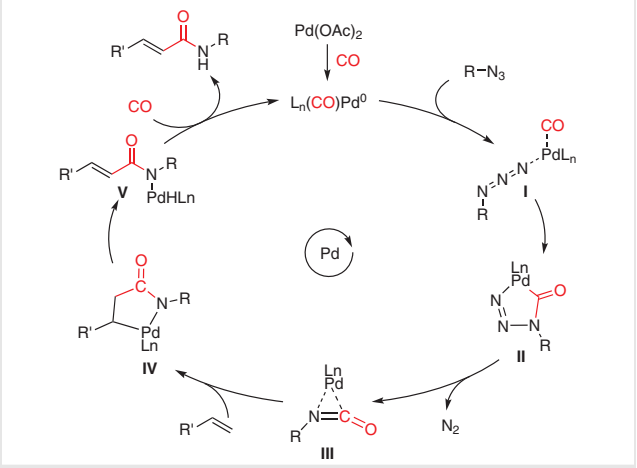
Then, several control experiments were performed to understand the reaction mechanism (Scheme 4). First, palladium-catalyzed carbonylation of tosyl azide (**2**) with CO occurred smoothly affording tosyl isocyanate (**45**), which was quickly converted into tosyl amine (**46**) by reaction with water during analysis by GC-MS (Scheme 4a). We then tested carbonylation of DHP (**1**) with CO and tosyl amine (**46**), and no reaction occurred (Scheme 4b). Reaction of THP (**1**) with tosyl isocyanate (**45**) in the presence of $Pd(OAc)_2$/CO is much faster than that without Pd catalyst (Scheme 4c). These results indicate that isocyanate should



Scheme 4 Control experiments

be the most possible reaction intermediate in the amidation of alkene with CO and azide. Next, $Pd_2(dba)_3$ can also catalyze the reaction albeit the reaction is slower than that with $Pd(OAc)_2$ as catalyst, demonstrating the Pd(0) might be the active catalyst (Table 1, entry 2). In addition, when performing the kinetic isotope effect (KIE) experiment with benzyloxyethene and benzyloxyethene-d_5, the KIE value (k_H/k_D) was determined as 2.7 (Scheme 4d). This result indicates that the terminal alkenyl C–H cleavage might be involved in the rate-determining step, which is consistent with the DFT calculations.

Based on the DFT calculations and control experiments, the plausible reaction pathway has been proposed in Scheme 5. Initially, Pd(II) precatalyst is reduced to the active Pd(0) catalyst in the presence of CO, which may be stabilized by acetonitrile as the ligand. The organic azide undergoes ligand exchange with CO coordinated Pd(0) catalyst to form intermediate **I**. Subsequently, migratory insertion of CO into the azide generates palladacycle species **II**. After release of N_2, palladium coordinated isocyanate species **III** is formed. Next, coordination of alkene substrate and regioselective migratory insertion generates palladacycle **IV**. The following β-H elimination produces amidopalladium intermediate **V**. Finally, reductive elimination leads to the alkenyl amide and regenerates the Pd(0) catalyst.



Scheme 5 Plausible reaction pathway

In summary, we have developed an atom- and step-economic palladium-catalyzed intermolecular C–H amidation of olefins to produce alkenyl amides from an inexpensive and abundant carbonyl source (CO) and organic azides. This protocol provides a simple and practical strategy for the straightforward synthesis of alkenyl amides with a range of substrates. Remarkably, neither directing group on the alkenes or additive is needed for the reaction. Dinitrogen (N_2) is generated as the only by-product. The mechanistic studies and control experiments have revealed a novel reaction mechanism involving tandem Pd-catalyzed in situ generation of isocyanate intermediate and subsequent cycloaddition and β-H elimination processes. However, no reaction occurred when simple aliphatic unactivated olefins, styrenes with electron-withdrawing groups, dienes and simple cycloalkenes were tested under our current conditions. And further investigations of C–H amidation of unactivated olefins are currently under study in our laboratory.

All intermolecular amidation reactions were carried out under atmospheric pressure of CO in oven-dried Schlenk tube. TLC analyses were done on glass 0.25 mm silica gel plates. Flash chromatography columns were packed with 200–300 mesh silica gel in PE (bp 60–90 °C). High-resolution MS analyses were performed on Thermo Fisher Scientific LTQ FT Ultra with DART Positive Mode or Agilent 6530 Accurate–Mass Q-TOF LC/MS with ESI mode. NMR spectra were recorded on a 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR, using TMS as an internal reference DMSO-d_6 and $CDCl_3$ as solvent. Chemical shift values for protons are reported in parts per million (ppm, δ scale) downfield from TMS and are referenced to residual proton of DMSO-d_6 (δ = 2.50) and residual proton (δ = 7.26) in $CDCl_3$. Multiplicities are indicated by standard abbreviations. ^{13}C NMR spectra were recorded at 100 MHz. Chemical shifts for carbons are reported in parts per million (ppm, δ scale) downfield from TMS and are referenced to the carbon resonance of DMSO-d_6 (δ = 40.00) and $CDCl_3$ (δ = 77.00). Materials were purchased from Tokyo Chemical Industry Co., Aldrich Inc., Alfa Aesar, Adamas, or other commercial suppliers and used as received, unless otherwise noted. Sulfonyl azides were purchased, if commercially available, or prepared from sulfonyl chlorides and NaN_3 according to the well-established methods.

The experimental procedures for synthetic applications (Scheme 3) and control experiments (Scheme 4) are described in the Supporting Information.

Amide Products; General Procedure

To an oven-dried Schlenk tube (10 mL) was added the organic azide (0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol%). The tube was purged and backfilled with CO (3 cycles) from a balloon. Anhyd MeCN (3.0 mL) was injected into the tube, and then alkene (0.5 mmol) was injected into the tube. After stirring at 80 °C for 12 h under CO atmosphere (balloon), the mixture was concentrated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc 3:1–1:1) to give the desired product.

N-Tosyl-3,4-dihydro-2*H*-pyran-5-carboxamide (3)

Yield: 115.3 mg (82%); white solid; mp 241.3–243.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (s, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.53 (s, 1 H), 7.33 (d, *J* = 8.2 Hz, 2 H), 4.00 (t, *J* = 5.2 Hz, 2 H), 2.43 (s, 3 H), 2.19 (t, *J* = 6.0 Hz, 2 H), 1.83 (tt, *J* = 6.0, 6.0 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.7, 155.5, 144.8, 135.8, 129.5, 128.4, 106.9, 66.7, 21.7, 20.7, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}NO_4S$ [M + H]$^+$: 282.0795; found: 282.0787.

2-Methoxy-*N*-tosyl-3,4-dihydro-2*H*-pyran-5-carboxamide (4)

Yield: 124.5 mg (80%); Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (s, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.39 (s, 1 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 4.98 (t, *J* = 2.9 Hz, 1 H), 3.43 (s, 3 H), 2.43 (s, 3 H), 2.27–2.15 (m, 2 H), 1.96–1.90 (m, 1 H), 1.75–1.67 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.4, 152.1, 144.8, 135.8, 129.5, 128.5, 107.9, 98.8, 56.2, 25.1, 21.6, 15.1.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{17}NO_5SNa$ [M + Na]$^+$: 334.0720; found: 334.0719.

2-[(Benzyloxy)methyl]-*N*-tosyl-3,4-dihydro-2*H*-pyran-5-carboxamide (5)

Yield: 172.6 mg (86%); Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 7.97 (d, *J* = 8.4 Hz, 2 H), 7.54 (s, 1 H), 7.33–7.26 (m, 7 H), 4.54 (d, *J* = 2.0 Hz, 2 H), 4.07–4.01 (m, 1 H), 3.58 (dd, *J* = 10.4, 6.0 Hz, 1 H), 3.53 (dd, *J* = 10.4, 6.0 Hz, 1 H), 2.42 (s, 3 H), 2.30–2.24 (m, 1 H), 2.20–2.11 (m, 1 H), 1.94–1.87 (m, 1 H), 1.69–1.59 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7, 154.9, 144.8, 137.5, 135.9, 129.5, 128.4, 127.8, 127.7, 107.0, 75.7, 73.4, 71.2, 22.7, 21.6, 18.5.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{24}NO_5S$ [M + H]$^+$: 402.1370; found: 402.1358.

***N*-Tosyl-4,5-dihydrofuran-3-carboxamide (6)**

Yield: 81.5 mg (61%); white solid; mp 227.6–228.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.96 (d, *J* = 7.2 Hz, 2 H), 7.39–7.33 (m, 3 H), 4.50 (t, *J* = 9.8 Hz, 2 H), 2.80 (t, *J* = 9.6 Hz, 2 H), 2.43 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.6, 157.8, 144.9, 135.8, 129.5, 128.3, 110.5, 73.3, 27.4, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}NO_4S$ [M + H]$^+$: 268.0638; found: 268.0636.

(*E*)-3-Ethoxy-*N*-tosylacrylamide (7)

Yield: 72.7 mg (54%); white solid; mp 214.5–216.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.32 (s, 1 H), 7.93 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 12.2 Hz, 1 H), 7.29 (d, *J* = 8.4 Hz, 2 H), 5.34 (d, *J* = 12.2 Hz, 1 H), 3.87 (q, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 164.0, 144.6, 136.1, 129.4, 128.1, 96.4, 67.6, 21.5, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{16}NO_4S$ [M + H]$^+$: 270.0795; found: 270.0785.

(*E*)-3-Propoxy-*N*-tosylacrylamide (8)

Yield: 83.6 mg (59%); white solid; mp 199.5–200.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.99 (s, 1 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 12.4 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 3.78 (t, *J* = 6.4 Hz, 2 H), 2.42 (s, 3 H), 1.71–1.62 (m, 2 H), 0.91 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 164.4, 144.8, 136.0, 129.5, 128.1, 96.2, 73.6, 22.2, 21.6, 10.1.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}NO_4S$ [M + H]$^+$: 284.0951; found: 284.0961.

(*E*)-3-Butoxy-*N*-tosylacrylamide (9)

Yield: 65.4 mg (44%); white solid; mp 191.3–193.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.09 (s, 1 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 12.2 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 5.30 (d, *J* = 12.2 Hz, 1 H), 3.82 (t, *J* = 6.4 Hz, 2 H), 2.42 (s, 3 H), 1.65–1.58 (m, 2 H), 1.39–1.30 (m, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 164.4, 144.7, 136.0, 129.5, 128.1, 96.1, 71.9, 30.8, 21.6, 18.8, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{19}NO_4SNa$ [M + Na]$^+$: 320.0927; found: 320.0920.

(*E*)-3-Isobutoxy-*N*-tosylacrylamide (10)

Yield: 77.3 mg (52%); white solid; mp 186.7–188.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.0 Hz, 2 H), 7.61 (d, *J* = 12.4 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.31 (d, *J* = 12.0 Hz, 1 H), 3.59 (d, *J* = 6.4 Hz, 2 H), 2.41 (s, 3 H), 1.97–1.86 (m, 1 H), 0.90 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0, 164.5, 144.6, 136.0, 129.5, 128.1, 96.1, 78.3, 27.9, 21.6, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{19}NO_4SNa$ [M + Na]$^+$: 320.0927; found: 320.0931.

(*E*)-3-(Cyclohexyloxy)-*N*-tosylacrylamide (11)

Yield: 132.6 mg (82%); white solid; mp 242.2–243.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 7.94 (d, *J* = 8.4 Hz, 2 H), 7.58 (d, *J* = 12.0 Hz, 1 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.32 (d, *J* = 12.0 Hz, 1 H), 3.90 (tt, *J* = 8.8, 3.8 Hz, 1 H), 2.43 (s, 3 H), 1.86–1.82 (m, 2 H), 1.72–1.71 (m, 2 H), 1.48–1.40 (m, 2 H), 1.31–1.25 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.9, 163.6, 144.7, 136.1, 129.5, 128.2, 96.9, 82.1, 31.7, 25.0, 23.2, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}NO_4SNa$ [M + Na]$^+$: 346.1083; found: 346.1089.

(*E*)-3-(Benzyloxy)-*N*-tosylacrylamide (12)

Yield:116.0 mg (70%); white solid; mp 208.1–209.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 12.0 Hz, 1 H), 7.36–7.27 (m, 7 H), 5.42 (d, *J* = 12.4 Hz, 1 H), 4.88 (s, 2 H), 2.42 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.6, 163.7, 144.8, 135.9, 134.7, 129.5, 128.7, 128.6, 128.1, 127.8, 97.3, 73.7, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}NO_4SNa$ [M + Na]$^+$: 332.0951; found: 332.0957.

(*E*)-3-(2-Chloroethoxy)-*N*-tosylacrylamide (13)

Yield: 95.7 mg (63%); white solid; mp 192.7–193.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 12.4 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 5.40 (d, *J* = 12.0 Hz, 1 H), 4.09 (t, *J* = 5.6 Hz, 2 H), 3.67 (t, *J* = 6.0, 2 H), 2.42 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5, 163.5, 145.0, 135.9, 129.7, 128.2, 97.5, 71.7, 41.5, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}ClNO_4SNa$ [M + Na]$^+$: 326.0224; found: 326.0231.

(*E*)-3-Ethoxy-2-methyl-*N*-tosylacrylamide (14)

Yield: 107.7 mg (76%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.00 (br s, 1 H), 7.96 (d, *J* = 8.4 Hz, 2 H), 7.34–7.30 (m, 3 H), 3.96 (q, *J* = 7.2 Hz, 2 H), 2.40 (s, 3 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.1, 157.7, 144.6, 136.0, 129.4, 128.2, 106.6, 70.2, 21.5, 15.1, 8.7.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}NO_4S$ [M + H]$^+$: 284.0951; found: 284.0962.

(*E*)-3-Ethoxy-*N*-tosylbut-2-enamide (15)

Yield: 123.2 mg (87%); colorless oil. The stereochemistry of **15** was confirmed by 2D NOESY analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (s, 1 H), 7.95 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 5.03 (s, 1 H), 3.72 (q, *J* = 7.0 Hz, 2 H), 2.42 (s, 3 H), 2.20 (s, 3 H), 1.25 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.8, 164.5, 144.5, 136.3, 129.5, 128.0, 90.9, 64.2, 21.6, 19.6, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{18}NO_4S$ [M + H]$^+$: 306.0770; found: 306.0771.

(*E*)-3-(Naphthalen-2-yloxy)-*N*-tosylacrylamide (16)

Yield: 86.3 mg (47%); white solid; mp 238.2–239.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96–7.93 (m, 3 H), 7.81 (d, *J* = 8.4 Hz, 2 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.51–7.43 (m, 2 H), 7.39 (d, *J* = 2.8 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.69 (d, *J* = 12 Hz, 1 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 160.4, 153.3, 145.0, 135.8, 133.8, 130.9, 130.3, 129.6, 128.3, 127.8, 127.4, 127.0, 125.6, 118.2, 113.5, 102.0, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{18}NO_4S$ [M + H]$^+$: 368.0951; found: 368.0962.

(*E*)-3-[4-(Dimethylamino)phenyl]-*N*-tosylacrylamide (18)

Yield: 130.9 mg (76%); yellow solid; mp > 300 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.4 Hz, 2 H), 7.61 (d, *J* = 15.2 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 6.62 (d, *J* = 9.2 Hz, 2 H), 6.19 (d, *J* = 15.6 Hz, 1 H), 3.01 (s, 6 H), 2.41 (s, 3 H).

The other spectral and analytical data are in accordance with the literature.[1]

(*E*)-3-[4-(Diethylamino)phenyl]-*N*-tosylacrylamide (19)

Yield: 147.1 mg (79%); yellow solid; mp > 300 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.63 (br s, 1 H), 8.00 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 15.6 Hz, 1 H), 7.35–7.30 (m, 4 H), 6.58 (d, *J* = 8.8 Hz, 2 H), 6.18 (d, *J* = 15.2 Hz, 1 H), 3.37 (q, *J* = 7.2 Hz, 4 H), 2.41 (s, 3 H), 1.17 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.1, 149.9, 146.7, 144.7, 136.2, 130.7, 129.5, 128.3, 120.7, 111.2, 110.5, 44.5, 21.6, 12.5.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{24}N_2O_3SNa$ [M + Na]$^+$: 395.1400; found: 395.1403.

(*E*)-3-(4-Morpholinophenyl)-*N*-tosylacrylamide (20)

Yield: 160.4 mg (83%); yellow solid; mp > 300 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.99 (br s, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.47–7.41 (m, 5 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 6.38 (d, *J* = 15.6 Hz, 1 H), 3.72–3.70 (m, 4 H), 3.22–3.19 (m, 4 H), 2.39 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.2, 153.0, 144.6, 144.5, 137.2, 130.1, 130.0, 128.1, 124.3, 114.69, 114.66, 66.3, 47.6, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{23}N_2O_4S$ [M + H]$^+$: 387.1373; found: 387.1373.

(*E*)-3-[4-(4-Methylpiperazin-1-yl)phenyl]-*N*-tosylacrylamide (21)

Yield: 173.8 mg (87%); yellow solid; mp 294.7–295.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.81 (d, *J* = 8.4 Hz, 2 H), 7.41–7.36 (m, 5 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 3.30–3.28 (m, 4 H), 2.63–2.60 (m, 4 H), 2.37 (s, 3 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.5, 152.3, 143.6, 143.0, 138.6, 129.9, 129.6, 127.9, 124.6, 116.9, 115.1, 54.3, 46.9, 45.4, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{26}N_3O_3S$ [M + H]$^+$: 400.1689; found: 400.1693.

(*E*)-3-[4-(Dimethylamino)phenyl]-*N*-tosylbut-2-enamide (22)

Yield: 163.1 mg (91%); yellow solid; mp > 300 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.78 (br s, 1 H), 7.84 (d, *J* = 8.0 Hz, 2 H), 7.43–7.38 (m, 4 H), 6.70 (d, *J* = 8.4 Hz, 2 H), 6.21 (s, 1 H), 2.93 (s, 6 H), 2.39 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.6, 156.0, 151.7, 144.3, 137.5, 129.9, 128.0, 127.7, 127.7, 112.5, 112.1, 40.2, 21.5, 16.9.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{22}N_2O_3SNa$ [M + Na]$^+$: 367.1087; found: 367.1088.

***N*-(Phenylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (23)**

Yield: 97.6 mg (73%); white solid; mp 202.3–204.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 8.09 (d, *J* = 7.8 Hz, 2 H), 7.64–7.52 (m, 4 H), 3.99 (t, *J* = 5.2 Hz, 2 H), 2.19 (t, *J* = 6.4 Hz, 2 H), 1.84–1.81 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.9, 155.6, 138.9, 133.7, 128.8, 128.3, 106.9, 66.7, 20.7, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{14}NO_4S$ [M + H]$^+$: 268.0638; found: 268.0640.

***N*-[(4-Methoxyphenyl)sulfonyl]-3,4-dihydro-2*H*-pyran-5-carboxamide (24)**

Yield: 121.9 mg (82%); white solid; mp 238.9–240.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.02 (d, *J* = 8.6 Hz, 2 H), 7.53 (s, 1 H), 6.99 (d, *J* = 8.4 Hz, 2 H), 4.00 (t, *J* = 4.8 Hz, 2 H), 3.86 (s, 3 H), 2.19 (t, *J* = 6.0 Hz, 2 H), 1.86–1.81 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 163.7, 155.4, 130.7, 130.2, 114.0, 106.9, 66.7, 55.6, 20.7, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}NO_5S$ [M + H]$^+$: 298.0744; found: 298.0753.

***N*-(Mesitylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (25)**

Yield: 125.3 mg (81%); white solid; mp 268.6–269.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (s, 1 H), 7.53 (s, 1 H), 6.97 (s, 2 H), 4.02 (t, *J* = 5.2 Hz, 2 H), 2.72 (s, 6 H), 2.29 (s, 3 H), 2.20 (t, *J* = 6.0 Hz, 2 H), 1.88–1.83 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.3, 155.2, 143.4, 140.3, 132.7, 132.0, 106.9, 66.6, 22.8, 21.0, 20.8, 18.9.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{19}NO_4SNa$ [M + Na]$^+$: 332.0927; found: 332.0939.

***N*-{[4-(Trifluoromethyl)phenyl]sulfonyl}-3,4-dihydro-2*H*-pyran-5-carboxamide (26)**

Yield: 145.7 mg (82%); white solid; mp 254.4–255.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (s, 1 H), 8.23 (d, *J* = 8.4 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 2 H), 7.56 (s, 1 H), 4.03 (t, *J* = 5.2 Hz, 2 H), 2.20 (t, *J* = 6.4 Hz, 2 H), 1.89–1.83 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.9, 156.0, 142.4, 135.3 (q, *J* = 32.7 Hz), 129.0, 126.0 (q, *J* = 3.5 Hz), 123.1 (q, *J* = 271.6 Hz), 106.8, 66.8, 20.7, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}F_3NO_4S$ [M + H]$^+$: 336.0512; found: 336.0502.

***N*-[(4-Fluorophenyl)sulfonyl]-3,4-dihydro-2*H*-pyran-5-carboxamide (27)**

Yield: 101.3 mg (71%); white solid; mp 208.9–210.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.14–8.09 (m, 2 H), 7.53 (s, 1 H), 7.24–7.18 (m, 2 H), 4.02 (t, *J* = 5.2 Hz, 2 H), 2.19 (t, *J* = 6.4 Hz, 2 H), 1.86 (tt, *J* = 10.8, 5.2 Hz, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.7 (d, *J* = 255.1 Hz), 164.7, 155.7, 134.7 (d, *J* = 3.3 Hz), 131.4 (d, *J* = 9.7 Hz), 116.2 (d, *J* = 22.9 Hz), 106.8, 66.8, 20.7, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}FNO_4S$ [M + H]$^+$: 286.0544; found: 286.0547.

***N*-[(4-Chlorophenyl)sulfonyl]-3,4-dihydro-2*H*-pyran-5-carboxamide (28)**

Yield: 113.1 mg (75%); white solid; mp 295.6–297.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.67 (br s, 1 H), 7.92 (d, *J* = 8.6 Hz, 2 H), 7.68 (d, *J* = 8.8 Hz, 3 H), 3.98 (t, *J* = 5.2 Hz, 2 H), 2.03 (t, *J* = 6.4 Hz, 2 H), 1.75–1.69 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 156.0, 139.4, 138.7, 130.1, 129.7, 108.2, 66.9, 20.9, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{12}ClNO_4SNa$ [M + Na]$^+$: 324.0068; found: 324.0078.

***N*-[(4-Bromophenyl)sulfonyl]-3,4-dihydro-2*H*-pyran-5-carboxamide (29)**

Yield: 143.7 mg (83%); white solid; mp 192.1–194.1 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.68 (s, 1 H), 7.86–7.81 (m, 4 H), 7.67 (s, 1 H), 3.98 (t, *J* = 4.8 Hz, 2 H), 2.03 (t, *J* = 6.0 Hz, 2 H), 1.75–1.69 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 156.0, 139.9, 132.6, 130.1, 127.7, 108.2, 66.8, 20.9, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{12}BrNO_4SNa$ [M + Na]$^+$: 367.9563; found: 367.9560.

***N*-(Naphthalen-1-ylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (30)**

Yield: 82.5 mg (52%); white solid; mp > 300 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.92 (s, 1 H), 8.69 (d, *J* = 8.6 Hz, 1 H), 8.34 (d, *J* = 7.6 Hz, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.80–7.65 (m, 4 H), 3.95 (t, *J* = 4.8 Hz, 2 H), 1.97 (t, *J* = 6.0 Hz, 2 H), 1.70–1.64 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.7, 155.6, 135.2, 135.1, 134.1, 131.6, 129.7, 128.7, 127.9, 127.3, 125.0, 124.3, 108.2, 66.7, 20.8, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}NO_4SNa$ [M + Na]$^+$: 340.0614; found: 340.0605.

***N*-(Naphthalen-2-ylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (31)**

Yield: 127.0 mg (80%); white solid; mp 298.5–299.9 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.68 (s, 1 H), 8.60 (d, *J* = 2.0 Hz, 1 H), 8.21 (d, *J* = 8.0 Hz, 1 H), 8.13 (d, *J* = 8.8 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.91 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.75–7.66 (m, 3 H), 3.97 (t, *J* = 4.8 Hz, 2 H), 2.01 (t, *J* = 6.4 Hz, 2 H), 1.73–1.67 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 155.8, 137.6, 135.0, 131.9, 129.9, 129.7, 129.6, 128.3, 128.2, 123.1, 108.3, 66.8, 20.9, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{15}NO_4SNa$ [M + Na]$^+$: 340.0614; found: 340.0613.

***N*-(Thiophen-2-ylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (32)**

Yield: 88.8 mg (65%); white solid; mp 182.7–183.3 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 7.91 (dd, *J* = 4.0, 1.2 Hz, 1 H), 7.67 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.57 (s, 1 H), 7.10 (dd, *J* = 4.8, 4.0 Hz, 1 H), 4.03 (t, *J* = 4.8 Hz, 2 H), 2.22 (t, *J* = 6.0 Hz, 2 H), 1.89–1.84 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.8, 155.7, 139.1, 135.0, 133.7, 127.3, 106.9, 66.8, 20.7, 18.8.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{12}NO_4S_2$ [M + H]$^+$: 274.0202; found: 274.0207.

***N*-(Benzylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (33)**

Yield: 116.7 mg (83%); white solid; mp 183.7–184.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 1 H), 7.51 (s, 1 H), 7.38–7.26 (m, 5 H), 4.65 (s, 2 H), 4.10–4.03 (t, *J* = 5.2 Hz, 2 H), 2.18 (t, *J* = 6.4 Hz, 2 H), 1.90–1.85 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0, 155.9, 130.7, 129.1, 128.8, 128.1, 106.8, 66.8, 59.0, 20.7, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}NO_4S$ [M + H]$^+$: 282.0795; found: 282.0801.

***N*-(Propylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (34)**

Yield: 75.8 mg (65%); white solid; mp 184.4–186.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (br s, 1 H), 7.58 (s, 1 H), 4.05 (t, *J* = 5.2 Hz, 2 H), 3.48–3.44 (m, 2 H), 2.24 (t, *J* = 6.0 Hz, 2 H), 1.91–1.81 (m, 4 H), 1.04 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.0, 155.8, 107.0, 66.7, 55.2, 20.7, 18.7, 16.9, 12.6.

HRMS (ESI): *m*/*z* calcd for $C_9H_{16}NO_4S$ [M + H]$^+$: 234.0795; found: 234.0805.

***N*-(Butylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (35)**

Yield: 86.6 mg (70%); white solid; mp 197.1–199.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.55 (br s, 1 H), 7.59 (s, 1 H), 4.06 (t, *J* = 5.2 Hz, 2 H), 3.51–3.47 (m, 2 H), 2.25 (t, *J* = 6.4 Hz, 2 H), 1.92–1.86 (m, 2 H), 1.82–1.74 (m, 2 H), 1.49–1.40 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 155.8, 107.0, 66.8, 53.3, 25.1, 21.2, 20.7, 18.8, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{10}H_{18}NO_4S$ [M + H]$^+$: 248.0951; found: 248.0954.

***N*-(Isopropylsulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (36)**

Yield: 88.6 mg (76%); white solid; mp 189.7–191.4 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.51 (br s, 1 H), 7.59 (s, 1 H), 4.05 (t, *J* = 5.2 Hz, 2 H), 3.97–3.90 (hept, *J* = 7.2 Hz, 1 H), 2.25 (t, *J* = 6.0 Hz, 2 H), 1.92–1.86 (m, 2 H), 1.39 (d, *J* = 6.8 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.9, 155.7, 107.1, 66.7, 53.9, 20.7, 18.8, 15.9.

HRMS (ESI): *m*/*z* calcd for $C_9H_{16}NO_4S$ [M + H]$^+$: 234.0795; found: 234.0802.

N-[(1-Allylcyclopropyl)sulfonyl]-3,4-dihydro-2*H*-pyran-5-carboxamide (37)

Yield: 59.7 mg (44%); white solid; mp 210.2–211.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (br s, 1 H), 7.57 (s, 1 H), 5.73 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1 H), 5.17–5.08 (m, 2 H), 4.08 (t, *J* = 5.2 Hz, 2 H), 2.65 (d, *J* = 6.8 Hz, 2 H), 2.26 (t, *J* = 6.4 Hz, 2 H), 1.95–1.89 (m, 2 H), 1.74–1.70 (m, 2 H), 1.01–0.97 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.6, 155.4, 132.8, 118.9, 107.1, 66.7, 40.0, 35.3, 20.8, 19.1, 11.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{18}NO_4S$ [M + H]$^+$: 272.0951; found: 272.0946.

(2*S*,3*R*,4*S*)-3,4-Di(benzyloxy)-2-[(benzyloxy)methyl]-*N*-tosyl-3,4-dihydro-2*H*-pyran-5-carboxamide (38)

Yield: 205.6 mg (67%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91 (s, 1 H), 7.84 (d, *J* = 8.4 Hz, 2 H), 7.55 (s, 1 H), 7.39–7.24 (m, 17 H), 4.66 (s, 2 H), 4.57–4.44 (m, 5 H), 4.32 (d, *J* = 4.0 Hz, 1 H), 4.09 (t, *J* = 4.4 Hz, 1 H), 3.75–3.65 (m, 2 H), 2.41 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 163.7, 156.6, 144.6, 137.4, 137.0, 136.1, 135.9, 129.3, 128.9, 128.6, 128.5, 128.43, 128.39, 128.37, 128.2, 127.9, 127.7, 105.8, 77.0, 73.4, 72.2, 70.8, 70.5, 70.0, 67.0, 21.6.

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{36}NO_7S$ [M + H]$^+$: 614.2207; found: 614.2214.

(*E*)-3-({(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-17-[(2*R*,5*S*,*E*)-5-Ethyl-6-methylhept-3-en-2-yl]-10,13-dimethyl-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl}oxy)-*N*-tosylacrylamide (39)

Yield: 67.4 mg (53%), with 0.2 mmol alkene substrate; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.4 Hz, 2 H), 7.57 (d, *J* = 11.6 Hz, 1 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 5.36–5.33 (m, 2 H), 5.15 (dd, *J* = 15.2, 8.4 Hz, 1 H), 5.02 (dd, *J* = 15.2, 8.4 Hz, 1 H), 3.79–3.71 (m, 1 H), 2.42 (s, 3 H), 2.31 (d, *J* = 7.6 Hz, 2 H), 2.07–1.84 (m, 6 H), 1.61–1.42 (m, 11 H), 1.28–1.13 (m, 6 H), 1.02 (d, *J* = 6.8 Hz, 3 H), 0.98 (s, 3 H), 0.85–0.79 (m, 9 H), 0.69 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.9, 163.3, 144.6, 138.9, 138.2, 136.3, 129.5, 129.3, 128.2, 123.2, 97.3, 83.4, 56.8, 55.9, 51.2, 50.0, 42.2, 40.4, 39.6, 38.5, 36.7, 36.5, 31.8, 28.8, 28.1, 25.4, 24.3, 21.6, 21.2, 21.0, 19.2, 19.0, 12.2, 12.0.

HRMS (ESI): *m*/*z* calcd for $C_{39}H_{58}NO_4S$ [M + H]$^+$: 636.4081; found: 636.4080.

N-({4-[2-(5-Chloro-2-methoxybenzamido)ethyl]phenyl}sulfonyl)-3,4-dihydro-2*H*-pyran-5-carboxamide (44)

Yield: 186.8 mg (78%); white powder; mp 190.5–192.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (br s, 1 H), 8.12 (d, *J* = 2.8 Hz, 1 H), 8.01 (d, *J* = 8.0 Hz, 2 H), 7.88–7.84 (m, 1 H), 7.56 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.37–7.34 (m, 1 H), 6.86 (d, *J* = 8.8 Hz, 1 H), 4.01 (t, *J* = 5.2 Hz, 2 H), 3.77–3.72 (m, 5 H), 3.00 (t, *J* = 7.2 Hz, 2 H), 2.18 (t, *J* = 6.4 Hz, 2 H), 1.87–1.81 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.1, 164.2, 155.9, 155.5, 145.6, 137.4, 132.4, 131.7, 129.3, 128.6, 126.5, 122.4, 112.9, 107.2, 66.7, 56.2, 40.5, 35.5, 20.7, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{23}ClN_2O_6SNa$ [M + Na]$^+$: 501.0858; found: 501.0847.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

We acknowledge financial support from NSFC (21772208, 22001226, 21633013), Natural Science Foundation of Jiangsu Province (BK20201183), Key Research Program of Frontier Sciences of CAS (QYZDJSSW-SLH051), The Natural Science Foundation of the Jiangsu Higher Education Institutions of China (20KJB150016), and Funding for School-Level Research Projects of Yancheng Institute of Technology (xjr2019032).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1401-4486.

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(22) The transition state leading to the formation of β-lactam intermediate is located as **TS3c'**, which is much higher in energy than the pathway via **TS3a'** (Figure 1).
(23) After the formation of the isocyanate intermediate, a possible Pd(II)-catalyzed pathway to afford the final product is also considered (Figure S2 in Supporting Information). The main mechanistic difference for Pd(II)-catalyzed pathway is that the acetate ligand could serve as a proton shuttle to assist the H-migration to yield the final product.