JOC The Journal of Organic Chemistry

university of groningen

Subscriber access provided by University of Groningen

Article

Rh-Catalyzed Chemoselective [4+1] Cycloaddition Reaction towards Diverse 4-Methyleneprolines

Wangshui Cai, Junxian Wu, Haowei Zhang, Hitesh B Jalani, Guigen Li, and Hongjian Lu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01466 • Publication Date (Web): 06 Aug 2019

Downloaded from pubs.acs.org on August 6, 2019

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

Rh-Catalyzed Chemoselective [4+1] Cycloaddition Reaction towards Diverse 4-Methyleneprolines

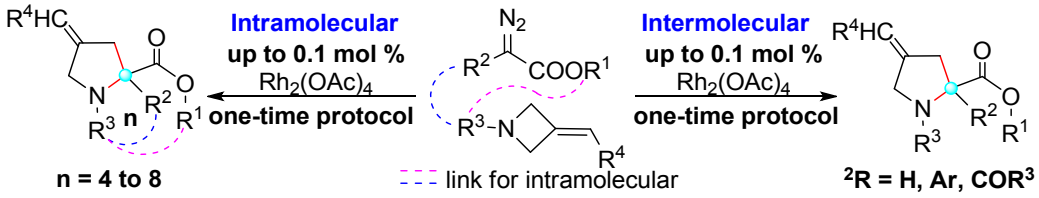
Wangshui Cai,† Junxian Wu,† Haowei Zhang,† Hitesh B. Jalani,†,‡ Guigen Li*,†,δ and Hongjian Lu*,†

† Institute of Chemistry & BioMedical Sciences, Nanjing University, Nanjing 210023, China

‡ Smart BioPharm, 310-Pilotplant, Incheon Techno-Park, 12-Gaetbeol-ro, Yeonsu-gu, Incheon 21999 & Yonsei University, College of Pharmacy, 85-Songdogwahak-ro, Incheon 21983, South Korea

δ Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

Email: guigenli@nju.edu.cn; hongjianlu@nju.edu.cn



ABSTRACT: An efficient synthesis of 4-methyleneproline derivatives has been developed through an Rh-catalyzed [4+1] cycloaddition strategy using 3-methyleneazetidines and diazo compounds. The reaction proceeds under very mild conditions with a high degree of chemoselectivity and competing experiments revealed that it is the preferred reaction, dominant over the C−H insertion, O−H insertion and olefin cyclopropanation reactions which are commonly observed in Rh carbene chemistry. This method can incorporate the proline ester scaffold in pharmaceuticals and natural products. Intramolecular version of the reaction effectively provides proline-fused small to medium sized tricyclic heterocycles. Gram

scale reactions wherein one-time addition of diazo compounds and a minimum catalyst loading of 0.1 mol%, proceeded smoothly, implying its practicality.

Introduction

Introduction of rigid amino acid residues into native peptides often helps to overcome the peptides' shortcomings in pharmacology, by means of low bioavailability, enzymatic instability or lack of selectivity towards specific receptors. This evidently results in restricted conformational freedom, often is a defense against the consequences of proteolytic degradation and thereby, can lead to improved selectivity or potency.[1] Because of the conformational rigidity of pyrrolidine structures and the hinge-like behavior displayed at peptide bonds, proline analogues play a unique role in the formation of secondary structures, which affect the overall biological outcome of peptides.[2] Application of proline analogues has enormous potential in drug discovery, which continuously fuels their synthetic endeavor. 4-Methyleneproline is a rare, naturally occurring racemic amino acid isolated from the seeds of the loquat tree fruits, and the plants of the Raphiolepis indica and Afzelia bella families,[3] is a key fragment in some natural products (Figure 1A). Moreover, olefin functionalization of 4-methyleneproline is a known procedure for the synthesis of different 4-substituted-prolines,[4] which are important scaffolds found in natural products, drugs and peptides.[5] However, the methods for the synthesis of 4-methyleneproline and its analogues are poorly developed, and to date, are mostly limited to the use of the Wittig reaction of 4-oxoproline derivatives (Path a, Figure 1B).[6] Although much more efficient than other strategies incorporating intramolecular ring formations of complex linear substrates (Path b, Figure 1B),[7] cycloaddition strategies have not been explored well and are primarily based on [3+2] reactions which has a narrow substrates scope (Path c, Figure 1B).[8]

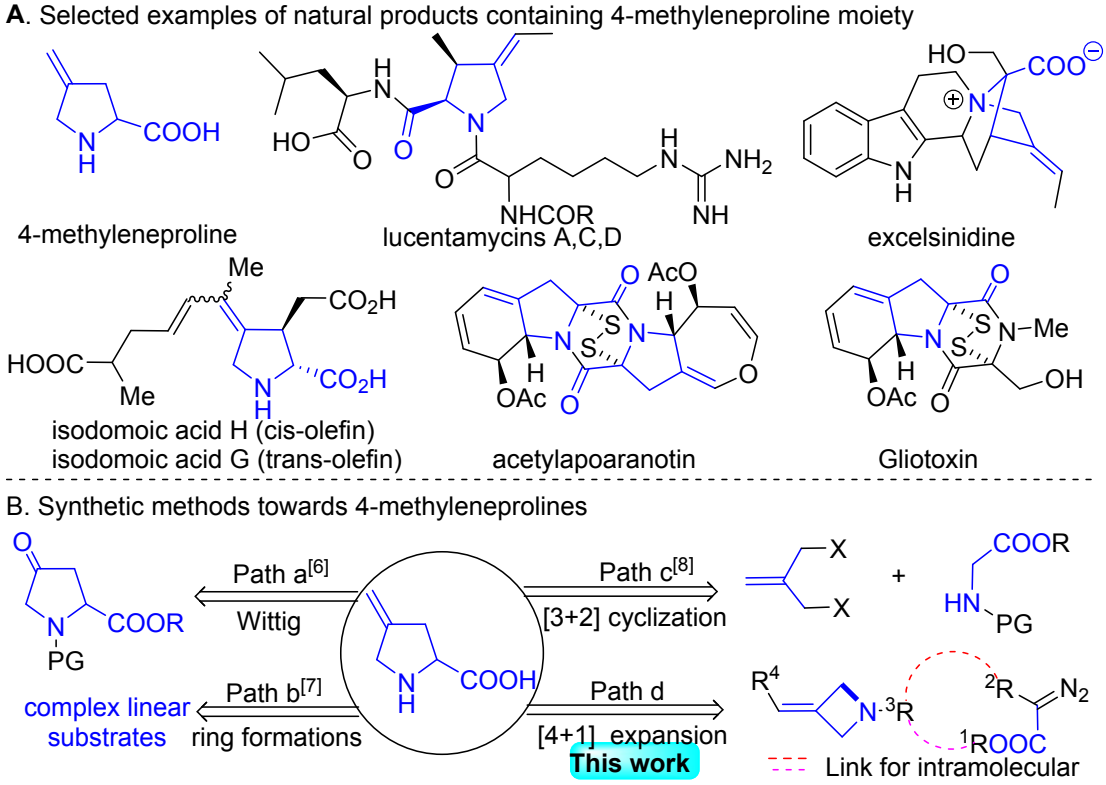


Figure 1. Synthetic Methods for 4-Methyleneproline Analogues

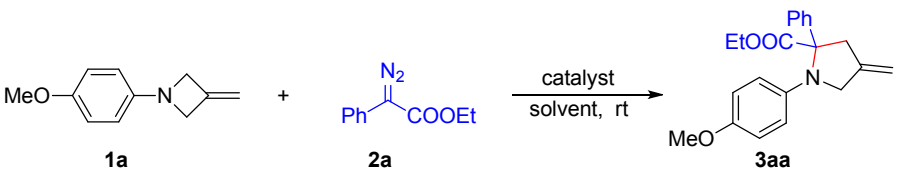
The exocyclic C=C bond can assist in breaking intrinsically strained rings due to its ability in stabilizing formed ions or radicals, and transfer to products which can be further functionalized. Therefore, strained rings containing an exocyclic double bond, such as vinylcyclopropanes,[9] methylenecyclopropanes,[10] vinylaziridines[11] and methyleneaziridines[12] are reactive in various chemical transformations. Taking the advantage of high reactivity of methyleneaziridines [12] and combining with the cycloaddition strategies to access interesting heterocycles,[13,14] Schomaker and co-workers recently reported an cycloaddition protocol of methyleneaziridines into methyleneazetidines. In this reaction, new C−C and C−N bonds were constructed efficiently with adjacent functionalized stereocenters.[15] The substrates scope in this reaction was found to be limited to carbamate-derived bicyclic methyleneaziridines which resulted in the restricted applications of the protocol and thereby prevented the intramolecular reaction to achieve more complex products. Homologous to

methyleneaziridines, 3-methyleneazetidines are easily prepared and stable,[16] however, very few reports on their transformations towards *N*-heterocycles have appeared.[17] Inspired by the possibility of interesting cycloaddition strategies,[14,18] and our earlier work on the synthesis of fused pyridines/quinolines from 3-methyleneaazetidines,[19] we report herein a general method for the synthesis of 4-methyleneproline derivatives, proceeding through Rh-catalyzed [4+1] cycloaddition of 3-methyleneazetidines with diazo compounds (Path d, Figure 1B).

Results and Discussion

Our investigation commenced with the reaction between 3-methyleneazetidine (**1a**) and phenyl diazoacetate (**2a**) in the presence of a metal catalyst (Scheme 1).[20] Firstly, different Rh catalysts were screened and found that $Rh_2(OAc)_4$ was the optimal (entries 1-5). Other types of metal catalysts were then tested, the desired product **3aa** was achieved in 36% yield by using $Cu(acac)_2$ catalyst under the reflux conditions. After screening catalyst loading (entries 10-12) and solvent (entries 13-16), the optimal condition was achieved (entry 12). The catalyst loading can be as low as 0.5 mol % without reducing the efficiency, however, in order to set up the reactions easily, 2 mol % catalyst loading was used when exploring the scope of the substrates (entry 1).

Scheme 1. Optimization of the Reaction Conditions



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

Entry	catalyst (mol %)	solvent	time (h)	yield (%)
1	**$Rh_2(OAc)_4$ (2)**	**DCM**	**2**	**94[a]**
2	Rh_2 (TFA)$_4$ (2)	DCM	2	84[b]

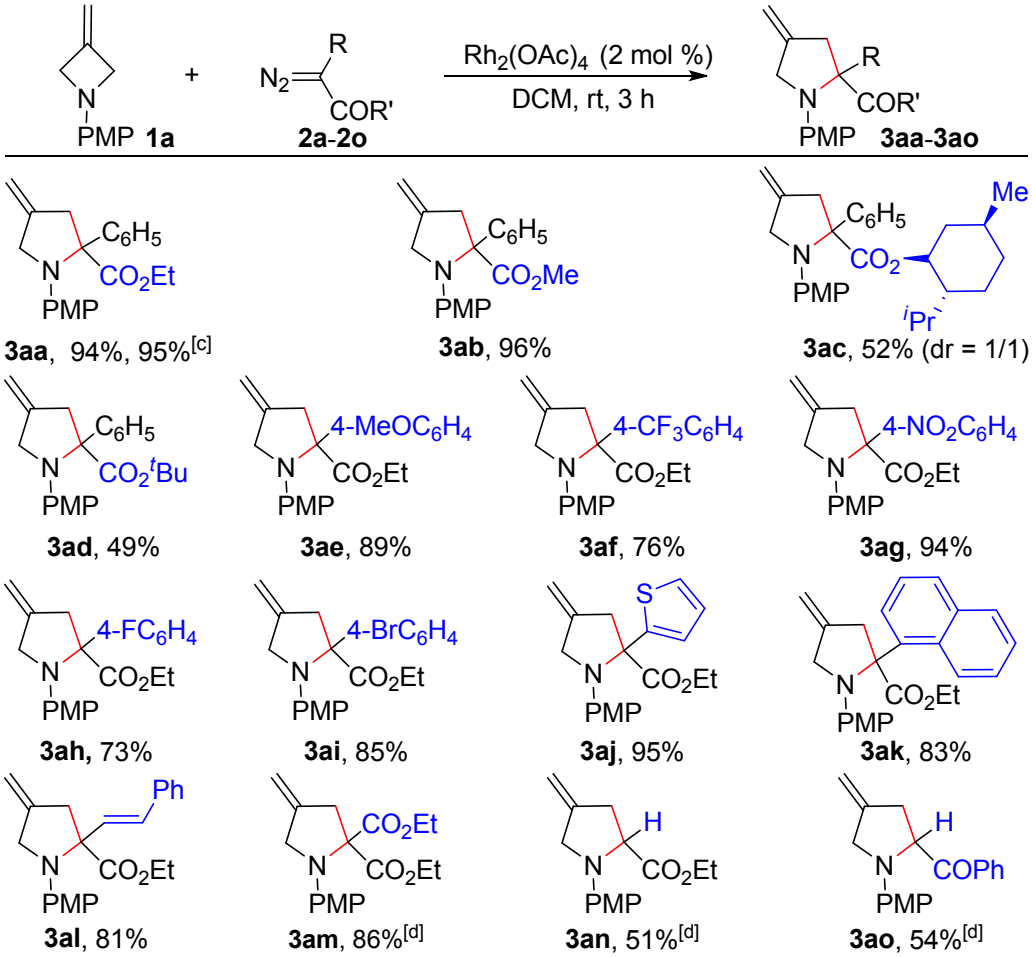
3	$[Rh(cod)Cl]_2$ (2)	DCM	2	8[b]
4	$[Cp^*RhCl_2]_2$ (2)	DCM	2	trace
5	$Rh_2(esp)_2$ (2)	DCM	2	72[b]
6	Ph_3PAuCl (5)	DCM	2	trace
7	AgOAc (5)	DCM	2	trace
8	$AgSbF_6$ (5)	DCM	2	trace
9[d]	$Cu(acac)_2$ (5)	toluene	8	36[b]
10	$Rh_2(OAc)_4$ (5)	DCM	1	85[a]
11	$Rh_2(OAc)_4$ (1)	DCM	4	94[a]
12	**$Rh_2(OAc)_4$ (0.5)**	**DCM**	**12**	**95[a]**
13	$Rh_2(OAc)_4$ (1)	toluene	4	28[b]
14	$Rh_2(OAc)_4$ (1)	Et_2O	4	55[b]
15	$Rh_2(OAc)_4$ (1)	THF	4	70[b]
16	$Rh_2(OAc)_4$ (1)	MeCN	4	68[b]

[a] Reactions were performed with 3-methyleneazetidine **1a** (0.2 mmol) and diazo ester **2a** (0.24 mmol) under Ar. The solution of diazo ester **2a** should be dropwise added during 1h. [b] isolated yield. [c] 3-methyleneazetidine **1a** was recovered after the reaction. [d] the reaction temperature was set to reflux.

The ester functionality in diazo compounds with sterically different groups was tolerated well (Scheme 2), and the sterically hindered groups produced the desired products, albeit with moderate yields (**3aa-3ad**). The reactions of both electron-rich and electron-poor aryl diazoacetates were successful (**3ae-3ag**). Halogen substitution on the aryl rings was tolerated well (**3ah-3ai**) and can provide an opportunity for further transformations. Thiophene and naphthalene tethered diazo esters provided desired **3aj-3ak** in good yields. When the phenyl group of **2a** was replaced by styrene, **3al** was formed in high yield with no regio- or chemo-selectivity issues. As a representative example of acceptor/acceptor diazo compounds, diethyl

2-diazomalonate was successfully employed (**3am**). Ethyl diazoacetate also worked well, producing *N*-phenyl-4- methyleneproline (**3an**). With 2-diazo-1-phenylethanone, the pyrrolidine (**3ao**) was formed in moedrate yield.

Scheme 2. Scope of Diazo Compound **2**[a, b]

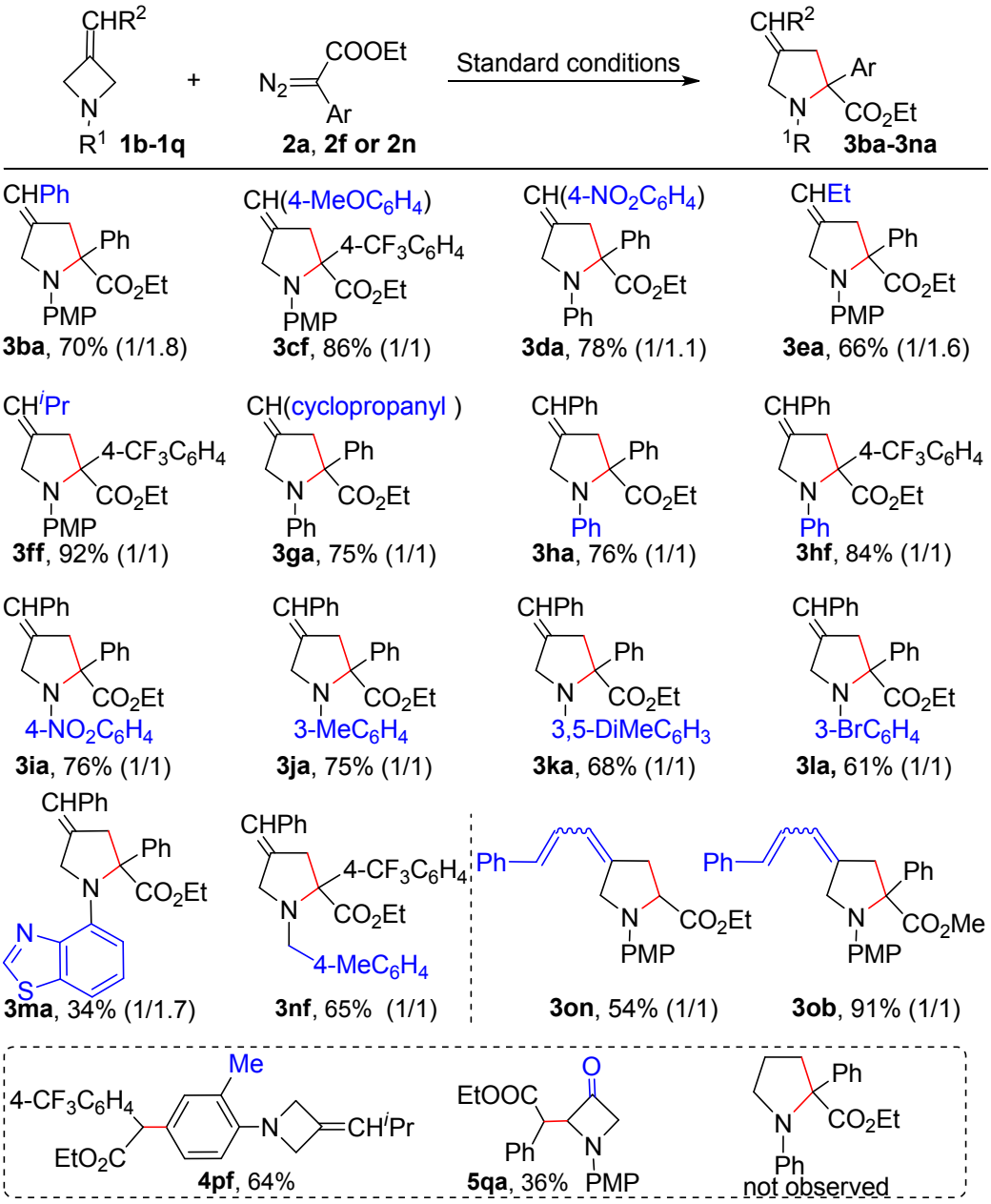


[a] Standard Conditions: 1 (0.2 mmol), $Rh_2(OAc)_4$ (2 mol %), DCM (1 mL), 2 (0.24 mmol) in DCM (0.5 mL) was added dropwise over 1 h, then rt for 2 h. [b] Isolated yield. [c] 0.5 mol% $Rh_2(OAc)_4$. [d] Reflux in DCM .

After demonstrating the general scope of the diazo compounds, the scope of the substrates with respect to the 3-methyleneazetidines was then explored (Scheme 3).

Azetidines whose terminal carbon of the methylene group is substituted by electron-rich or electron-deficient phenyl or alkyl groups were examined to determine their influence on the reaction. They all reacted well (**3ba**-**3ga**). The *N*-phenyl group, unsubstituted or with a *meta*- or *para*-substituent led to the corresponding proline esters in good yields (**3ha**-**3la**). An *N*-heteroaryl group such as benzothiazole reduced the efficiency (**3ma**), but the *N*-benzyl-3-methyleneazetidine provided **3nf** in good

Scheme 3. Scope of 3-Methyleneazetidine **1**[a, b]



[a] Standard conditions, see note a in Scheme 2. [b] Isolated yield, the ratio of Z/E olefin isomers in the parentheses.

yield. Since the 4-conjugated-dienyl proline is also a key fragment of natural products as shown in Figure 1, **1o** was applied and the desired 4-conjugated-dienyl proline esters (**3on**, **3ob**) were obtained with good to excellent yields. In case of an *N*-phenyl group with an *ortho*-methyl group, C(sp^2)–H alkylation in the *para*-position was

observed as a major pathway instead of cycloaddition reaction (**4pf)**, suggesting that steric hindrance near the nitrogen atom can influence the reaction. When the methylene group was replaced with an oxygen atom, the C(sp^3)−H alkylation was obtained (**5qa**). The reaction failed to provide the desired product when *N*-phenylazetidine was the substrate. These results clearly indicate that the presence of the exocyclic double bond in azetidine is critical. When the exocyclic double bond is absent, competitive side reactions predominate over the cycloaddition pathway.

Several experiments were carried out in order to understand the reaction mechanism (Figure 2). The competitive reactions between two 3-methyleneazetidines with different *N*-substituents were conducted, and showed that an electron-rich *N*-substituted group could accelerate the reaction (Figure 2A). 3-Methyleneazetidine with two deuteriums on the terminal carbon of the methylene (D_2-**1a**) was reacted and gave product D_2-**3aa** with deuteriums remaining in the methylene group and some deuteriums appearing in the pyrrolidine ring (Figure 2B). No shift of deuterium was observed using the deuterium labeled compound D_6-**1b** (D_6-**3ba**). These results suggest that the reaction may proceed through a stepwise reaction mechanism. When applying a commercially available chiral catalyst Rh_2(*S*-DOSP)$_4$, no enantioselectivity was observed (Figure 2C). Rh-carbene is known to participate in O−H insertion[21] and olefin cyclopropanation[22], and we employed benzyl alcohol or styrene as an additive to test the chemoselectivity of this reaction (Figure 2D). It was found that **3aa** is still formed predominantly and neither O−H insertion nor olefin cyclopropanation was observed, suggesting that cycloaddition has a high degree of chemoselectivity and is preferred over other reactions of Rh carbenes. Based on previous reports[15] and our own investigation, we propose a possible transformation *via* a two pathways mechanism (Figure 2E). Rh-bound carbene is attacked by the azetidine nitrogen with the release of Rh to form an ylide (**A**). The formation of **A** over competing C−H insertion, alkene cyclopropanation or O−H insertion is supported by the known reactivity of the nitrogen with electrophiles.[20] Subsequently, **A** is transformed into

3aa *via* direct 1, 2-migration (path I), or ring opening with zwitterionic species followed by ring closure (path II).

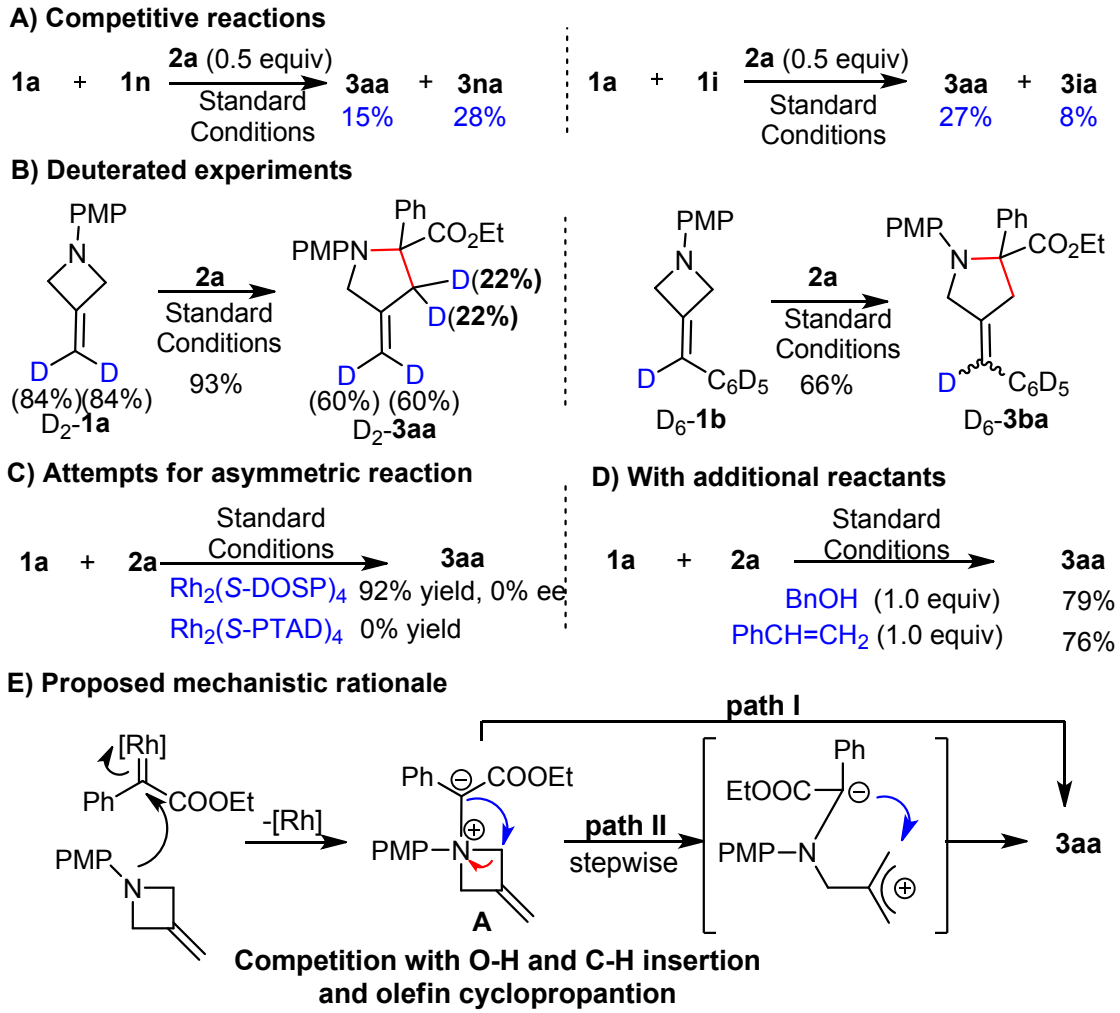


Figure 2. Control Experiments and Proposed Mechanism

The high chemoselectivity observed in this reaction, further tempted us to apply this strategy to the late stage, predictable functionalization of natural products and pharmaceutical compounds (Figure 3A). Although benzyl aryldiazoacetates are known to undergo *β*-lactone formation through Rh-catalyzed intramolecular C−H

alkylation of weak benzylic C−H bonds,[23] the benzyl aryldiazoacetate derivative (**2p**) selectively underwent an intermolecular Rh-catalyzed [4+1] reaction in the presence of 3-methyleneazetidine, providing the Adapalene derivative (**3ap**) in good yield. Similarly, the estrone-derived 3-benzylidineazetidine was converted to the corresponding proline ester derivative (**3sa**) without being affected by weak benzylic C−H bonds. A very interesting spiro-carbapenem compound (**3aq**) was achieved in moderate yield, such structurally diverse carbapenam analog could be useful in structural activity relation studies for better activity and ADME properties. Next, we examined the chemoselectivity in the intramolecular reaction as it allows the construction of fused rings (Figure 3B). In the reaction of *N*-phenyl-3-methyleneazetidine (**6a**) with an *o*-substituted diazo ester function in its *N*-phenyl ring, the common intramolecular 1, 5-C−H alkylation was not observed, but instead, the intramolecular [4+1] reaction led efficiently to a tricyclic *N*-heterocycle (**7a**), with a newly formed strained azetidine between benzene and proline ester. Inclusion of extra carbons may result in a larger ring attached directly to the pyrrolidine or proline ring. In this context, a 5-membered ketone ring or 6- to 8-membered ester ring incorporating pyrrolidine were achieved with good yields (**7b-7e**).

Functional group transformations of these newly synthesized structures were then carried out (Figure 3C). Palladium-catalyzed selective reduction of **3aa** provided 4-methylproline ester (**8aa**) in high yield. Olefinic cyclopropanation of **3aa** produced the corresponding difluoro-substituted spiro-cyclopropane derivative (**9aa**) as a single isomer. The ester group was selectively reduced to a hydroxymethylene group (**10aa**). In chloroform, this compound (**10aa**) converted spontaneously to a bridged morpholine-like compound (**11aa**), a structural unit found in a number of pharmaceuticals and natural products.[24] A practical application of this method was also tested with gram scale reactions (Figure 3D), in which both inter- and intra-molecular reactions worked well with 0.1 mol % of catalyst loading and adding

the diazo compound in one portion instead of in a dropwise manner.

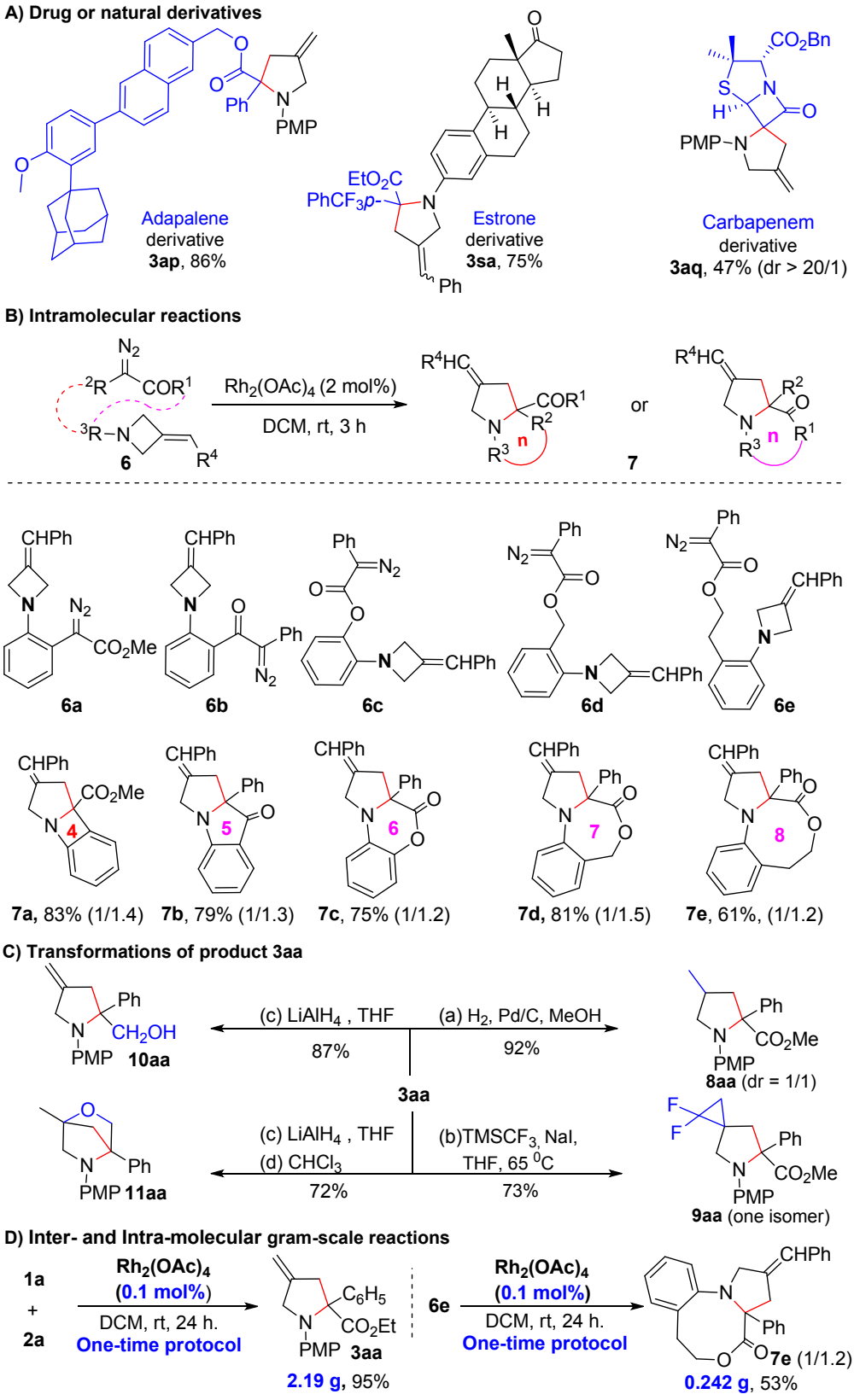


Figure 3. Applications and Large Scale Reactions

Conclusions

In summary, we have described a versatile and highly chemoselective and regioselective Rh-catalyzed [4+1] cycloaddition strategy incorporating 3-methyleneazetidines and diazo compounds, leading to the synthesis of diverse 4-methyleneprolines. Competitive experiments revealed the [4+1] cycloaddition reaction is predominant over C−H insertion, O−H insertion and olefin cyclopropanation which are common transformations in Rh carbene chemistry, indicating the robustness of this method. Subsequently, intramolecular reaction was well explored, and allowed the formation of various tricyclic fused small to moderate *N*-heterocycles, which are otherwise difficult to produce by conventional methods, showing the significant contribution of the present protocol towards diverse structural features. This protocol allows the modifications of drug substances and natural products analogs incorporating 4-methyleneproline systems as a result of post synthetic functional group transformation. Additionally, the gram scale reactions worked well using 0.1 mol % catalyst with the addition of diazo compounds in one portion. We expect this work will support a better understanding and exploitation of the reaction of 3-methyleneazetidines.

Experimental Section

General. The reactions were carried out under Argon atmosphere. Commercially available reagents were used without further purification. 1H NMR spectra were recorded on a NMR instrument operated at 400 MHz. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 ppm, CD_3OD: δ 3.31 ppm, CD_3SOCD_3: δ 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or unresolved), coupling constants (Hz), and integration. ^{13}C {H} NMR spectra were recorded on a NMR instrument operated at 100 MHz with complete proton decoupling. Infrared spectra were recorded from thin films of pure samples. Mass and HRMS spectra were measured in EI or ESI mode and the mass analyzer type used for the HRMS was TOF. Flash column chromatography was performed on silica gel.

General methods for preparation of substrates 1 are according literature.[19] Compounds **1a, 1c, 1d, 1e, 1f, 1i, 1l, 1n, 1o** and **1q** are new compounds. Compounds **1b, 1g, 1h, 1j, 1k, 1m** and **1p** are known compounds and the corresponding NMR dates are consistent with literature reports.[19]

1-(4-Methoxyphenyl)-3ethyleneazetidine (1a): R_f = 0.3 (EA : PE = 1 : 10), yellow solid, yield: 0.54 g, 31%, mp: 50.3-51.8 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 5.01 (t, *J* = 2.4 Hz, 2H), 4.43 (s, 4H), 3.79 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.3, 146.1, 139.8, 114.6, 113.2, 105.7, 61.6, 55.8. IR (film): 3028, 2899, 1625, 1453, 1120, 1121, 747, 691cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{14}NO$ 176.1070; Found 176.1074.

3-Benzylidene-1-(4-methoxyphenyl)azetidine (1b): R_f = 0.2 (EA : PE = 1 : 10), yellow solid, yield: 1.56 g, 62%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 6.89 – 6.84 (m, 2H), 6.56 – 6.51 (m, 2H), 6.28 (p, *J* = 2.3 Hz, 1H), 4.77 (q, *J* = 2.8 Hz, 2H), 4.58 (q, *J* = 2.6 Hz, 2H), 3.78 (s,3H).

3-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)azetidine (1c): R_f = 0.2 (EA : PE = 1 : 10), yellow solid, yield: 1.53 g, 62%. 1H NMR (400 MHz, $CDCl_3$) δ 7.12 (m, 2H), 6.89 (m, 4H), 6.55 (m, 2H), 6.24 (t, *J* = 2.3 Hz, 1H), 4.77 (d, *J* = 2.9 Hz, 2H), 4.59 (d, *J* = 2.8 Hz, 2H), 3.84 (s, 3H),

3.80 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 153.5, 141.4, 136.6, 133.3, 128.6, 127.2, 120.7, 116.4, 115.4, 113.3, 62.8, 62.8, 55.9. IR (film): 3057, 2894, 1605, 1450, 1180, 1120, 741, 686 cm-1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{19}NO$ 282.1489; Found 282.1491.

3-(4-Nitrobenzylidene)-1-phenylazetidine (1d): R_f = 0.2 (EA : PE = 1 : 5), yellow solid, yield: 2.02 g, 76%, mp: 102.5-103.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (m, 2H), 7.40 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.19 (m, 2H), 6.46 (m, 2H), 6.43 (m, 1H), 4.98 (q, *J* = 3.1 Hz, 2H), 4.80 (q, *J* = 2.9 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 153.8, 138.1, 135.8, 129.2, 128.8, 127.4, 127.2, 126.2, 122.8, 109.7, 60.8, 60.7. IR (film): 3048, 2891, 1615, 1452, 1181, 1121, 742, 686 cm-1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_2$ 267.1128; Found 267.1130.

1-(4-Methoxyphenyl)-3-propylideneazetidine (1e): R_f = 0.5 (EA : PE = 1 : 20), yellow solid, yield: 1.24 g, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.9 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 5.31 (td, *J* = 7.2, 2.3 Hz, 1H), 4.40 (ddd, *J* = 15.4, 2.8, 1.4 Hz, 4H), 3.78 (s, 3H), 1.98 (ddd, *J* = 8.8, 5.1, 1.4 Hz, 2H), 1.02 (t, *J* = 7.5 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.1, 146.2, 128.9, 122.8, 114.7, 113.1, 60.9, 59.8, 55.8, 22.0, 13.9. IR (film): 3032, 2889, 1635, 1452, 1181, 1121, 742, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}NO$ 204.1383; Found 204.1385.

1-(4-Methoxyphenyl)-3-(2-methylpropylidene)azetidine (1f): R_f = 0.3 (EA : PE = 1 : 10), yellow solid, yield: 1.00 g, 46%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, *J* = 8.8 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 5.18 (dt, *J* = 8.6, 2.3 Hz, 1H), 4.44 (q, *J* = 2.5 Hz, 2H), 4.37 (t, *J* = 2.4 Hz, 2H), 3.78 (s, 3H), 2.38 – 2.24 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.1, 146.2, 128.2, 127.3, 114.6, 113.0, 60.9, 59.9, 55.8, 28.6, 22.6. IR (film): 3049, 2901, 1605, 1461, 1175, 1103, 749, 695 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}NO$ 218.1539; Found 218.1541. **3-(Cyclopropylmethylene)-1-phenylazetidine (1g):** R_f = 0.4 (EA : PE = 1 : 10), yellow solid, yield: 1.24 g, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (td, *J* = 7.3, 2.1 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.59 – 6.49 (m, 2H), 4.84 (dt, *J* = 9.3, 2.3 Hz, 1H), 4.58 (q, *J* = 2.6 Hz, 2H), 4.45 (q, *J* = 2.4 Hz, 2H), 1.36 – 1.23 (m, 1H), 0.81 – 0.71 (m, 2H), 0.41 (dt, *J* = 6.5, 4.5 Hz, 2H).

1-([1,1'-Biphenyl]-4-yl)-3-benzylideneazetidine (1h): R_f = 0.4 (EA : PE = 1 : 10), yellow solid, yield: 1.69 g, 78%, mp: 61.7-62.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 4H), 7.44 (m, 4H), 7.37 – 7.28 (m, 2H), 7.27 – 7.20 (m, 2H), 6.73 – 6.64 (m, 2H), 6.36 (m, 1H), 4.91 (q, *J* = 2.9 Hz, 2H), 4.72 (q, *J* = 2.7 Hz, 2H).

3-Benzylidene-1-(4-nitrophenyl)azetidine (1i): R_f = 0.2 (EA : PE = 1 : 5), yellow solid, yield:1.94 g, 73%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.30 (m, 1H), 7.20 (m, 2H), 6.46 (m, 2H), 6.40 (m, 1H), 4.98 (q, *J* = 3.1 Hz, 2H), 4.80 (q, *J* = 2.9 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 153.8, 138.1, 135.8, 129.2, 128.8, 127.4, 127.2, 126.1, 122.8, 109.7, 60.8, 60.6. IR (film): 3048, 2891, 1615, 1452, 1181, 1121, 742, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_2$ 267.1128; Found 267.1132.

3-Benzylidene-1-(m-tolyl)azetidine (1j): R_f = 0.2 (EA : PE = 1 : 5), yellow solid, yield: 1.57 g, 67%, mp: 66.6-67.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.30 (m, 1H), 7.26 – 7.18 (m, 3H), 6.68 (m, 1H), 6.44 (m, 2H), 6.34 (m, 1H), 4.86 (q, *J* = 2.9 Hz, 2H), 4.67 (q, J = 2.7 Hz, 2H), 2.40 (s, 3H).

3-Benzylidene-1-(3,5-dimethylphenyl) azetidine (1k): R_f = 0.4 (EA : PE = 1 : 10), yellow solid, yield: 1.89 g, 76%, mp: 71.8-72.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 2H), 7.30 – 7.24 (m, 1H), 7.21 (m, 2H), 6.50 (s, 1H), 6.32 (m, 1H), 6.25 (s, 2H), 4.84 (d, *J* = 2.7 Hz, 2H), 4.64 (d, *J* = 2.6 Hz, 2H), 2.34 (s, 6H).

3-Benzylidene-1-(3-bromophenyl)azetidine (1l): R_f = 0.5 (EA : PE = 1 : 20), yellow solid, yield: 2.11 g, 70%, the ratio of *Z/E* olefin isomers 1/3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 6.3 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.99 (t, *J* = 7.9 Hz, 0.25H), 6.92 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 0.75H), 6.49 (ddd, *J* = 14.9, 8.1, 2.3 Hz, 1H), 6.34 (p, *J* = 2.3 Hz, 1H), 4.83 (q, *J* = 3.1 Hz, 2H), 4.64 (q, *J* = 2.9 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.0, 136.3, 131.8, 131.8, 130.4, 130.3, 128.7, 127.1, 127.0, 126.4, 123.1, 121.7, 121.7, 120.6, 120.4, 114.7, 111.0, 110.4, 61.4, 61.3. IR (film): 3049, 2908, 1615, 1467, 1303, 1200, 771, 691 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}BrN$ 300.0382; Found 300.0385.

4-(3-Benzylideneazetidin-1-yl)benzo[d]thiazole (1m): R_f = 0.3 (EA : PE = 1 : 5), yellow solid, yield:0.58 g, 21%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 7.40 (m, 2H), 7.37 – 7.31 (m, 2H), 7.27 (m, 3H), 6.52 (m, 1H), 6.35 (t, *J* = 2.4 Hz, 1H), 5.27 (q, *J* = 3.0 Hz, 2H), 5.02 (q, *J* = 2.8 Hz, 2H).

3-Benzylidene-1-(4-methylbenzyl)azetidine (1n): R_f = 0.3 (EA : PE = 1 : 5), yellow solid, yield: 2.38 g, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.11 (m, 2H), 6.19 (t, *J* = 2.4 Hz, 1H), 4.23 (q, *J* = 2.7 Hz, 1H), 4.07 (q, *J* = 2.4 Hz, 2H), 3.80 (s, 2H), 2.38 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 138.1, 137.2, 136.9, 136.7, 135.3, 129.2, 128.4, 127.1, 126.4, 120.7, 65.1, 63.2, 63.1, 21.1. IR (film): 3030, 2913, 1624, 1454, 1219, 1171, 756, 687 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{20}N$ 250.1590; Found 250.1594.

(*Z/E*)-1-(4-Methoxyphenyl)-3-(3-phenylallylidene)azetidine (1o): R_f = 0.3 (EA : PE = 1 : 20), yellow solid, yield: 1.5 g, 54%, mp: 127.9-128.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 2H), 7.28 (d, *J* = 1.1 Hz, 1H), 7.25 (t, *J* = 7.3 Hz, 1H), 6.88 (m, 2H), 6.66 (dd, *J* = 15.6, 10.7 Hz, 1H), 6.51 (m, 2H), 4.63 (d, *J* = 3.1 Hz, 2H), 4.53 (s, 2H), 3.79 (d, *J* = 1.2 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.4, 145.9, 137.3, 134.6, 131.2, 128.6, 127.5, 126.2, 124.1, 121.2, 114.7, 113.1, 61.2, 60.4, 55.8. IR (film): 3028, 2915, 1625, 1454, 1219, 1171, 756, 687 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO$ 278.1539; Found 278.1543.

3-(2-Methylpropylidene)-1-(o-tolyl)azetidine (1p): R_f = 0.3 (EA : PE = 1 : 20), yellow oil, yield: 1.13 g, 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 1H), 7.14 – 7.07 (m, 1H), 6.81 (m, 1H), 6.57 (m, 1H), 5.20 (dt, *J* = 8.7, 2.2 Hz, 1H), 4.57 (q, *J* = 2.4 Hz, 2H), 4.50 (q, *J* = 2.3 Hz, 2H), 2.34 (dq, *J* = 8.8, 6.8 Hz, 1H), 2.29 (s, 3H), 1.05 (d, *J* = 6.7 Hz, 6H).

1-(4-Methoxyphenyl)azetidin-3-one (1q): R_f = 0.4 (EA : PE = 1 : 5), yellow solid, yield: 1.52 g, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.9 Hz, 2H), 6.59 (d, *J* = 8.9 Hz, 2H), 4.64 (s, 4H), 3.80 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 198.0, 153.1, 144.3, 114.8, 114.5, 73.8, 55.7. IR (film): 3042, 2978, 1710, 1645, 1478, 1246, cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_2$ 178.0863; Found 178.0866.

1-Phenylazetidine (1r): R_f = 0.4 (EA : PE = 1 : 50), pale yellow solid, yield: 1.23 g, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.48 (m, 2H), 3.91 (t, *J* = 7.2 Hz, 4H), 2.39 (p, *J* = 7.2 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.3, 128.9, 117.3, 111.3, 52.4, 17.0. IR (film): 3029, 2898, 1645, 1465, 1109, 789, 687 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_9H_{12}N$ 134.0964; Found 134.0966.

(8R,9S,13S,14S)-3-(3-Benzylideneazetidin-1-yl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (1s): R_f = 0.4 (EA : PE = 1: 10), pale yellow solid, yield: 3.66 g, 92%, mp: 150.9-151.8 °C, the ratio of *Z*/*E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (t, *J* = 7.5 Hz, 2H), 7.24 (dd, *J* = 12.0, 7.8 Hz, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 6.44 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.38 – 6.22 (m, 2H), 4.82 (q, *J* = 2.9 Hz, 2H), 4.62 (q, *J* = 2.7 Hz, 2H), 2.94 (dd, *J* = 10.1, 6.3 Hz, 2H), 2.53 (dd, *J* = 18.8, 8.5 Hz, 1H), 2.43 (d, *J* = 9.9 Hz, 1H), 2.28 (s, 1H), 2.23 – 1.94 (m, 4H), 1.56 (d, *J* = 23.2 Hz, 6H), 0.93 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 149.3, 137.1, 136.5, 133.0, 129.3, 128.6, 127.1, 126.7, 126.0, 121.1, 112.2, 110.0, 61.7, 61.6, 50.4, 48.0, 44.0, 38.5, 35.9, 31.6, 29.7, 26.6, 25.9, 21.6, 13.8. IR (film): 3044, 2936, 1680, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{28}H_{32}NO$ 398.2478; Found 398.2472.

1-(4-Methoxyphenyl)-3-(methylene-d$_2$)azetidine (D_2-1a): R_f = 0.3 (EA : PE = 1 : 10), yellow solid, yield: 0.55 g, 31%. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.86 (d, *J* = 8.9 Hz, 2H), 6.49 (d, *J* = 8.9 Hz, 2H), 5.01 (t, *J* = 2.4 Hz, 0.32H), 4.43 (s, 4H), 3.79 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) *δ* 152.3, 146.1, 139.8, 114.7, 113.2, 105.8, 61.6, 55.9. IR (film): 3028, 2899, 1625, 1453, 1120, 1121, 747, 691cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{12}D_2NO$ 178.1195; Found 178.1198.

3-(Hepta-2,4,6-triyn-1-ylidene-d$_6$)-1-(4-methoxyphenyl)azetidine (D_6-1b): R_f = 0.3 (EA : PE = 1 : 10), yellow solid, yield: 2.01 g, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.3 Hz, 2H), 6.57 (d, *J* = 8.4 Hz, 2H), 4.81 (t, *J* = 3.0 Hz, 2H), 4.62 (t, *J* = 3.0 Hz, 2H), 3.82 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 153.5, 141.4, 136.6, 133.2, 128.6, 127.2, 126.8, 121.7, 120.7, 116.4, 115.4, 113.3, 62.8, 62.8, 55.9. IR (film): 3047, 2924, 1605, 1450, 1180, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{17}H_{12}D_6NO$ 258.1760; Found 258.1764.

Methods for preparation of diazo compounds 2 are according to the literature. [25] Diazo compounds **2** are known compounds and the NMR dates of diazo compounds **2** are consistent with literature reports. [25] Compounds **2m** and **2n** are commercially available.

Ethyl 2-Diazo-2-phenylacetate (2a): R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 1.53 g, 81%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.25 – 7.15 (m, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H).

Methyl 2-Diazo-2-phenylacetate (2b): R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 1.41 g, 80%.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.48 (m, 2H), 7.41 (dd, *J* = 8.5, 7.3 Hz, 2H), 7.25 – 7.17 (m, 1H), 3.90 (s, 3H).

(1S, 2R, 5S)-2-Isopropyl-5-methylcyclohexyl 2-diazo-2-phenylacetate (2c): R_f = 0.5 (EA : PE = 1 : 20), pale yellow oil, yield: 2.68 g, 89%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.46 – 7.34 (m, 2H), 7.25 – 7.15 (m, 1H), 4.90 (td, *J* = 10.9, 4.4 Hz, 1H), 2.14 (dtd, *J* = 12.0, 4.0, 1.7 Hz, 1H), 1.94 (pd, *J* = 7.0, 2.8 Hz, 1H), 1.80 – 1.66 (m, 2H), 1.62 – 1.52 (m, 2H), 1.46 (ddt, *J* = 10.9, 9.2, 3.1 Hz, 1H), 1.20 – 1.04 (m, 2H), 0.94 (dd, *J* = 6.8, 5.3 Hz, 6H), 0.83 (d, *J* = 6.9 Hz, 3H).

Tertbutyl 2-diazo-2-phenylacetate (2d): R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 1.33 g, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.25 (m, 5H), 1.58 (s, 9H).

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate (2e): R_f = 0.4 (EA : PE = 1 : 20), pale yellow oil, yield:1.83 g, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.33 (m, 2H), 7.08 – 6.83 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-Diazo-2-(4-(trifluoromethyl)phenyl)acetate (2f): R_f = 0.8 (EA : PE = 1 : 20), pale yellow oil, yield: 2.35 g, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 4H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-diazo-2-(4-nitrophenyl)acetate (2g): R_f = 0.4 (EA : PE = 1 : 5), pale yellow solid, yield: 2.01 g, 84 %. δ 8.01 (s, 1H), 7.84 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.49− 7.38 (m, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).**Ethyl 2-Diazo-2-(4-fluorophenyl)acetate (2h):** R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 1.89 g, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.11 (t, *J* = 8.6 Hz, 2H),

4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-(4-Bromophenyl)-2-diazoacetate (2i): R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 2.21 g, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.39 (d, *J* = 8.7 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

Ethyl 2-Diazo-2-(thiophen-2-yl)acetate (2j): R_f = 0.7 (EA : PE = 1 : 20), pale yellow oil, yield: 1.49 g, 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 1H), 6.98 (d, *J* = 6.4 Hz, 2H), 4.28 – 4.15 (m, 2H), 1.30 (dd, *J* = 8.0, 6.5 Hz, 3H).

Ethyl 2-Diazo-2-(naphthalen-2-yl)acetate (2k): R_f = 0.6 (EA : PE = 1 : 20), pale yellow oil, yield: 1.49 g, 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.26-8.23 (m, 2H), 7.70-7.67 (m, 2H), 4.36-4.31 (q, *J* = 7.5 Hz, 2H), 1.36-1.32 (t, *J* = 7.5 Hz, 3H).**Ethyl (E)-2-Diazo-4-phenylbut-3-enoate (2l):** R_f = 0.6 (EA : PE = 1 : 20), pale yellow oil, yield: 1.43 g, 66%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.25 – 7.19 (m, 1H), 6.51 (d, *J* = 16.3 Hz, 1H), 6.22 (d, *J* = 16.3 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H).

2-Diazo-1-phenylethan-1-one (2o): R_f = 0.5 (EA : PE = 1 : 20), pale yellow oil, yield: 1.00 g, 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.74 (m, 2H), 7.60 – 7.53 (m, 1H), 7.51 – 7.44 (m, 2H), 5.93 (s, 1H).

(6-(3-((1R, 3S, 5R 7R)-Adamantan-2-yl)-4-methoxyphenyl)naphthalen-2-yl)methyl 2-diazo-2-phenylacetate (2p): R_f = 0.5 (EA : PE = 1 : 10), pale yellow oil, yield: 385 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.87 (dd, *J* = 12.2, 8.5 Hz, 2H), 7.79 – 7.74 (m, 2H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.45 (d, *J* = 1.7 Hz, 1H), 7.37 – 7.32 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 1H), 3.93 (s, 3H), 3.74 (d, *J* = 4.0 Hz, 2H), 2.22 (d, *J* = 2.9 Hz, 6H), 2.13 (t, *J* = 3.3 Hz, 3H), 1.83 (d, *J* = 3.0 Hz, 6H).

Benzyl (2S)-6-Diazo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate (2q): R_f = 0.3 (EA : PE = 1 : 10), pale yellow oil, yield: 2.16 g, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 22.5, 8.1 Hz, 5H), 6.17 (d, *J* = 3.3 Hz, 1H), 5.19 (s, 2H), 4.39 (d, *J* = 3.4 Hz, 1H), 1.57 (d, *J* = 3.4 Hz, 3H), 1.32 (d, *J* = 3.3 Hz, 3H).

Methods for preparation of substrates 6.

Methyl 2-(2-(3-Benzylideneazetidin-1-yl)phenyl)-2-diazoacetate (6a): the method as follows: R_f = 0.3 (EA : PE = 1 : 10), pale yellow solid, yield: 352 mg, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 1H), 7.40 (m, 3H), 7.26 (m, 1H), 7.17 (m, 2H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.28 (p, *J* = 2.4 Hz, 1H), 4.87 (d, *J* = 3.0 Hz, 2H), 4.68 (d, *J* = 2.8 Hz, 2H), 3.95 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 167.8, 150.5, 136.4, 132.5, 132.4, 131.6, 128.7, 127.2, 126.8, 120.9, 117.3, 115.6, 114.4, 63.1, 62.9, 52.0. IR (film): 3028, 2894, 2234, 1680, 1605, 1450, 1180, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}N_3O_2$ 320.1394; Found 320.1394.

To a two-necked flask 2-(2-bromophenyl)acetic acid (2.13 g, 10 mmol) and MeOH (80 mL), DMF (0.2 mL) were added under N_2 atmosphere. $(COCl)_2$ (1.3 mL, 15 mmol) was added at 0 °C, then the mixture was stirred at room temperature overnight. The mixture was evaporated and give the crude product methyl 2-(2-bromophenyl)acetate.

To a 100 mL schlenk tube methyl 2-(2-bromophenyl)acetate (2.28 g, 10 mmol) and 3-benzylidene-1-chloro-1-azetidine (2.17 g, 12 mmol), Pd_2dba_3 (460 mg, 0.5 mmol), RuPhos (466 mg, 1 mmol), dioxane (50 mL), Cs_2CO_3 (8.12 g, 25 mmol) were added under N_2 atmosphere. Then the mixture was stirred at 100 °C with oil bath overnight. The mixture was evaporated and purification by column chromatography with petroleum ether and ethyl acetate to give the product methyl 2-(2-(3-benzylideneazetidin-1-yl)phenyl)acetate. (2.11 g, 72%), R_f = 0.4 (EA : PE = 1 : 10).

To a two-necked flask methyl 2-(2-(3-benzylideneazetidin-1-yl)phenyl)acetate (586 mg, 2 mmol) and *P*-ABSA (720 mg, 3 mmol), THF (20 mL) was added under N_2 atmosphere. DBU (456 mg, 3 mmol) were added to the mixture dropwise at 0 °C. Then warmed the temperature to room temperature and stirred for overnight. The mixture was evaporated and purification by column chromatography with petroleum ether and ethyl acetate to give the product **6a** (350 mg, 55%).

1-(2-(3-Benzylideneazetidin-1-yl)phenyl)-2-diazo-2-phenylethen-1-one (6b): The method of synthesizing **6b** with 1-(2-bromophenyl)-2-phenylethan-1-one is the same as **6a**. R_f = 0.3 (EA : PE = 1 : 10), pale yellow solid, yield: 527 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (ddd, *J* = 15.2, 7.4, 1.8 Hz, 4H), 7.44 (dt, *J* = 18.0, 7.6 Hz, 4H), 7.37 – 7.28 (m, 2H), 7.27 – 7.20 (m, 2H),

6.73 – 6.64 (m, 2H), 6.36 (p, *J* = 2.3 Hz, 1H), 4.91 (q, *J* = 2.9 Hz, 2H), 4.72 (q, *J* = 2.7 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 169.9, 149.6, 146.7, 140.1, 139.9, 138.9, 134.4, 133.5, 129.6, 129.4, 129.0, 128.8, 128.4, 127.8, 127.7, 127.4, 127.2, 125.6, 75.1. IR (film): 3026, 2898, 2232, 1683, 1605, 1450, 1180, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O$ 366.1601; Found 366.1604.

To a two-necked flask 2-bromobenzoic acid (2.01 g, 10 mmol) and DCM (80 mL), DMF (0.2 mL) was added under N_2 atmosphere. $(COCl)_2$ (1.2 mg, 15 mmol) were added at 0 °C, then the mixture was stirred at room temperature overnight. The mixture was evaporated and give the crude product 2-bromobenzoyl chloride.

To a solution of bis[2-(*N,N*-dimethylaminoethyl)]ether (1 mL, 5.2 mmol) in THF (16 mL) was added BnMgBr (2.60 mL, 5.2 mmol, 2 M solution in THF) at 0 °C. The mixture was stirred at 0-5 °C for 30 min. This mixture was slowly added to a solution of 2-bromobenzoyl chloride (538 mg, 2.0 mmol) at -60 °C for 15 min, and the resulting mixture was stirred at -60 ° C for 10 min. The mixture was then quenched with aqueous ammonium chloride. After extraction of the mixture with EtOAc, the extract was dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel to give 1-(2-bromophenyl)-2-phenylethan-1-one (409 mg, 75%), R_f = 0.5 (EA : PE = 1 : 20).

2-(3-Benzylideneazetidin-1-yl)phenyl 2-Diazo-2-phenylacetate (6c): The method of synthesizing **6c** with 2-bromophenyl 2-phenylacetate is the same as **6a**. R_f = 0.3 (EA : PE = 1 : 10), pale yellow solid, yield: 634 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.27 (m, 6H), 7.20 (dd, *J* = 7.1, 5.5 Hz, 3H), 7.08 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.31 (t, *J* = 2.4 Hz, 1H), 4.88 (t, *J* = 2.8 Hz, 2H), 4.71 (t, *J* = 2.7 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 169.9, 149.7, 147.7, 140.2, 139.1, 134.0, 132.2, 130.8, 129.3, 128.7, 128.7, 128.3, 128.3, 128.0, 127.5, 127.1, 127.0, 125.5, 77.3, 77.0. IR (film): 3039, 2899, 2233, 1698, 1603, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}N_3O_2$ 382.1550; Found 382.1554.

To a two-necked flask 2-bromophenol (1.73 g, 10 mmol) and DCM (80 mL), NEt_3 (2.8 mL, 20 mmol) were added under N_2 atmosphere. BnCOCl (4.4 mL, 15 mmol) was added at 0 °C, then the

mixture was stirred at room temperature overnight. The mixture was evaporated and purification by column chromatography with petroleum ether and ethyl acetate to give the product 2-bromophenyl 2-phenylacetate (2.62 g, 90%). R_f= 0.4 (EA : PE = 1 : 4)

2-(3-Benzylideneazetidin-1-yl)benzyl 2-Diazo-2-phenylacetate (6d): The method of synthesizing **6d** with 2-bromobenzyl 2-phenylacetate is the same as **6a**. R_f= 0.4 (EA : PE = 1 : 4), pale yellow solid, yield: 584 mg, 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.37 (m, 6H), 7.21 (m, 4H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.67 (m, 1H), 6.32 (t, *J* = 2.3 Hz, 1H), 5.36 (s, 2H), 4.98 (q, *J* = 2.9 Hz, 2H), 4.79 (q, *J* = 2.6 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 165.1, 149.6, 136.4, 132.5, 132.1, 129.5, 128.9, 128.6, 127.1, 126.8, 125.9, 125.4, 124.0, 121.5, 120.9, 119.0, 113.6, 64.0, 62.9, 62.7. IR (film): 3041, 2902, 2230, 1698, 1603, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{21}N_3O_2$ 396.1707; Found 396.1711.

To a two-necked flask (2-bromophenyl)methanol (1.87 g, 10 mmol) and DCM (80 mL), NEt_3 (2.8 mL, 20 mmol) were added under N_2 atmosphere. BnCOCl (4.4 mL, 15 mmol) was added at 0 °C, then the mixture was stirred at room temperature overnight. The mixture was evaporated and purification by column chromatography with petroleum ether and ethyl acetate to give the product 2-bromobenzyl 2-phenylacetate (2.83 g, 93%). R_f= 0.3 (EA : PE = 1 : 5)

2-(3-Benzylideneazetidin-1-yl)phenethyl 2-Diazo-2-phenylacetate (6e): The method of synthesizing **6e** is the same as **6d**. R_f= 0.4 (EA : PE = 1 : 4), pale yellow solid, yield: 558 mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7 .4 Hz, 2H), 7.38 (qd, *J* = 9.4, 8.5, 4.5 Hz, 5H), 7.23 (dd, *J* = 15.9, 7.8 Hz, 5H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.33 (dd, *J* = 4.9, 2.6 Hz, 1H), 4.93 (t, *J* = 2.9 Hz, 2H), 4.75 (q, *J* = 2.6 Hz, 2H), 4.56 (t, *J* = 7.3 Hz, 2H), 3.07 (t, *J* = 7.3 Hz, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 165.2, 149.0, 136.5, 132.8, 131.4, 129.3, 128.9, 128.6, 127.5, 127.3, 127.2, 126.8, 125.7, 125.5, 124.0, 120.7, 119.7, 113.8, 64.0, 62.4, 62.1, 32.1. IR (film): 3041, 2902, 2230, 1698, 1603, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}N_3O_2$ 410.1863; Found 410.1866.

General methods for preparation of products 3: To a schlenk flask 3-methyleneazetidine (0.2 mmol) and $Rh_2(OAc)_4$ (1.8 mg, 2 mol%), DCM (1 mL) were added under N_2 atmosphere. diazo ester (0.24 mmol) dissolved in DCM (0.5 mL) was added at room temperature, then stirred for 2 h.

the reaction was evaporated and the residue was purification by column chromatography with petroleum ether and ethyl acetate to give the corresponding products.

Ethyl 1-(4-Methoxyphenyl)-4-methylene-2-phenylpyrrolidine-2-carboxylate (3aa): R_f = 0.4 (EA : PE = 1 : 10), pale yellow oil, yield: 64 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.9 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.1 Hz, 1H), 6.69 (d, J = 9.1 Hz, 2H), 6.43 (d, J = 9.1 Hz, 2H), 5.04 (s, 1H), 4.91 (s, 1H), 4.36 (d, J = 12.8 Hz, 1H), 4.23 (d, J = 12.4 Hz, 1H), 4.17 – 4.03 (m, 2H), 3.70 (s, 3H), 3.45 (d, J = 15.6 Hz, 1H), 2.87 (dd, J = 15.6, 1.8 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 151.7, 143.2, 141.1, 140.5, 128.0, 127.4, 127.1, 115.3, 114.2, 106.5, 73.7, 61.3, 55.9, 55.6, 51.0, 14.1. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_3$ 338.1751; Found 338.1753.

Methyl 1-(4-Methoxyphenyl)-4-methylene-2-phnylpyrrolidine-2-carboxylate (3ab): R_f = 0.5 (EA : PE = 1 : 10), pale yellow oil, yield: 63 mg, 96%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.48 – 7.42 (m, 2H), 7.31 – 7.21 (m, 3H), 6.70 – 6.63 (m, 2H), 6.45 – 6.38 (m, 2H), 5.08 – 5.04 (m, 1H), 4.94 – 4.92 (m, 1H), 4.37 (dd, J = 12.9, 1.4 Hz, 1H), 4.22 (d, J = 12.1 Hz, 1H), 3.68 (d, J = 5.5 Hz, 3H), 3.61 (s, 3H), 3.47 (d, J = 15.5 Hz, 1H), 2.86 (dd, J = 15.5, 1.8 Hz, 1H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 174.4, 151.8, 143.2, 140.8, 140.2, 127.4, 127.1, 126.7, 114.7, 113.7, 105.5, 73.5, 55.2, 54.6, 51.3, 50.6. IR (film): 3041, 2913, 1675, 1637, 1459, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_3$ 324.1594; Found 324.1591.

(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl-1-(4-methoxyphenyl)-4-methylene-2-phenylpyrrolidine-2-carboxylate (3ac): R_f = 0.4 (EA : PE = 1 : 5), orange oil, yield 47 mg, 52%, The ratio of Z/E is 1/1. ^{1}H NMR (400 MHz, CD_3OD) δ 7.56 – 7.49 (m, 2H), 7.33 – 7.24 (m, 3H), 6.71 – 6.65 (m, 2H), 6.43 (t, J = 9.1 Hz, 2H), 5.08 (d, J = 2.0 Hz, 1H), 4.94 (t, J = 2.2 Hz, 1H), 4.67 – 4.53 (m, 1H), 4.43 (dd, J = 12.9, 1.9 Hz, 1H), 4.19 (ddd, J = 13.0, 8.0, 2.2 Hz, 1H), 3.68 (d, J = 2.6 Hz, 3H), 3.42 (dd, J = 15.7, 12.6 Hz, 1H), 2.85 (ddd, J = 15.8, 4.2, 2.1 Hz, 1H), 1.71 – 1.40 (m, 4H), 1.04 – 0.95 (m, 2H), 0.93 (d, J = 6.6 Hz, 2H), 0.86 (d, J = 7.0 Hz, 3H), 0.76 (t, J = 6.9 Hz, 3H), 0.59 (d, J = 7.0 Hz, 2H), 0.35 (d, J = 6.9 Hz, 2H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.8, 173.5, 152.0, 151.8, 143.5, 141.3, 141.2, 140.7, 140.6, 127.5, 127.4, 127.1, 127.0, 126.6, 126.6,

115.3, 114.9, 113.8, 113.6, 105.3, 105.3, 75.0, 75.0, 73.8, 73.4, 55.8, 54.7, 54.6, 48.2, 48.0, 47.8, 47.6, 47.4, 47.1, 46.9, 40.2, 40.0, 33.8, 33.8, 31.2, 31.0, 25.7, 24.3, 22.5, 22.2, 21.0, 20.9, 20.0, 19.8, 14.79, 14.3. IR (film): 3013, 2932, 1675, 1637, 1459, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{38}NO_3$ 448.2847; Found 448.2848.

Tertbutyl-1-(4-methoxyphenyl)-4-methylene-2-phenylpyrrolidine-2-carboxylate (3ad): R_f = 0.3 (EA : PE = 1 : 10), orange oil, yield: 36 mg, 49%. ^1H NMR (400 MHz, CD_3OD) δ 7.48 (dd, J = 5.3, 3.3 Hz, 2H), 7.29 – 7.24 (m, 2H), 7.23 – 7.18 (m, 1H), 6.66 (d, J = 9.2 Hz, 2H), 6.44 (d, J = 9.1 Hz, 2H), 5.08 – 5.02 (m, 1H), 4.94 – 4.89 (m, 1H), 4.40 – 4.31 (m, 1H), 4.15 (d, J = 12.7 Hz, 1H), 3.66 (s, 3H), 3.40 (d, J = 15.6 Hz, 1H), 2.79 (dd, J = 15.7, 1.9 Hz, 1H), 1.24 (s, 9H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 172.7, 151.8, 143.7, 141.4, 140.8, 127.3, 127.1, 126.5, 115.1, 113.5, 105.0, 81.3, 74.0, 55.7, 54.6, 50.6, 26.6. IR (film): 3042, 2914, 1676, 1638, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}NO_3$ 366.2064; Found 366.2058.

Ethyl 1,2-Bis(4-methoxyphenyl)-4-methylenepyrrolidine-2-carboxylate (3ae): R_f = 0.5 (EA : PE = 1 : 5), pale yellow oil, yield: 66 mg, 89%. ^1H NMR (400 MHz, CD_3OD) δ 7.35 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 6.64 (d, J = 9.1 Hz, 2H), 6.40 (d, J = 9.1 Hz, 2H), 5.03 (s, 1H), 4.89 (s, 1H), 4.32 (d, J = 12.9 Hz, 1H), 4.17 (d, J = 12.8 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 3.39 (d, J = 15.4 Hz, 1H), 2.79 (dd, J = 15.5, 1.3 Hz, 1H), 1.00 (t, J = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 174.0, 158.6, 151.7, 143.5, 140.5, 132.8, 128.3, 114.9, 113.6, 112.8, 105.3, 73.1, 60.8, 55.3, 54.6, 54.2, 50.6, 12.9. IR (film): 3042, 2911, 1675, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{26}NO_4$ 368.1856; Found 368.1850.

Ethyl

1-(4-Methoxyphenyl)-4-methylene-2-(4-(trifluoromethyl)phenyl)pyrroledine-2-carboxylate (3af): R_f = 0.5 (EA : PE = 1 : 10), pale yellow oil, yield: 62 mg, 76%. ^1H NMR (400 MHz, CD_3OD) δ 7.67 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 9.1 Hz, 2H), 6.40 (d, J = 9.1 Hz, 2H), 5.07 (s, 1H), 4.92 (s, 1H), 4.38 (d, J = 12.7 Hz, 1H), 4.24 (d, J = 12.7 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.65 (s, 3H), 3.49 (d, J = 15.6 Hz, 1H), 2.82 (dd, J = 15.6, 1.3 Hz, 1H), 0.99 (t, J = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.3, 152.1, 145.6, 142.9, 140.0, 128.8 (q,

J = 31.8 Hz), 128.0, 125.7 (q, *J* = 269.5 Hz), 124.3 (q, *J* = 3.8 Hz), 114.8, 113.9, 105.8, 73.2, 61.1, 55.5, 54.6, 50.2, 12.9. ^{19}F NMR (376 MHz, CD_3OD) δ -63.89. IR (film): 3040, 2910, 1670, 1630, 1450, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}F_3NO_3$ 406.1625; Found 406.1621.

Ethyl 1-(4-Methoxyphenyl)-4-methylene-2-(4-nitrophenyl)pyrrolidine-2-carboxylate (3ag): R_f = 0.2 (EA : PE = 1 : 5), yellow solid, yield: 72 mg, 94%. ^{1}H NMR (400 MHz, CD_3OD) δ 8.19 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 9.1 Hz, 2H), 6.42 (d, *J* = 9.1 Hz, 2H), 5.11 (s, 1H), 4.96 (s, 1H), 4.43 (d, *J* = 12.7 Hz, 1H), 4.28 (d, *J* = 12.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 3.54 (d, *J* = 15.6 Hz, 1H), 2.86 (d, *J* = 15.7 Hz, 1H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 174.5, 153.7, 150.2, 148.4, 144.1, 141.3, 130.1, 123.9, 116.2, 115.4, 107.4, 74.6, 62.6, 56.9, 56.0, 51.4, 14.3. IR (film): 3044, 2915, 1676, 1637, 1458, 1189, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}N_2O_5$ 383.1601; Found 383.1599.

Ethyl 2-(4-Fluorophenyl)-1-(4-methoxyphenyl)-4-methylenepyrrolidine-2-carboxylate (3ah): R_f = 0.4 (EA : PE = 1 : 10), pale yellow oil, yield: 52 mg, 73%. ^{1}H NMR (400 MHz, CD_3OD) δ 7.47 (dd, *J* = 8.8, 5.5 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 2H), 6.40 (d, *J* = 9.1 Hz, 2H), 5.05 (s, 1H), 4.91 (s, 1H), 4.34 (d, *J* = 12.8 Hz, 1H), 4.21 (d, *J* = 12.8 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.66 (s, 3H), 3.43 (d, *J* = 15.5 Hz, 1H), 2.80 (d, *J* = 15.5 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.7, 161.8 (d, *J* = 243.1 Hz), 151.9, 143.2, 140.2, 136.9 (d, *J* = 3.2 Hz), 129.2 (d, *J* =7.9 Hz), 114.8, 114.0 (d, *J* = 21.5 Hz), 113.7, 105.6, 73.0, 60.9, 55.4, 54.6, 50.5, 12.9. ^{19}F NMR (376 MHz, CD_3OD) δ -118.22. IR (film): 3049, 2918, 1677, 1636, 1455, 1184, 1043, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}FNO_3$ 356.1656; Found 356.1655.

Ethyl 2-(4-Bromophenyl)-1-(4-methoxyphenyl)-4-methylenepyrrolidine-2-carboxylate (3ai): R_f = 0.3 (EA : PE = 1 : 10), pale yellow oil, yield: 71 mg, 85%. ^{1}H NMR (400 MHz, CD_3CD) δ 7.43-7.35 (m, 4H), 6.67 (d, *J* = 9.1 Hz, 2H), 6.39 (d, *J* = 9.1 Hz, 2H), 5.05 (s, 1H), 4.91 (s, 1H), 4.35 (d, *J* = 12.8 Hz, 1H), 4.21 (d, *J* = 12.9 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.65 (s, 3H), 3.43 (d, *J* = 15.6 Hz, 1H), 2.79 (dd, *J* = 15.6, 1.2 Hz, 1H), 0.99 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101

MHz, CD_3OD) δ 173.5, 152.0, 143.0, 140.4, 140.1, 130.4, 129.3, 120.5, 114.8, 113.8, 105.7, 73.0, 61.0, 5.4, 54.6, 50.3, 12.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}BrNO_3$ 416.0856; Found 416.0850.

Ethyl 1-(4-Methoxyphenyl)-4-methylene-2-(thiophen-2-yl)pyrrolidine-2-carboxylate (3aj): R_f = 0.2 (EA : PE = 1 : 10), pale yellow oil, yield: 66 mg, 95%. ^1H NMR (400 MHz, CD_3OD) *δ* 7.24 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.89 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.66 (d, *J* = 9.1 Hz, 2H), 6.43 (d, *J* = 9.1 Hz, 2H), 5.09 (s, 1H), 4.95 (s, 1H), 4.37 (d, *J* = 12.9 Hz, 1H), 4.17 (d, *J* = 12.8 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.64 (s, 3H), 3.28 (d, *J* = 14.9 Hz, 1H), 2.92 (dd, *J* = 15.7, 1.3 Hz, 1H), 1.04 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.5, 152.0, 146.0, 142.8, 140.1, 125.9, 124.9, 124.9, 114.8, 113.6, 106.1, 71.0, 61.2, 55.4, 54.6, 51.4, 12.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_3S$ 344.1315; Found 344.1311.

Ethyl 1-(4-Methoxyphenyl)-4-methylene-2-(naphthalen-1-yl)pyrrolidine-2-carboxylate (3ak): R_f = 0.3 (EA : PE = 1 : 10), white solid, yield: 65 mg, 83%. ^1H NMR (400 MHz, d_6-DMSO) *δ* 7.99 – 7.94 (m, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.75 – 7.70 (m, 1H), 7.54 – 7.49 (m, 2H), 7.45 (d, *J* = 6.9 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 5.06 (s, 1H), 4.87 (s, 1H), 4.26 (s, 2H), 4.04 – 3.89 (m, 3H), 3.63 (s, 3H), 3.04 (d, *J* = 15.7 Hz, 1H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C {H} NMR (101 MHz, d_6-DMSO) δ 172.2, 152.2, 143.6, 140.1, 136.7, 134.6, 130.8, 129.3, 129.1, 127.7, 126.6, 125.8, 125.5, 125.0, 116.1, 114.3, 107.3, 75.2, 62.9, 61.4, 55.5, 48.5, 14.2. IR (film): 3042, 2915, 1678, 1633, 1456, 1189, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{26}NO_3$ 388.1907; Found 388.1904.

(*E*)-Ethyl-1-(4-methoxyphenyl)-4-methylene-2-styrylpyrrolidine-2-carboxylate (3al): R_f = 0.5 (EA : PE = 1 : 10), pale yellow oil, yield: 59 mg, 81%. ^1H NMR (400 MHz, CD_3OD) *δ* 7.30 (d, *J* = 7.2 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.1 Hz, 1H), 6.88 (d, *J* = 16.1 Hz, 1H), 6.74 (d, *J* = 9.1 Hz, 2H), 6.51 (d, *J* = 9.1 Hz, 2H), 6.38 (d, *J* = 16.1 Hz, 1H), 5.10 (s, 1H), 4.99 (s, 1H), 4.30 (d, *J* = 12.1 Hz, 1H), 4.21 (d, *J* = 13.0 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.67 (s, 3H), 3.14 (d, *J* = 15.4 Hz, 1H), 2.83 (dd, *J* = 15.5, 1.5 Hz, 1H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 174.8, 151.8, 142.9, 140.1, 136.8, 129.5, 128.3, 128.2, 127.2, 126.1, 114.5, 113.9,

106.1, 71.1, 61.0, 55.6, 54.6, 12.9. IR (film): 3023, 2952, 1680, 1633, 1462, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}NO_3$ 364.1907; Found 364.1904.

Diethyl 1-(4-Methoxyphenyl)-4-methylenepyrrolidine-2,2-dicarboxylate (3am): R_f = 0.3 (EA : PE = 1 : 5), pale yellow oil, yield: 58 mg, 86%. ^1H NMR (400 MHz, *d*$_6$-DMSO) δ 6.78 (d, J = 9.0 Hz, 2H), 6.60 (d, J = 9.1 Hz, 2H), 5.07 (dt, J = 8.0, 2.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 4H), 4.05 (d, J = 1.8 Hz, 2H), 3.67 (s, 3H), 3.19 (t, J = 1.8 Hz, 2H), 1.11 (t, J = 7.1 Hz, 6H). ^{13}C {H} NMR (101 MHz, *d*$_6$-DMSO) δ 169.9, 160.7, 152.4, 142.4, 139.8, 115.9, 114.3, 107.5, 73.9, 61.8, 61.5, 55.6, 55.2, 44.4, 14.6, 14.2. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{24}NO_5$ 334.1649; Found 334.1651.

Ethyl 1-(4-Methoxyphenyl)-4-methylenepyrrolidine-2-carboxylate (3an): R_f = 0.2 (EA : PE = 1 : 10), pale yellow oil, yield: 27 mg, 51%. ^1H NMR (400 MHz, CD_3OD) *δ* 6.80 (d, *J* = 9.0 Hz, 2H), 6.53 (d, *J* = 9.0 Hz, 2H), 5.08 (s, 1H), 5.05 (s, 1H), 4.49 – 4.41 (m, 1H), 4.09 (qd, *J* = 7.0, 2.3 Hz, 2H), 4.03 (q, *J* = 9.0 Hz, 2H), 3.70 (s, 3H), 3.12 (dd, *J* = 15.8, 9.2 Hz, 1H), 2.68 (d, *J* = 16.1 Hz, 1H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 174.3, 151.9, 144.7, 141.1, 114.4, 112.9, 105.8, 60.7, 60.5, 54.7, 52.8, 36.4, 13.1. IR (film): 3042, 2915, 1674, 1636, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_3$ 262.1438; Found 262.1440.

(1-(4-Methoxyphenyl)-4-methylenepyrrolidin-2-yl)(phenyl)methenone (3ao): R_f = 0.3 (EA : PE = 1 : 10), yellow oil, yield: 31 mg, 54%. ^1H NMR (400 MHz, CD_3OD) δ 8.08 (d, *J* = 7.4 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.47 (d, *J* = 8.7 Hz, 2H), 5.54 (dd, *J* = 9.9, 2.7 Hz, 1H), 5.12 (d, *J* = 2.8 Hz, 1H), 5.02 (t, *J* = 2.2 Hz, 1H), 4.20 – 4.12 (m, 2H), 3.69 (s, 3H), 3.34 (d, *J* = 1.6 Hz, 1H), 2.64 (d, *J* = 15.9 Hz, 1H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 201.1, 151.6, 144.5, 141.2, 134.8, 133.4, 128.6, 128.0, 114.4, 112.8, 106.3, 63.1, 54.7, 53.5, 36.7. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_2$ 294.1489; Found 294.1492.

Ethyl 1-(4-Methoxyphenyl)-4-(methylene-d2)-2-phenylpyrrolidine-2-carboxylate-3,3-d_2 (D_2-3aa): R_f = 0.3 (EA : PE = 1 : 10), yellow oil, yield: 63 mg, 93%. ^1H NMR (400 MHz, CD_3OD) δ 7.51 – 7.45 (m, 2H), 7.32 – 7.21 (m, 3H), 6.71 – 6.65 (m, 2H), 6.47 – 6.40 (m, 2H), 5.06 (dd, *J* =

5.7, 2.0 Hz, 0.4H), 4.93 (d, *J* = 2.2 Hz, 0.4H), 4.38 (d, *J* = 13.2 Hz, 1H), 4.22 (d, *J* = 13.0 Hz, 1H), 4.09 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.68 (s, 3H), 3.50 – 3.43 (m, 0.78H), 2.85 (dd, *J* = 15.6, 1.7 Hz, 0.78H), 1.03 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.8, 151.8, 141.0, 140.4, 129.4, 128.7, 127.4, 127.1, 126.6, 114.9, 113.6, 73.5, 60.8, 55.4, 54.6, 50.5, 12.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{20}D_4NO_3$ 342.2002; Found 342.2004.

Ethyl 4-(Hepta-2,4,6-triyn-1-ylidene-d6)-1,2-diphenylpyrrolidine-2-carboxylate (D_6-3ba): R_f = 0.4 (EA : PE = 1 : 10), yellow oil, yield: 51 mg, 66%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.52 (m, 2H), 7.36 – 7.27 (m, 3H), 6.78 – 6.71 (m, 2H), 6.53 (t, *J* = 9.0 Hz, 2H), 4.70 (dd, *J* = 29.8, 13.5 Hz, 1H), 4.54 – 4.42 (m, 1H), 4.18 – 4.04 (m, 2H), 3.74 (d, *J* = 2.2 Hz, 3H), 3.73 – 3.60 (m, 1H), 3.15 (ddd, *J* = 16.3, 14.2, 2.3 Hz, 1H), 1.03 (dt, *J* = 11.4, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.5, 151.8, 151.7, 141.3, 140.8, 140.5, 140.4, 136.9, 136.3, 136.2, 128.1, 128.0, 127.2, 127.1, 115.6, 115.3, 114.0, 74.1, 72.0, 61.2, 61.1, 58.0, 55.5, 54.3, 52.7, 48.6, 14.1, 14.0. IR (film): 3049, 2918, 1677, 1636, 1455, 1184, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{22}D_6NO_3$ 420.2440; Found 420.2442.

Ethyl (*Z/E*)-4-Benzylidene-1-(4-methoxyphenyl)-2-phenylpyrrolidine-2-carboxylate (3ba): R_f = 0.3 (EA : PE = 1 : 10), orange oil, yield: 58 mg, 70%. The ratio of *Z/E* is 0.64/0.36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.44 – 7.40 (m, 1H), 7.36 – 7.26 (m, 6H), 7.25 – 7.20 (m, 1H), 6.77 – 6.70 (m, 2H), 6.56 – 6.52 (m, 2H), 6.51 (d, *J* = 2.3 Hz, 0.36H), 6.35 (t, *J* = 2.3 Hz, 0.64H), 4.74 (d, *J* = 13.7 Hz, 0.64H), 4.66 (d, *J* = 13.3 Hz, 0.36H), 4.55 – 4.42 (m, 1H), 4.17 – 4.05 (m, 2H), 3.79 – 3.62 (m, 4H), 3.21 – 3.07 (m, 1H), 1.02 (dt, *J* = 11.5, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.4, 151.7, 140.8, 140.4, 137.2, 136.4, 136.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 127.1, 127.0, 126.7, 126.6, 122.0, 121.5, 115.6, 115.3, 114.0, 77.3, 77.0, 76.7, 74.1, 72.0, 61.2, 58.1, 55.5, 54.3, 52.7, 48.6, 14.0. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}NO_3$ 414.2064; Found 414.2068.

(*Z/E*)4-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3cf): R_f = 0.2 (EA : PE = 1 : 5), orange oil, yield: 88 mg, 86%. The ratio of *Z/E*

is 0.5/0.5. ^{1}H NMR (400 MHz, CD_3OD) δ 7.73 (dd, *J* = 8.3, 4.8 Hz, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.76 – 6.69 (m, 2H), 6.55 – 6.47 (m, 2H), 6.45 (s, 0.5H), 6.31 (s, 0.5H), 4.71 (d, *J* = 13.7 Hz, 0.5H), 4.62 (d, *J* = 12.7 Hz, 0.5H), 4.44 (t, *J* = 12.0 Hz, 1H), 4.09 (dt, *J* = 10.8, 7.1 Hz, 2H), 3.80 (d, *J* = 19.0 Hz, 3H), 3.76 – 3.59 (m, 4H), 3.05 (dd, *J* = 16.2, 9.0 Hz, 1H), 0.99 (q, *J* = 7.3 Hz, 3H). ^{13}C {H} NMR (101 MHz, CD_3OD) δ 173.4, 173.2, 158.6, 158.5, 152.2, 152.1, 145.5, 140.1, 140.0, 133.2, 133.0, 129.7, 129.6 (q, *J* = 32.7 Hz), 129.2, 129.1, 128.0 (q, *J* = 267.2 Hz), 127.8, 124.4 (q, *J* = 3.8 Hz), 121.6, 121.2, 115.1, 114.9, 113.9, 113.8, 113.5, 113.4, 73.7, 71.5, 61.2, 61.1, 57.6, 54.6, 54.3, 54.2, 54.0, 52.2, 12.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.45, -62.46. IR (film): 3043, 2912, 1671, 1635, 1457, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}F_3NO_4$ 512.2043; Found 512.2046.

Ethyl (*Z/E*) 4-(4-Nitrobenzylidene)-1,2-diphenylpyrrolidine-2-carboxylate (3da): R_f = 0.4 (EA : PE = 1 : 5), orange oil, yield: 67 mg, 78%. The ratio of *Z/E* is 0.58/0.42. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 9.4, 2.8 Hz, 2H), 7.44 (tt, *J* = 7.9, 1.8 Hz, 3H), 7.41 – 7.28 (m, 5H), 7.28 – 7.19 (m, 2H), 6.61 (s, 0.42H), 6.52 (t, *J* = 9.2 Hz, 2H), 6.44 (t, *J* = 2.2 Hz, 0.58H), 4.75 (dd, *J* = 14.2, 5.9 Hz, 1H), 4.66 – 4.53 (m, 1H), 4.27 – 4.12 (m, 2H), 3.85 (d, *J* = 16.2 Hz, 0.42H), 3.74 (d, *J* = 15.3 Hz, 0.58H), 3.30 – 3.15 (m, 1H), 1.18 – 1.04 (m, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.4, 146.1, 146.0, 140.9, 140.5, 137.1, 136.0, 135.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 127.2, 127.1, 126.9, 126.8, 126.6, 122.3, 121.8, 117.4, 117.3, 114.5, 114.3, 76.7, 73.9, 71.8, 61.4, 61.3, 57.6, 53.77, 52.8, 48.6, 14.0, 13.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd $C_{26}H_{25}N_2O_4$ for 429.1809; Found: 429.1812.

Ethyl (*Z/E*) 1-(4-Methoxyphenyl)-4-propylidene-2-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3ea): R_f = 0.3 (EA : PE = 1 : 10), orange oil, yield: 55 mg, 63%. The ratio of *Z/E* is 0.4/0.6. ^{1}H NMR (400 MHz, $CDCl_3$) ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 (ddd, *J* = 8.1, 3.4, 1.4 Hz, 2H), 7.34 – 7.25 (m, 3H), 6.71 (dd, *J* = 9.2, 2.5 Hz, 2H), 6.46 (dd, *J* = 9.2, 7.1 Hz, 2H), 5.45 (td, *J* = 7.2, 6.2, 3.7 Hz, 0.4H), 5.26 (tt, *J* = 7.2, 2.2 Hz, 0.6H), 4.39 (dd, *J* = 16.8, 12.7 Hz, 1H), 4.24 –

4.15 (m, 1H), 4.15 – 4.07 (m, 2H), 3.73 (d, *J* = 1.7 Hz, 3H), 3.47 – 3.33 (m, 1H), 2.84 (dd, *J* = 19.5, 15.6 Hz, 1H), 2.10 (q, *J* = 7.5 Hz, 1H), 2.05 – 1.91 (m, 1H), 1.11 – 0.91 (m, 6H). ^{13}C {H} NMR (101 MHz, CD_3CD) δ 173.8, 151.5, 151.5, 141.5, 141.1, 140.8, 140.6, 132.8, 132.8, 127.9, 127.3, 127.2, 126.9, 123.5, 123.3, 115.2, 114.0, 73.6, 73.0, 61.1, 56.1, 55.5, 53.0, 50.9, 47.0, 22.7, 22.2, 14.0, 13.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}NO_3$ 366.2064; Found 366.2062.

Ethyl(*Z/E*)

1-(4-Methoxyphenyl)-4-(2-methylpropylidene)-2-(4-(trifluoromethyl)phenyl)pyrolidine-2-carboxylate (3ff): R_f = 0.3 (EA : PE = 1 : 10), orange oil, yield: 83 mg, 92%. The ratio of *Z/E* is 0.5/0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.66 (m, 2H), 7.57 (dd, *J* = 8.4, 4.3 Hz, 2H), 6.73 (dd, *J* = 9.1, 2.5 Hz, 2H), 6.42 (t, *J* = 8.8 Hz, 2H), 5.40 – 5.00 (m, 1H), 4.41 (dd, *J* = 26.9, 14.6 Hz, 1H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.11 (d, *J* = 7.1 Hz, 2H), 3.73 (d, *J* = 1.8 Hz, 3H), 2.81 – 2.76 (m, 1H), 2.34 – 2.25 (m, 1H), 1.00 (dd, *J* = 17.1, 6.6 Hz, 9H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 176.3, 173.5, 151.8, 145.6, 140.2, 132.6, 130.6, 130.5 (q, *J* = 31.9 Hz), 129.7, 129.6, 128.3, 127.7 (q, *J* = 267.2 Hz), 124.8 (q, *J* = 3.8 Hz), 115.2, 115.1, 114.7, 114.7, 114.2, 113.0, 105.1, 73.2, 61.3, 55.5, 53.0, 50.6, 46.7, 28.5, 22.7, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.45, -62.46. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}F_3NO_3$ 448.2094; Found 448.2098.

Ethyl (*Z/E*)-4-(Cyclopropylmethylene)-1,2-diphenylpyrrolidine-2-carboxylate (3ga): R_f = 0.4 (EA : PE = 1 : 20), orange oil, yield: 53 mg, 75%. The ratio of *Z/E* is 0.43/0.57. ^{1}H NMR (400 MHz, CD_3OD) δ 7.49 (ddt, *J* = 11.2, 6.0, 1.4 Hz, 2H), 7.31 – 7.20 (m, 4H), 7.05 (qd, *J* = 7.0, 1.4 Hz, 2H), 6.64 (td, *J* = 7.3, 4.5 Hz, 1H), 6.56 – 6.40 (m, 2H), 4.95 – 4.90 (m, 0.43H), 4.71 (dt, *J* = 9.5, 2.1 Hz, 0.57H), 4.54 (d, *J* = 13.0 Hz, 0.55H), 4.39 – 4.28 (m, 1H), 4.26 – 4.20 (m, 0.5H), 4.10 (td, *J* = 7.2, 1.8 Hz, 2H), 3.57 – 3.51 (m, 0.43H), 3.42 – 3.35 (m, 0.57H), 2.96 (dt, *J* = 15.7, 2.1 Hz, 0.43H), 2.84 (dt, *J* = 15.2, 2.0 Hz, 0.57H), 1.50 – 1.30 (m, 1H), 1.03 (q, *J* = 7.2 Hz, 3H), 0.81 – 0.60 (m, 2H), 0.39 – 0.21 (m, 2H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.9, 173.7, 146.1, 141.0, 140.6, 138.0, 137.9, 137.1, 136.2, 136.1, 128.5, 128.3, 128.2, 128.2, 128.0, 127.9, 127.4, 127.3, 126.9, 126.7, 126.6, 122.2, 121.6, 119.6, 119.5, 112.5, 112.1, 73.8, 71.7, 61.4, 61.3, 57.6, 53.6,

52.9, 48.7, 21.7, 14.0, 13.9. IR (film): 3033, 2952, 1670, 1643, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}NO_2$ 348.1958; Found 348.1962.

Ethyl (*Z/E*)-4-Benzylidene-1,2-diphenylpyrrolidine-2-carboxylate (3ha): R_f = 0.3 (EA : PE = 1 : 20), orange oil, yield: 59 mg, 76%. The ratio of *Z/E* is 0.5/0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.52 (m, 2H), 7.45 – 7.39 (m, 1H), 7.37 – 7.28 (m, 5H), 7.23 (dd, *J* = 7.7, 5.6 Hz, 2H), 7.15 (ddd, *J* = 8.7, 7.3, 1.4 Hz, 2H), 6.74 (td, *J* = 7.2, 4.9 Hz, 1H), 6.60 (s, 0.5H), 6.57 (d, *J* = 8.5 Hz, 2H), 6.39 – 6.33 (m, 0.5H), 4.71 (dd, *J* = 21.2, 13.8 Hz, 1H), 4.54 (dd, *J* = 19.7, 13.4 Hz, 1H), 4.18 – 4.02 (m, 2H), 3.78 (d, *J* = 16.5 Hz, 0.5H), 3.71 – 3.65 (m, 0.5H), 3.25 – 3.12 (m, 1H), 1.02 (dt, *J* = 11.9, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.4, 146.1, 146.0, 140.9, 140.5, 137.1, 136.0, 135.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 127.2, 127.1, 127.0, 126.8, 126.6, 122.3, 121.8, 117.4, 117.3, 114.5, 114.3, 77.3, 77.2, 77.0, 76.9, 76.7, 73.9, 71.8, 61.4, 61.3, 57.6, 53.7, 52.8, 48.6, 14.0, 13.9. IR (film): 3046, 2922, 1674, 1653, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}NO_2$ 384.1958; Found 384.1961.

Ethyl 4-Benzylidene-1-phenyl-2-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3hf): R_f = 0.3 (EA : PE = 1 : 20), orange oil, yield: 76 mg, 84%. The ratio of *Z/E* is 0.5/0.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 11.8, 8.3 Hz, 2H), 7.59 (dd, *J* = 8.6, 1.8 Hz, 2H), 7.43 (dd, *J* = 8.7, 6.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.28 – 7.13 (m, 4H), 6.78 (q, *J* = 7.1 Hz, 1H), 6.59 (t, *J* = 2.2 Hz, 0.5), 6.62 – 6.50 (m, 2H), 6.37 (t, *J* = 2.2 Hz, 0.5), 4.78 – 4.66 (m, 1H), 4.63 – 4.51 (m, 1H), 4.20 – 4.06 (m, 2H), 3.83 – 3.65 (m, 1H), 3.14 (ddt, *J* = 24.1, 15.7, 2.2 Hz, 1H), 1.01 (dt, *J* = 9.9, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.3, 173.2, 145.7, 145.0, 144.7, 136.9, 136.9, 135.3, 135.2, 129.4 (q, *J* = 32.1 Hz), 128.7, 128.6, 128.4, 128.3 (q, *J* = 277.1 Hz), 128.2, 127.8, 127.7, 126.9, 126.8, 125.0 (q, *J* = 1.9 Hz) 122.8, 122.2, 117.9, 117.8, 114.4, 114.1, 73.6, 71.4, 61.6, 61.6, 57.6, 53.7, 52.5, 48.3, 13.9, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.47, -62.49. IR (film): 3046, 2922, 1674, 1653, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{25}NF_3O_2$ 452.1832; Found 452.1834.

Ethyl (*Z/E*)4-Benzylidene-1-(4-nitrophenyl)-2-phenylpyrrolidine-2-carboxylate (3ia): R_f = 0.4 (EA : PE = 1 : 5), orange oil, yield: 65 mg, 76%. The ratio of *Z/E* is 0.58/0.42. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 9.4, 2.8 Hz, 2H), 7.44 (tt, *J* = 7.9, 1.8 Hz, 3H), 7.41 – 7.28 (m, 5H), 7.28 –

7.19 (m, 2H), 6.61 (s, 0.42H), 6.52 (t, *J* = 9.2 Hz, 2H), 6.44 (t, *J* = 2.2 Hz, 0.58H), 4.75 (dd, *J* = 14.2, 5.9 Hz, 1H), 4.66 – 4.53 (m, 1H), 4.27 – 4.12 (m, 2H), 3.85 (d, *J* = 16.2 Hz, 0.42H), 3.74 (d, *J* = 15.3 Hz, 0.58H), 3.30 – 3.15 (m, 1H), 1.18 – 1.04 (m, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.4, 146.1, 146.0, 140.9, 140.5, 137.1, 136.0, 135.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 127.2, 127.1, 127.0, 126.8, 126.6, 122.3, 121.8, 117.4, 117.3, 114.5, 114.3, 76.7, 73.9, 71.8, 61.3, 61.3, 57.6, 53.7, 52.8, 48.6, 14.0, 13.9. IR (film): 3026, 2936, 1671, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_2O_4$ 429.1809; Found 429.1812.

Ethyl (*Z/E*)-4-Benzylidene-2-phenyl-1-(m-tolyl)pyrrolidine-2-carboxylate (3ja): R_f = 0.4 (EA : PE = 1 : 20), orange oil, yield: 60 mg, 75%. The ratio of *Z/E* is 0.5/0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.54 (m, 2H), 7.44 (dd, J = 8.3, 7.1 Hz, 1H), 7.39 – 7.29 (m, 6H), 7.29 – 7.22 (m, 2H), 7.05 – 7.01 (m, 1H), 6.61 – 6.57 (m, 1H), 6.47 (q, *J* = 2.3 Hz, 1H), 6.36 (dt, *J* = 5.0, 2.4 Hz, 1H), 4.71 (ddt, *J* = 17.1, 13.3, 1.9 Hz, 1H), 4.58 (d, J = 14.0 Hz, 0.5H), 4.55 – 4.51 (m, 0.5H), 4.22 – 4.12 (m, 2H), 3.79 (dd, *J* = 16.4, 1.9 Hz, 0.5H), 3.74 – 3.65 (m, 0.5H), 3.26 – 3.20 (m, 0.5H), 3.16 (dt, *J* = 15.7, 2.0 Hz, 0.5H), 2.29 (s, 3H), 1.05 (dt, *J* = 11.6, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.8, 173.6, 146.1, 141.0, 140.6, 138.2, 137.1, 136.2, 136.0, 128.6, 128.4, 128.3, 128.3, 128.3, 128.2, 128.1, 128.0, 127.4, 127.3, 127.1, 127.1, 126.8, 126.6, 122.3, 121.7, 118.4, 118.3, 115.1, 114.7, 112.0, 111.7, 61.3, 61.3, 57.6, 53.7, 52.9, 48.7, 21.9 , 14.0, 13.9. IR (film): 3045, 2916, 1672, 1644, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}NO_2$ 398.2115; Found 398.2118.

Ethyl (Z/E)-4-Benzylidene-1-(3,5-dimethylphenyl)-2-phenylpyrrolidine-2-carbxylate (3ka): R_f = 0.5 (EA : PE = 1 : 20), orange oil, yield: 56 mg, 68%. The ratio of *Z/E* is 0.5/0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.51 (m, 2H), 7.44 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.37 – 7.28 (m, 5H), 7.28 – 7.20 (m, 2H), 6.56 (t, *J* = 2.3 Hz, 0.5H), 6.44 (d, *J* = 4.3 Hz, 1H), 6.35 (t, *J* = 2.3 Hz, 0.5H), 6.23 (d, *J* = 4.8 Hz, 2H), 4.69 (dd, *J* = 14.8, 12.9 Hz, 1H), 4.59 (d, *J* = 13.9 Hz, 0.5H), 4.54 (d, *J* = 14.6 Hz, 0.5H), 4.23 – 4.10 (m, 2H), 3.78 (dd, *J* = 16.5, 2.1 Hz, 0.5H), 3.69 (dd, *J* = 15.5, 1.8 Hz, 0.5H), 3.23 (dt, *J* = 16.4, 2.3 Hz, 0.5H), 3.15 (dt, *J* = 15.5, 1.9 Hz, 0.5H), 2.22 (d, *J* = 1.9 Hz, 6H), 1.07 (dt, *J* = 11.4, 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.9, 173.7, 146.1, 141.1, 140.6,

138.0, 137.9, 137.1, 136.2, 136.1 128.5, 128.4, 128.3, 128.2, 127.9, 127.9, 127.4, 127.3, 126.9, 126.7, 126.6, 122.2, 121.6, 119.5, 119.5, 112.5, 112.1, 77.3, 77.0, 76.7, 73.8, 71.7, 61.3, 61.3, 57.6, 53.6, 52.9, 48.7, 21.7, 14.0, 13.9. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}NO_2$ 412.2271; Found 412.2274.

Ethyl (*Z/E*)-4-Benzylidene-1-(3-bromophenyl)-2-phenylpyrrolidine-2-carboxylate (3la): R_f = 0.3 (EA : PE = 1 : 20), orange oil, yield: 56 mg, 61%. The ratio of *Z/E* is 0.5/0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.47 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.25 (m, 6H), 7.24 – 7.20 (m, 1H), 7.09 – 6.75 (m, 3H), 6.56 (d, *J* = 2.2 Hz, 0.5H), 6.38 (q, *J* = 2.5 Hz, 1.5H), 4.73 – 4.60 (m, 1H), 4.56 – 4.43 (m, 1H), 4.24 – 4.08 (m, 2H), 3.84 – 3.75 (m, 0.5H), 3.73 – 3.65 (m, 0.5H), 3.21 (dd, *J* = 16.4, 2.5 Hz, 0.5H), 3.15 (dd, J = 15.5, 2.2 Hz, 0.5H), 1.14 – 1.01 (m, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.1, 172.9, 147.2, 147.1, 147.0, 140.2, 139.7, 136.9, 136.8, 135.2, 135.1, 134.9, 129.7, 129.6, 129.5, 128.6, 128.4, 128.3, 128.2, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.3, 122.9, 122.8, 122.7, 122.5, 122.4, 120.3, 120.2, 117.0, 116.7, 114.1, 113.9, 113.5, 113.2, 77.3, 77.0, 76.7, 74.1, 72.0, 61.6, 61.6, 57.4, 53.4, 52.9, 48.7, 14.1, 14.0. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}BrNO_2$ 462.1063; Found 462.1065.

Ethyl (*Z/E*)-4-Benzylidene-1-(4-methoxyphenyl)-2-phenylpyrrolidine-2-carboxylate (3ma): R_f = 0.5 (EA : PE = 1 : 5), orange oil, yield: 30 mg, 34%. The ratio of *Z/E* is 0.63/0.37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 8.3, 1.4 Hz, 0.5H), 7.70 – 7.63 (m, 2H), 7.59 – 7.46 (m, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.27 – 7.20 (m, 4.5H), 7.09 (td, *J* = 8.0, 1.6 Hz, 1H), 6.55 (t, *J* = 2.3 Hz, 0.63H), 6.45 (dd, *J* = 13.1, 8.0 Hz, 1H), 6.35 (t, *J* = 2.2 Hz, 0.37H), 5.70 (dd, *J* = 14.9, 2.3 Hz, 0.63H), 5.04 (d, *J* = 15.7 Hz, 0.37H), 4.95 (dt, *J* = 15.0, 2.2 Hz, 0.63H), 4.19 – 4.10 (m, 2H), 3.71 (d, *J* = 16.1 Hz, 0.63H), 3.57 (d, *J* = 15.1 Hz, 0.38H), 3.27 (t, *J* = 16.1 Hz, 1H), 1.06 – 0.97 (m, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.5, 151.7, 140.8, 140.4, 137.2, 136.4, 136.3, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.3, 127.2, 127.1, 127.0, 126.7, 126.6, 122.0, 121.5, 115.6, 115.3, 114.0, 77.3, 77.2, 77.0, 76.7, 74.1, 72.0, 61.2, 61.2, 58.1, 55.5, 54.3, 52.7, 48.6, 14.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{25}SN_2O_2$ 441.1631; Found 441.1634.

Ethyl 1-Benzyl-4-benzylidene-2-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3nf): R_f = 0.3 (EA : PE = 1: 4), orange oil, yield: 60 mg, 65%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (q, *J* = 8.4 Hz, 4H), 7.32 – 7.26 (m, 4H), 7.20 (dd, *J* = 7.6, 5.3 Hz, 3H), 7.13 – 7.08 (m, 2H), 6.18 (t, *J* = 2.4 Hz, 1H), 4.39 – 4.12 (m, 6H), 3.89 (s, 2H), 2.39 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 172.9, 142.4, 136.9, 136.9, 134.8, 134.8, 134.6, 131.0, 130.4 (q, *J* = 32.2 Hz), 129.1, 128.9, 128.5, 127.1, 126.9, 126.4, 125.5, 125.5, 125.4 (q, *J* = 3.8 Hz), 125.3, 124.0 (q, *J* = 270.3 Hz), 120.8, 72.4, 63.0, 62.8, 62.7, 62.4, 21.1, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.45, -62.46. IR (film): 3045, 2914, 1678, 1645, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{29}F_3NO_2$ 480.2145; Found 480.2148.

Ethyl 1-(4-Methoxyphenyl)-4-(3-phenylallylidene)pyrrolidine-2-carboxylate (3on): R_f = 0.5 (EA : PE = 1: 10), orange oil, yield: 46 mg (86% purity), 54%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.4 Hz, 2H), 7.35 (td, *J* = 7.6, 3.6 Hz, 2H), 7.29 – 7.24 (m, 1H), 6.89 (dt, *J* = 6.4, 3.2 Hz, 2H), 6.86 – 6.79 (m, 1H), 6.67 – 6.57 (m, 2H), 6.53 (dd, *J* = 15.5, 8.6 Hz, 1H), 6.29 (d, *J* = 11.4 Hz, 0.5H), 6.21 (d, *J* = 11.1 Hz, 0.5H), 4.56 (dd, *J* = 9.2, 2.4 Hz, 0.5H), 4.50 (dd, *J* = 8.9, 2.1 Hz, 0.5H), 4.26 (d, *J* = 7.1 Hz, 2H), 4.20 – 4.10 (m, 2H), 3.78 (d, *J* = 4.3 Hz, 3H), 3.31 – 3.17 (m, 1H), 3.03 (d, *J* = 16.9 Hz, 0.5H), 2.83 (d, *J* = 16.8 Hz, 0.5H), 1.19 (dd, *J* = 7.1, 3.3 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.9, 151.9, 141.0, 138.4, 137.4, 131.5, 128.6, 127.5, 127.4, 126.3, 126.2, 125.3, 122.1, 115.0, 114.9, 113.4, 113.3, 60.8, 60.3, 55.7, 51.3, 37.3, 14.2. IR (film): 3031, 2915, 1676, 1641, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{26}NO_3$ 364.1907; Found 364.1911.

Methyl 1-(4-Methoxyphenyl)-2-phenyl-4-(3-phenylallylidene)pyrrolidine-2-carboxylate (3ob): R_f = 0.5 (EA : PE = 1: 10), orange oil, yield: 77 mg, 91%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, *d*$_6$-DMSO) δ 7.55 (d, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 13.5, 7.6 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.38 – 7.22 (m, 6H), 7.09 (dd, *J* = 15.6, 11.1 Hz, 0.5H), 6.93 (dd, *J* = 15.6, 11.0 Hz, 0.5H), 6.77 – 6.67 (m, 2H), 6.56 – 6.46 (m, 2H), 6.45 – 6.37 (m, 1H), 6.27 (d, *J* = 11.1 Hz, 0.5H), 6.09 (d, *J* = 11.1 Hz, 0.5H), 4.71 (d, *J* = 14.9 Hz, 0.5H), 4.53 (d, *J* = 14.7 Hz, 0.5H), 4.31 (dd, *J* = 32.5, 14.8 Hz, 1H), 3.75 (d, *J* = 17.1 Hz, 0.5H), 3.63 (d, *J* = 5.5 Hz, 3H), 3.58 (d, *J* = 5.5 Hz, 3H), 3.55 (d, *J* = 11.4 Hz, 0.5H), 3.07 (d, *J* = 17.2 Hz, 0.5 H), 2.94 (d, *J* = 16.7 Hz, 0.5H). ^{13}C {H} NMR

(101 MHz, d_6-DMSO) δ 174.0, 173.9, 151.7, 151.6, 141.3, 141.0, 140.4, 140.3, 137.9, 137.8, 137.6, 137.5, 131.6, 131.5, 129.1, 129.0, 128.3, 127.8, 127.8, 127.6, 127.4, 126.84, 126.78, 126.2, 126.1, 121.7, 115.4, 115.3, 114.5, 114.4, 73.4, 72.9, 56.6, 55.7, 55.6, 55.3, 53.8, 52.8, 52.7, 51.3, 47.9 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{28}NO_3$ 426.2064; Found 426.2067.

Ethyl 2-(3-Methyl-4-(3-(2-methylpropylidene)azetidin-1-yl)phenyl)-2-(4-(trifluoromethyl)phenyl)acetate (4pf): R_f = 0.3 (EA : PE = 1: 10), orange oil, yield: 55 mg, 64%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.06 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.98 (d, *J* = 2.2 Hz, 1H), 6.49 (d, *J* = 8.3 Hz, 1H), 5.17 (dt, *J* = 8.6, 2.3 Hz, 1H), 4.96 (s, 1H), 4.54 (q, *J* = 2.5 Hz, 2H), 4.47 (t, *J* = 2.3 Hz, 2H), 4.23 (qd, *J* = 7.1, 2.8 Hz, 2H), 2.38 – 2.27 (m, 1H), 2.23 (s, 3H), 1.28 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 164.4, 149.8, 131.4, 130.3, 127.6, 127.4 (q, *J* = 32.6 Hz), 127.3, 126.4, 125.4 (q, *J* = 3.9 Hz), 125.0, 123.4, 121.4 (q, *J* = 270.1 Hz), 119.2, 113.0, 61.4, 61.2, 60.2, 31.5, 28.6, 22.6, 19.5, 14.4, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.50. IR (film): 3043, 2912, 1670, 1633, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{29}F_3NO_2$ 432.2145; Found 432.2148.

Ethyl 2-(1-(4-Methoxyphenyl)-3-oxoazetidin-2-yl)-2-phenylacetate (5qa): R_f = 0.3 (EA : PE = 1: 6), orange oil, yield: 24 mg, 36%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 5H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.31 (d, *J* = 8.9 Hz, 2H), 5.08 (t, *J* = 4.9 Hz, 1H), 4.78 (dd, *J* = 15.5, 4.3 Hz, 1H), 4.35 (d, *J* = 15.5 Hz, 1H), 4.24 – 4.22 (m, 1H), 4.19 (t, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.6, 143.1, 140.9, 140.4, 127.9, 127.3, 127.0, 115.2, 114.1, 61.2, 55.8, 55.6, 50.9, 14.0. IR (film): 3024, 2932, 1679, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_4$ 340.1543; Found 340.1545.

General methods for preparation of products 7. To a schlenk flask $Rh_2(OAc)_4$ (0.9 mg, 2 mol%), DCM (1 mL) were added under N_2 atmosphere. 3-methyleneazetidine (0.1 mmol) dissolved in DCM (0.5 mL) was added dropwise for 2 h. Then, the reaction was evaporated and the residue was purification by column chromatography with petroleum ether and ethyl acetate to give the corresponding products.

Methyl 2-Benzylidene-2,3-dihydrobenzo[3,4]azeto[1,2-a]pyrrole-8b(1H)-carboxylate (7a): R_f = 0.3 (EA : PE = 1: 20), orange oil, yield: 24 mg, 83%. The ratio of *Z/E* is 1/1.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.21 (m, 5H), 6.77 – 6.70 (m, 2H), 6.56 – 6.52 (m, 2H), 6.51 (d, *J* = 2.3 Hz, 0.4H), 6.35 (t, *J* = 2.3 Hz, 0.6H), 4.74 (d, *J* = 13.7 Hz, 0.6H), 4.66 (d, *J* = 13.3 Hz, 0.4H), 4.55 – 4.42 (m, 1H), 3.74 (d, *J* = 2.3 Hz, 3H), 3.65 (dd, *J* = 15.6, 1.7 Hz, 1H), 3.21 – 3.07 (m, 1H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.4, 151.7, 140.8, 140.4, 137.2 136.4, 136.3, 128.5, 128.3, 128.2, 128.1, 128.0, 128.0, 127.3, 127.1, 127.0, 126.7, 126.6, 122.0, 121.5, 115.6, 115.3, 114.0, 77.3, 77.0, 76.7, 74.1, 72.0, 61.2, 58.1, 55.5, 54.3, 52.7, 48.6. IR (film): 3045, 2943, 1668, 1646, 1457, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found 292.1336.

2-Benzylidene-9a-phenyl-1,2,3,9a-tetrahydro-9H-pyrrolo[1,2-a]indol-9-one (7b): R_f = 0.3 (EA : PE = 1: 20), orange oil, yield: 27 mg, 79%. The ratio of *Z/E* is 1/1.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.20 (m, 14H), 6.55 (t, *J* = 2.3 Hz, 0.33H), 6.37 (t, *J* = 2.1 Hz, 0.68H), 4.93 (dd, *J* = 14.2, 5.5 Hz, 1H), 4.55 (d, *J* = 21.6 Hz, 0.33H), 4.50 – 4.44 (m, 0.68H), 4.23 (dq, *J* = 16.0, 2.2 Hz, 0.67H), 4.13 (dd, *J* = 15.3, 2.1 Hz, 0.33H), 3.13 (dd, *J* = 15.9, 1.7 Hz, 0.68H), 2.93 (dt, *J* = 15.1, 1.3 Hz, 0.33H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.6, 173.4, 151.8, 151.7, 141.3, 140.8, 140.5, 140.4, 136.9, 136.2, 136.2, 128.0, 128.0, 127.2, 127.1, 115.6, 115.3, 114.0, 76.6, 72.0, 61.2, 61.1, 58.0, 48.6. IR (film): 3034, 2962, 1689, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO$ 338.1539; Found 338.1542.

2-Benzylidene-3a-phenyl-1,2,3,3a-tetrahydro-4H-benzo[b]pyrrolo[1,2-d][1,4]oxazin-4-one (7c): R_f = 0.3 (EA : PE = 1: 20), orange oil, yield: 27 mg, 75%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.47 (m, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.25 (m, 6H), 7.24 – 7.20 (m, 1H), 7.14 – 6.93 (m, 1H), 6.94 – 6.86 (m, 1H), 6.84 – 6.75 (m, 1H), 6.56 (d, *J* = 2.2 Hz, 0.5H), 6.38 (q, *J* = 2.5 Hz, 1.5H), 4.73 – 4.60 (m, 1H), 4.61 – 4.41 (m, 1H), 3.84 – 3.75 (m, 0.5H), 3.73 – 3.65 (m, 0.5H), 3.21 (dd, *J* = 16.4, 2.5 Hz, 0.5H), 3.15 (dd, *J* = 15.5, 2.2 Hz, 0.5H). ^{13}C {H}NMR (101 MHz, $CDCl_3$) δ 173.3, 173.1, 145.6, 136.8, 136.8, 135.2, 135.1, 128.7, 128.5, 128.4, 128.2, 128.2, 127.8, 127.7, 126.9, 126.8, 125.1, 125.0, 124.9, 124.9, 122.8, 122.2, 117.9, 117.8, 114.4, 114.1, 73.6, 71.4, 57.6, 53.7, 52.5, 48.3. IR (film): 3035, 2937, 1679, 1635, 1452,

1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}NO_2$ 354.1489; Found 354.1491.

2-Benzylidene-3a-phenyl-1,2,3,3a-tetrahydro-4H,6H-benzo[e]pyrrolo[2,1-c][1,4]oxazepin-4-one (7d): R_f = 0.3 (EA : PE = 1: 20), orange oil, yield: 30 mg, 81%. The ratio of *Z/E* is 1/1.5. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.24 (m, 7H), 7.21 (qd, *J* = 5.6, 5.2, 2.3 Hz, 4H), 6.98 – 6.87 (m, 2H), 6.77 (q, *J* = 7.3 Hz, 1H), 6.55 (t, *J* = 2.4 Hz, 0.6H), 6.37 (t, *J* = 2.1 Hz, 0.4H), 4.93 (dd, *J* = 14.2, 5.5 Hz, 1H), 4.67 – 4.54 (m, 2H), 4.50 (dd, *J* = 14.2, 7.4 Hz, 1H), 4.23 (dq, *J* = 16.0, 2.2 Hz, 0.6H), 4.13 (dq, *J* = 15.1, 2.0 Hz, 0.4H), 3.13 (dd, *J* = 15.9, 1.7 Hz, 0.6H), 2.93 (dd, *J* = 15.2, 1.3 Hz, 0.4H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 170.2, 170.2, 144.6, 144.5, 143.3, 143.2, 136.8, 136.7, 133.3, 133.2, 130.4, 130.3, 130.0, 129.9, 129.6, 129.5, 128.4, 128.3, 128.3, 128.2, 127.9, 126.9, 126.8, 123.4, 123.3, 123.2, 122.9, 119.2, 119.0, 117.8, 117.7, 114.7, 114.5, 75.6, 73.4, 69.9, 69.8, 58.3, 54.4, 51.6, 47.1. IR (film): 3025, 2934, 1679, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{22}NO_2$ 368.1645; Found 368.1648.

2-Benzylidene-3a-phenyl-1,2,3,3a-tetrahydro-4H,6H-benzo[e]pyrrolo[2,1-c][1,4]oxazepin-4-one (7e): R_f = 0.3 (EA : PE = 1: 20), orange oil, yield: 23 mg, 61%. The ratio of *Z/E* is 1/1.2. ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 7.7, 2.3 Hz, 2H), 7.41 – 7.18 (m, 12H), 6.48 (t, *J* = 2.4 Hz, 0.57H), 6.43 (t, *J* = 2.3 Hz, 0.43H), 4.79 (ddd, *J* = 32.4, 10.5, 6.2 Hz, 1H), 4.68 – 4.47 (m, 1H), 4.44 – 4.29 (m, 1H), 4.28 – 4.06 (m, 1H), 4.01 (d, *J* = 17.5 Hz, 0.43H), 3.90 (d, *J* = 16.4 Hz, 0.57H), 3.23 (tdd, *J* = 14.0, 12.0, 6.4 Hz, 1H), 3.15 – 2.99 (m, 1H), 2.79 (ddd, *J* = 48.9, 14.3, 4.1 Hz, 1H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.7, 173.5, 146.0, 146.0, 141.0, 140.5, 138.2, 137.1, 136.1, 136.0, 128.5, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 128.0, 127.4, 127.2, 127.0, 127.0, 126.8, 126.6, 122.3, 121.7, 118.4, 118.3, 115.1, 114.7, 112.0, 111.7, 77.0, 76.7, 73.9, 71.7, 61.3, 61.3, 57.6, 53.7, 52.9, 48.7. IR (film): 3044, 2938, 1693, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}NO_2$ 382.1802; Found 382.1806.

(6-(3-((3R, 5R, 7R)-Adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)methyl-1-(4-methoxyphenyl)-4-methylene-2-phenylpyrrolidine-2-carboxylate (3ap): The method of synthesis **3ap** as follows. R_f = 0.3 (EA : PE = 1: 5), orange solid, yield: 59 mg, 86%. ^1H NMR (400 MHz, DMSO-d_6) δ 8.10 (s,

1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 2.0 Hz, 2H), 7.61 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.54 (d, *J* = 2.3 Hz, 2H), 7.44 (dd, *J* = 7.6, 1.7 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.72 – 6.63 (m, 2H), 6.45 – 6.33 (m, 2H), 5.31 – 5.15 (m, 2H), 5.05 (s, 1H), 4.95 (s, 1H), 4.38 (d, *J* = 13.4 Hz, 1H), 4.17 (s, 1H), 3.87 (s, 3H), 3.60 (s, 3H), 3.52 (d, *J* = 15.7 Hz, 1H), 2.85 (d, *J* = 15.8 Hz, 1H), 2.18 – 2.05 (m, 9H), 1.79 – 1.74 (m, 6H). ^{13}C {H} NMR (101 MHz, DMSO-d_6) δ 173.4, 158.7, 151.7, 143.3, 141.1, 140.3, 138.6, 138.4, 133.3, 132.3, 131.8, 128.7, 128.5, 128.3, 127.6, 127.5, 126.4, 126.2, 125.9, 125.8, 125.3, 124.5, 115.2, 114.5, 113.2, 107.2, 73.5, 67.1, 55.9, 55.8, 55.6, 51.0, 37.0, 37.0, 28.8. IR (film): 3027, 2935, 1679, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{47}H_{48}NO_4$ 690.3578; Found 690.3582.

To a two-necked flask Adapalene (412 mg, 1 mmol) and THF (10 mL) were added under N_2 atmosphere. $LiAlH_4$ (76 mg, 2 mmol) was added slowly at room temperature, then the mixture was stilled stirred at room temperature overninght. the reaction was quenched by water (2 mL) and then extracted with dickhloromethene, dried over Na_2SO_4 and evaporated to give the crude product **S1** (6-(3-((3R, 5R, 7r)-Adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)methenol (394 mg, 99%).

To a two-necked flask **S1** (394 mg, 0.99 mmol) and NEt_3 (0.4 mL, 2.97 mmol), DCM (10 mL) were added under N_2 atmosphere. BnCOCl (183 mg, 1.19 mmol) was added dropwise at 0 ^{o}C, then warmed to room temperature and stirred for 18 h. the reaction was quenched with $NaHCO_3$ (5%) and then extracted with dichloromethene, dried over Na_2SO_4 and evaporated The residue was purification by column chromatography with petroleum ether and ethyl acetate to give the product **S2** (6-(3-((3R, 5R, 7R)-adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)methyl 2-phenylacetate (428 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 1H), 7.87 (dd, *J* = 12.2, 8.5 Hz, 2H), 7.79 – 7.74 (m, 2H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.44 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.37 – 7.32 (m, 5H), 7.02 (d, *J* = 8.4 Hz, 1H), 5.33 (s, 2H), 3.93 (s, 3H), 3.74 (s, 2H), 2.22 (d, *J* = 2.9 Hz, 6H), 2.13 (s, 3H), 1.84 (d, *J* = 3.0 Hz, 6H).

To a two-necked flask **S2** (428 mg, 0.83 mmol) and *p*-ABSA (240 mg, 1 mmol), THF (10 mL) were added under N_2 atmosphere. DBU (198 mg, 1.3 mmol) was added dropwise at 0 ^{o}C, then

warmed to room temperature and stirred for 15 h. the reaction was quenched with water and then extracted with dichloromethene, dried over Na_2SO_4 and evaporated The residue was purification by column chromatography with petroleum ether and ethyl acetate to give the product **S3** (6-(3-((3R, 5R, 7R)-Adamantan-1-yl)-4-methoxyphenyl)naphthalen-2-yl)methyl-2-diazo-2-phenylacetate (288 mg, 64%).

To a schlenk flask **1a** (26 mg, 0.15 mmol) and $Rh_2(OAc)_4$ (0.9 mg, 0.002 mmol), DCM (1 mL) were added under N_2 atmosphere. **S3** (54 mg, 0.1 mmol) dissolved in DCM (1 mL) was added dropwise over 2 hours at room temperature, then still stirred for 2 h. the reaction was evaporated and the residue was purification by column chromatography with petroleum ether and ethyl acetate to give the corresponding product **3ap.**

Ethyl (*Z/E*)-4-Benzylidene-1-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-2-yl)-2-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (3sa): R_f = 0.5 (EA : PE = 1: 5), pale yellow oil, yield: 91 mg, 72%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (ddd, *J* = 12.1, 8.3, 3.4 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.43 (dd, *J* = 8.6, 6.7 Hz, 1H), 7.37 – 7.16 (m, 4H), 7.04 (t, *J* = 8.2 Hz, 1H), 6.56 (t, *J* = 2.2 Hz, 1H), 6.40 – 6.21 (m, 2H), 4.75 – 4.61 (m, 1H), 4.55 (d, *J* = 14.4 Hz, 1H), 4.22 – 4.08 (m, 2H), 3.70 (dd, *J* = 33.5, 16.1 Hz, 1H), 3.11 (dd, *J* = 21.4, 16.1 Hz, 1H), 2.89 – 2.68 (m, 2H), 2.51 (dd, *J* = 18.9, 8.6 Hz, 1H), 2.34 – 1.92 (m, 6H), 1.61 – 1.41 (m, 6H), 1.12 – 1.02 (m, 3H), 0.92 (d, *J* = 1.5 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.3, 143.6, 136.9, 136.7, 135.5, 135.4, 129.3 (q, *J* = 29.7 Hz), 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 126.9, 126.8 (q, *J* = 290.0 Hz), 125.5, 124.9 (q, *J* = 3.5 Hz), 122.6, 122.1, 114.6, 114.5, 114.3, 114.2, 112.6, 112.5, 112.3, 112.2, 73.6, 71.4, 61.6, 61.5, 57.6, 53.7, 52.6, 50.4, 48.4, 48.0, 43.9, 38.4, 35.8, 31.6, 29.8, 29.7, 26.6, 25.7, 21.5, 14.1, 14.0, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.48, -62.50. IR (film): 3014, 2932, 1675, 1632, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{39}H_{41}F_3NO_3$ 628.3033; Found 628.3035.

Benzyl (2S,5R)-1'-(4-Methoxyphenyl)-3,3-dimethyl-4'-methylene-7-oxo-4-thia-1-azaspiro[bicyclo[3.2.0]Heptane-6,2'-pyrrolidine]-2-carboxylate (3aq): R_f = 0.5 (EA : PE = 1: 5), yellow oil, yield: 46 mg, 47%. ^{1}H NMR (400 MHz, Acetone-D_6) δ 7.50 – 7.34 (m, 5H), 7.00 (d, *J* = 9.1 Hz, 2H), 6.81 (d, *J* = 9.1 Hz, 2H), 5.50 (s, 1H), 5.26 (d, *J* = 12.2 Hz, 1H), 5.16 (d, *J* = 12.3 Hz, 1H), 5.09 (d, *J* = 2.2 Hz, 2H), 4.53 (s, 1H), 4.07 – 4.01 (m, 1H), 4.01 – 3.94 (m, 1H), 3.73 (s, 3H), 3.51 – 3.43 (m, 1H), 2.97 – 2.88 (m, 1H), 1.56 (s, 3H), 1.42 (s, 3H). ^{13}C {H} NMR (101 MHz, Acetone) δ 173.9, 167.1, 153.6, 142.3, 138.7, 135.5, 128.5, 128.4, 118.4, 116.8, 114.4, 106.4, 82.0, 72.5, 67.1, 66.8, 63.3, 54.8, 54.5, 38.6, 32.4, 25.1. IR (film): 3028, 2936, 1679, 1676, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{28}N_2O_4SNa$ 487.1662; Found 487.1664.

Methyl 1-(4-Methoxyphenyl)-4-methyl-2-phenylpyrrolidine-2-carboxylate (8aa): To a two-necked flask **3aa** (68 mg, 0.2 mmol) and Pd/C (2 mg, 0.02 mmol), MeOH (2 mL) were added under H_2 atmosphere. The reaction was stirred at room temperature overninght. The mixture was evaporated and the residue was purificated by column chromatography to give **8aa** (62 mg, 91%). R_f = 0.5 (EA : PE = 1 : 10), yellow oil, yield: 91%. The ratio of *Z/E* is 1/1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.43 – 7.22 (m, 4H), 6.73 (dd, *J* = 20.7, 9.1 Hz, 2H), 6.46 – 6.37 (m, 2H), 3.81 (t, *J* = 8.1 Hz, 0.5H), 3.75 (s, 1.5H), 3.72 (d, *J* = 2.4 Hz, 3H), 3.57 (s, 1.5H), 3.43 (t, *J* = 8.0 Hz, 0.5H), 3.29 (dd, *J* = 10.2, 8.3 Hz, 0.5H), 2.97 (dd, *J* = 12.6, 6.6 Hz, 0.5H), 2.60 (dt, *J* = 9.8, 6.9 Hz, 0.5H), 2.52 – 2.43 (m, 0.5H), 2.39 (dd, *J* = 11.5, 5.9 Hz, 0.5H), 2.31 (ddd, *J* = 12.5, 6.2, 3.9 Hz, 0.5H), 1.94 (dd, *J* = 12.6, 9.8 Hz, 0.5H), 1.13 (dd, *J* = 11.3, 6.5 Hz, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 175.1, 174.8, 151.3, 151.0, 141.4, 141.1, 140.7, 140.4, 128.2, 128.0, 127.5, 127.1, 126.9, 126.8, 114.8, 114.4, 114.0, 113.6, 77.3, 77.1, 76.7, 58.4, 57.3, 55.7, 55.6, 53.1, 52.4, 52.3, 52.2, 31.1, 30.6, 18.3, 16.3. IR (film): 3035, 2917, 1679, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{24}NO_3$ 326.1751; Found 326.1753.

Methyl 1,1-Difluoro-5-(4-methoxyphenyl)-6-phenyl-5-azaspiro[2.4]heptane-6-carBoxylate (9aa): To a two-necked flask **3aa** (68 mg, 0.2 mmol) and NaI (10 mg, 0.07 mmol), THF (2 mL) were added under N_2 atmosphere. $TMSCF_3$ (100 mg, 0.7 mmol) was added at room temperature,

then the mixture was stirred at 65 °C with oil bath over night. The mixture was evaporated and the residue was purificated by column chromatography to give **9aa** (53 mg, 72%). R_f = 0.4 (EA : PE = 1 : 10), pale yellow oil, yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.33 (dt, *J* = 19.8, 6.7 Hz, 3H), 6.77 – 6.70 (m, 2H), 6.48 – 6.39 (m, 2H), 3.85 (d, *J* = 8.9 Hz, 1H), 3.78 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.97 (dd, *J* = 12.6, 4.8 Hz, 1H), 2.41 (d, *J* = 12.5 Hz, 1H), 1.49 (ddd, *J* = 11.8, 8.3, 5.6 Hz, 1H), 1.41 – 1.35 (m, 1H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 173.8, 151.8, 139.8, 139.7, 128.0, 127.3, 114.6, 114.2, 115.3 (t, *J* = 286.7 Hz), 112.5, 74.2, 55.5, 52.7, 46.8, 29.7, 28.6 (q, *J* = 9.9 Hz), 18.2 (t, *J* = 10.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -138.02, -138.43, -138.58, -138.99. IR (film): 30133, 2912, 1679, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{22}F_2NO_3$ 374.1562; Found 374.1550.

(1-(4-Methoxyphenyl)-4-methylene-2-phenylpyrrolidin-2-yl)methenol (10aa): To a round bottom of **3aa** (68 mg, 0.2 mmol) and THF (5 mL), $LiAlH_4$ (8 mg, 0.4 mmol) were added at room temperature, then the mixture was stirred at rt overninght. The mixture was evaporated and the residue was purificated by column chromatography to give **10aa** (45 mg, 76%). R_f = 0.5 (EA : PE = 1 : 4), pale yellow oil, yield: 76%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 7.1 Hz, 1H), 7.22 – 7.16 (m, 2H), 6.79 – 6.69 (m, 2H), 6.49 (d, *J* = 9.1 Hz, 2H), 5.09 (q, *J* = 2.1 Hz, 1H), 4.94 (q, *J* = 2.1 Hz, 1H), 4.54 (d, *J* = 11.4 Hz, 1H), 4.46 (dt, *J* = 12.9, 2.0 Hz, 1H), 4.18 (ddt, *J* = 11.3, 3.3, 1.6 Hz, 2H), 3.73 (s, 3H), 3.44 (dt, *J* = 15.2, 2.3 Hz, 1H), 2.61 (dt, *J* = 15.3, 1.6 Hz, 1H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 151.6, 144.4, 143.5, 139.0, 128.7, 126.8, 125.4, 115.3, 114.5, 106.4, 70.4, 63.5, 57.1, 55.6, 47.5. IR (film): 3018, 2937, 1675, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_2$ 296.1645; Found 296.1645.

5-(4-Methoxyphenyl)-1-methyl-4-phenyl-2-oxa-5-azabicyclo[2.2.1]heptane (11aa): To a round bottom of **3aa** (68 mg, 0.2 mmol) and THF (5 mL), $LiAlH_4$ (8 mg, 0.4 mmol) were added at room temperature, then the mixture was stirred at rt overnight. The mixture was evaporated, then added into $CDCl_3$ (0.5 mL) and stirred at rt for 2 h. The mixture was evaporated and the residue was purificated by column chromatography to give **11aa** (49 mg, 83%). R_f = 0.5 (EA : PE = 1 : 4) ,

pale yellow oil, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.28 (m, 5H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.64 (d, *J* = 9.0 Hz, 2H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.95 (d, *J* = 12.0 Hz, 1H), 3.76 (s, 3H), 3.66 (d, *J* = 9.3 Hz, 1H), 3.57 (dd, *J* = 9.5, 2.1 Hz, 1H), 2.90 (d, *J* = 13.1 Hz, 1H), 2.21 (dd, *J* = 13.1, 2.1 Hz, 1H), 1.46 (s, 3H). ^{13}C {H} NMR (101 MHz, $CDCl_3$) δ 152.2, 145.1, 139.3, 129.0, 127.1, 125.9, 115.4, 114.7, 75.8, 71.3, 65.1, 63.7, 55.6, 53.5, 24.3. IR (film): 3015, 2926, 1675, 1635, 1452, 1181, 1040, 741, 686 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_2$ 296.1645; Found 296.1645.

Supporting Information

NMR spectra is available free of charge *via* the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* Email: hongjianlu@nju.edu.cn; guigenli@nju.edu.cn

ACKNOWLEDGMENT

We would like to acknowledge the financial support from the National Natural Science Foundation of China (No. 21672100, 21871131) and Robert A. Welch Foundation (D-1361, USA).

REFERENCES

(1) (a) Vagner, J.; Qu, H.; Hruby, V. J. Peptidomimetics, A Synthetic Tool of Drug Discovery. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292 - 296. (b) Cowell, S. M.; Lee, Y. S.; Cain, J. P.; Hruby, V. J. Exploring Ramachandran and Chi Space: Conformationally Constrained Amino Acids and Peptides in the Design of Bioactive Polypeptide Ligands. *Curr. Med. Chem.* **2004**, *11*, 2785 - 2798. (c) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. Control of Peptide Conformation by the Thorpe-Ingold Effect (C^{α}-tetrasubstitution). *Biopolymers* (Pept. Sci.) **2001**, *60*, 396 - 419.

(2) (a) Reiersen, H.; Rees, A. R. The Hunchback and its Neighbours: Proline as an Environmental Modulator. *Trends Biochem. Sci.* **2001**, *26*, 679 - 684. (b) Vanhoof, G.; Goossens, F.; De Meester, I.; Hendriks, D.; Scharpé, S. Structure-Activity Studes of Analogues of Blomhotin Mediation Contraction of Rat Fundus. *FASEB J.* **1995**, *9*, 736 - 744. (c) MacArthur, M. W.; Thornton, J. M. Influence of Proline Residues on Protein Conformation. *J. Mol. Biol.* **1991**, *218*, 397 - 412.

(3) Gray, D. O.; Fowden, L. 4-Methyleneproline : A New Naturally Occurring Proline Derivative. *Nature* **1962**, *193*, 1285 - 1286.

(4) (a) Hodgson, D. M.; Hachisu, S.; Andrews, M. D. Synthesis of α-Kainic Acid from a 7-Azabicyclo[2.2.1]heptadiene by Tandem Radical Addition−Homoallylic Radical Rearrangement. *Org. Lett.* **2005**, *7*, 815 - 817. (b) Pandey, S. K.; Orellana, A.; Greene, A. E.; Poisson, J.-F. High-Pressure Diels−Alder Approach to Natural Kainic Acid. *Org. Lett.* **2006**, *8*, 5665 - 5668. (c) Trost, B. M.; Kaneko, T.; Andersen, N. G.; Tappertzhofen, C.; Fahr, B. Total Synthesis of Aeruginosin 98B. *J. Am. Chem. Soc.* **2012**, *134*, 18944 - 18947. (d) Loosli, S.; Foletti, C.; Papmeyer, M.; Wennemers, H. Synthesis of 4-(Arylmethyl)proline Derivatives. *Synlett* **2019**, *30*, 508 - 510.

(5) (a) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G. Angiotensin-Converting Enzyme Inhibitors. Mercaptan, Carboxyalkyl Dipeptide, and Phosphinic Acid Inhibitors Incorporating 4-Substituted Prolines. *J. Med. Chem.* **1988**, *31*, 1148 - 1160. (b) Pandey, A. K.; Naduthambi, D.; Thomas, K. M.; Zondlo, N. J. Proline Editing: A General and Practical Approach to the Synthesis of Functionally and Structurally Diverse Peptides. Analysis of Steric versus Stereoelectronic Effects of 4-Substituted Prolines on Conformation within Peptides. *J. Am. Chem. Soc.* **2013**, *135*, 4333 - 4363. (c) Jiraskova, P.; Gazak, R.; Kamenik, Z.; Steiningerova, L.; Najmanova, L.; Kadlcik, S.; Novotna, J.; Kuzma, M.; Janata, J. New Concept of the Biosynthesis of 4-Alkyl-L-Proline Precursors of Lincomycin, Hormaomycin, and Pyrrolobenzodiazepines: Could a γ-Glutamyltransferase Cleave the C–C Bond?. *Front. Microbiol.* **2016**, *7*, 276 - 277.

(6) (a) Manfré, F.; Kern, J.-M.; Biellmann, J.-F. Syntheses of Proline Analogs as Potential Mechanism-Based Inhibitors of Proline Dehydrogenase: 4-Methylene-*L*-, (*E*)- and

(*Z*)-4-(fluoromethylene)-*L*-, *cis*- and trans-5-ethynyl-(+-)-, and *cis*- and *trans*-5-vinyl-*L*-proline. *J. Org. Chem.* **1992**, *57*, 2060 - 2065. (b) Littler, B. J.; Aizenberg, M.; Ambhaikar, N. B.; Blythe, T. A.; Curran, T. T.; Dvornikovs, V.; Jung, Y. C.; Jurkauskas, V.; Lee, E. C.; Looker, A. R.; Luong, H.; Martinot, T. A.; Miller, D. B.; Neubert-Langille, B. J.; Otten, P. A.; Rose, P. J.; Ruggiero, P. L. Development of a Manufacturing Process for an HCV Protease Inhibitor Candidate Molecule. *Org. Process Res. Dev.* **2015**, *19*, 270 - 283.

(7) (a) Brummond, K. M.; Curran, D. P.; Mitasev, B.; Fischer, S. Heterocyclic α-Alkylidene Cyclopentenones Obtained via a Pauson−Khand Reaction of Amino Acid Derived Allenynes. A Scope and Limitation Study Directed toward the Preparation of a Tricyclic Pyrrole Library. *J. Org. Chem.* **2005**, *70*, 1745 - 1753. (b) Tiwari, S. K.; Gais, H.-J.; Lindenmaier, A.; Babu, G. S.; Raabe, G.; Reddy, L. R.; Köhler, F.; Günter, M.; Koep, S.; Iska, V. B. R. Functionalized Chiral Vinyl Aminosulfoxonium Salts: Asymmetric Synthesis and Application to the Synthesis of Enantiopure Unsaturated Prolines, β,γ-Dehydro Amino Acids, and Cyclopentanoid Keto Aminosulfoxonium Ylides. *J. Am. Chem. Soc.* **2006**, *128*, 7360 - 7373. (c) Lu, J.-M.; Shi, M. Lewis Acid Catalyzed Reaction of Arylvinylidenecyclopropanes with Ethyl (Arylimino)acetates: A Facile Synthetic Protocol for Pyrrolidine and 1,2,3,4-Tetrahydroquinoline Derivatives. *Org. Lett.* **2007**, *9*, 1805 - 1808. (d) Ranatunga, S.; Kim, J. S.; Pal, U.; Del Valle, J. R. An Ester Enolate–Claisen Rearrangement Route to Substituted 4-Alkylideneprolines. Studies toward a Definitive Structural Revision of Lucentamycin A. *J. Org. Chem.* **2011**, *76*, 8962 - 8976.

(8) (a) Burgstahler, A. W.; Trollope, M. L.; Aiman, C. E. Synthesis of 4-Methylene-*DL*-proline: a Naturally Occurring Racemic Amino-acid. *Nature* **1964**, *202*, 388. (b) MazÓn, A.; Náijera, C. Asymmetric Synthesis of Cyclic α-Amino Acids (−)-Baikiain and (−)-4-Methyleneproline from (*S*)-Boc-BMI. *Tetrahedron: Asymmetry*, **1997**, *8*, 1855 - 1859.

(9) (a) Goldschmidt, Z.; Crammer, B. Vinylcyclopropane Rearrangements. *Chem. Soc. Rev.* **1988**, *17*, 229. (b) Baldwin, J. E. Thermal Rearrangements of Vinylcyclopropanes to Cyclopentenes. *Chem. Rev.* **2003**, *103*, 1197 -1212.

(10) (a) Yang, S.; Shi, M. Recent Advances in Transition-Metal-Catalyzed/Mediated Transformations of Vinylidenecyclopropanes. *Acc. Chem. Res.* **2018**, *51*, 1667 - 1680. (b) Brandi,

A.; Cicchi, S.; Cordero, F. M.; Goti, A. Progress in the Synthesis and Transformations of Alkylidenecyclopropanes and Alkylidenecyclobutanes. *Chem. Rev.* **2014**, *114*, 7317 - 7420.

(11) Ohno, H. Synthesis and Applications of Vinylaziridines and Ethynylaziridines. *Chem. Rev.* **2014**, *114*, 7784-7814.

(12) (a) L'abbé, G. Heterocyclic Analogues of Methylenecyclopropanes. *Angew. Chem. Int. Ed.* **1980**, *19*, 276. (b) Shipman, M. Methyleneaziridines: Unusual Vehicles for Organic Synthesis. *Synlett.* **2006**, *15,* 3205 - 3217. (c) Adams, C. S.; Weatherly, C. D.; Burke, E. G.; Schomaker, J. M. The Conversion of Allenes to Strained Three-Membered Heterocycles. *Chem. Soc. Rev.* **2014,** *43*, 3136 - 3163.

(13) For selected reviews in C−N bond cleavages: (a) Ouyang, K.; Hao, W.; Zhang, W. -X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C–N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045 - 12090. (b) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-Metal Catalysed C–N Bond Activation. *Chem. Soc. Rev.* **2016**, *45*, 1257 - 1270.

(14) (a) Couty, F.; David, O. R. P.; *In Synthesis of 4- to 7-membered Heterocycles by Ring Expansion*, Vol. *1* (Eds.: M. DQhooghe, H.-J. Ha), *Springer, Cham*, 2016, pp 1-47. (b) Ghorai, M. K.; Bhattacharyya, A.; Das, S.; Chauhan, N.; *In Synthesis of 4- to 7-membered Heterocycles by Ring Expansion*, Vol. *1* (Eds.: M. DQhooghe, H.-J. Ha), *Springer, Cham*, 2016, pp 49-142. (c) Dolfen, J.; Yadav, N. N.; Kimpe, N. D.; D'Hooghe, M.; Ha, H.-J. Bicyclic Aziridinium Ions in Azaheterocyclic Chemistry-Preparation and Synthetic Application of 1-Azoniabicyclo[n.1.0]alkanes. *Adv. Synth. Catal.* **2016**, *358*, 3485 - 3511.

(15) (a) Schmid, S. C.; Guzei, I. A.; Schomaker, J. M. A Stereoselective [3+1] Ring Expansion for the Synthesis of Highly Substituted Methylene Azetidines. *Angew. Chem. Int. Ed.* **2017**, *56,* 12229 - 12233. (b) Schmid, S. C.; Guzei, I. A.; Fernandez, I.; Schomaker, J. M. Ring Expansion of Bicyclic Methyleneaziridines *via* Concerted, Near-Barrierless [2,3]-Stevens Rearrangements of Aziridinium Ylides. *ACS Catal.* **2018**, *8*, 7907 - 7914.

(16) (a) Alan, P.; Marchand, D. R.; Simon, G. B. Reactions of 1-Ethyl-3-azabicyclo[1.1.0]butane with Electrophiles. A facile Entry into New, *N*-Substituted 3-Ethylideneazetidines and 2-Azetines. *J. Org. Chem.* **1994**, *59,* 1608. (b) Fantauzzi, S.; Gallo, E.; Caselli, A.; Piangiolino, C.; Ragaini, F.;

Re, N.; Cenini, S. Rearrangement of *N*-Aryl-2-Vinylaziridines to Benzoazepines and Dihydropyrroles: A Synthetic and Theoretical Study. *Chem–. Eur. J.* **2009**, *15*, 1241 - 1251. (c) Music, A.; Baumann, A. N.; Eisold, M.; Didier, D. Regiodivergent Stereoselective Access to Fused Alkylideneazetidines. *J. Org. Chem.* **2018**, *83*, 783 - 792.

(17) (a) Marc, V. A.; Serge, C. M. A Convenient Method for the Preparation of 3-Azetidinylidene Acetic Acid. *Chem. Lett.* **1999**, *28,* 605 - 606. (b) Crepin, D.; Dawick, J.; Aissa, C. Combined Rhodium-Catalyzed Carbon–Hydrogen Activation and β-Carbon Elimination to access Eight-Membered Rings. *Angew. Chem. Int. Ed.* **2010**, *49,* 620 - 623. (c) Stanković, S.; D'hooghe, M.; Vanderhaegen, T.; Tehrani, K. A.; Kimpe, N. D. Concise Synthesis of 3-(Aminomethyl)pyrrolizidines via an $In(OTf)_3$-Mediated Ring Rearrangement of 2-[2-(1-Pyrrolin-2-yl)-alkyl]aziridines. *Synlett.* **2014**, 25, 75 - 77.

(18) Metal-catalyzed intermolecular [4+1] reaction of azetidine for the syntheis of pyrrolidines has been reported, however, substrate scope was limited and harsh reaction conditions such as high temperature, high catalyst loading, slowly dropping of diazo compounds and long reaction time employed, see: (a) Vanecko, J. A.; West, F. G. Ring Expansion of Azetidinium Ylides: Rapid Access to the Pyrrolizidine Alkaloids Turneforcidine and Platynecine. *Org. Lett.* **2005**, *7,* 2949 - 2952. (b) Bott, T. M.; Vanecko, J. A.; West, F. G. One-Carbon Ring Expansion of Azetidines via Ammonium Ylide [1,2]-Shifts: A Simple Route to Substituted Pyrrolidines. *J. Org. Chem.* **2009**, *74,* 2832 - 2836. Only one example of intramolecular [4+1] reaction for achieving a bicyclic pyrrolidine, see ref. 18a.

(19) Cai, W.-S.; Wang, S.; Jalani, H. B.; Wu, J.-X.; Lu, H.-J.; Li, G.-G. Oxidative Cascade Reaction of N-Aryl-3-alkylideneazetidines and Carboxylic Acids: Access to Fused Pyridines. *Org. Lett.* **2018**, *20,* 3833 - 3837.

(20) (a) Xia, Y.; Qiu, D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.* **2017**, *117*, 13810 - 13889. (b) Bach, R.; Harthong, S.; Lacour, J. *Comprehensive Organic Synthesis III;* P. Knochel, G. A. Molander, *Elsevier Science*, York, **2014**, 992. (c) Davies, M. L.; Denton, J. R. Application of Donor/Acceptor-Carbenoids to the Synthesis of Natural Products. *Chem. Soc. Rev.* **2009**, *38,* 3061 - 3071. (d) Doyle, M. P.; McKervey, M. A.;

Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*, Wiley-Interscience, New York, **1998**.

(21) Nicolle, S. M.; Li, W.; Hayes, C. J.; Moody, C. J. Stereoselective Synthesis of Highly Substituted Tetrahydrofurans through Diverted Carbene O–H Insertion Reaction. *Angew. Chem., Int. Ed.* **2015**, *54,* 8485 - 8489.

(22) Marichev, K. O.; Ramey, J. T.; Arman, H.; Doyle, M. P. Highly Regio-, Diastereo-, and Enantioselective Rhodium-Catalyzed Intramolecular Cyclopropanation of (*Z*)–1,3-Dienyl Aryldiazoacetates. *Org. Lett.* **2017**, *19*, 1306 - 1309.

(23) Fu, L.; Wang, H.; Davies, H. M. Role of Ortho-Substituents on Rhodium-Catalyzed Asymmetric Synthesis of *β*-Lactones by Intramolecular C–H Insertions of Aryldiazoacetates. *Org. Lett.* **2014**, *16*, 3036 - 3039.

(24) Zask, A.; Verheijen, J. C.; Richard, D. J.; Kaplan, J.; Curran, K.; Barza, L. T.; Lucas, J.; Hollander, I.; Yu, K. Discovery of 2-Ureidophenyltriazines Bearing Bridged Morpholines as Potent and Selective ATP-competitive mTOR Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2644 - 2647.

(25) (a) Hu, M.-Y.; He, Z.-B.; Gao, B.; Li, L.-C.; Ni, C.-F.; Hu, J.-b. Copper-Catalyzed *gem*-Difluoroolefination of Diazo Compounds with $TMSCF_3$ via C–F Bond Cleavage. *J. Am. Chem. Soc.* **2013**, *135*, 17302 - 17305. (b) Doyle, M. P.; Yan, M.; Hu, W.-H.; L. Gronenberg, S. Highly Selective Catalyst-Directed Pathways to Dihydropyrroles from Vinyldiazoacetates and Imines. *J. Am. Chem. Soc.* **2003**, *125*, 4692 - 4693. (c) Schwartz, B. D.; Denton, J. R.; Lian, Y.-J.; Davies, H. M. L.; Williams, C. M. Asymmetric [4 + 3] Cycloadditions between Vinylcarbenoids and Dienes: Application to the Total Synthesis of the Natural Product (−)-5-epi-Vibsanin E. *J. Am. Chem. Soc*. **2009**, *131*, 8329 - 8332. (d) Morton, D.; Dick, A. R.; Ghoshc, D. H.; Davies, M. L. Convenient Method for the Functionalization of the 4- and 6-Positions of the Androgen Skeleton. *Chem. Commun.* **2012**, *48*, 5838 - 5840. (e) Qin, C.-G,; Davies, H. M. L. Silver-Catalyzed Vinylogous Fluorination of Vinyl Diazoacetates. *Org. Lett.* **2013**, *15*, 6152 - 6154. (f) Bruna, S.; Santos, S. C. C.; Nunes. A. A. C.; Pais. T. M. V.; Pinho, M. Chiral Spiro-*β*-lactams from 6-diazopenicillanates. *Tetrahedron.* **2012***, 68,* 3729-3737. (g) Three-Component Ring-Opening

Reactions of Cyclic Ethers, α-Diazo Esters, and Weak Nucleophiles under Metal-Free Conditions. Lu, L.; Chen, C.-W.; Jiang, H.-F.; Yin, B.-L. *J. Org. Chem.,* **2018**, *83,* 14385 - 14395. (h) Palladium-catalyzed carbenoid based N–H bond insertions: application to the synthesis of chiral α-amino esters. Liu, G.; Li, J.; Qiu, L.; Liu, L.; Xu, G.-Y.; Ma B.; Sun J.-T. *Org. Bio. Chem.,* **2013,** *11*, 5998-6002;