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N-heterocyclic carbene-catalyzed intramolecular aza-Michael addition of alkyl amines to α,β-unsaturated carboxylic acid: Synthesis of pyrrolidines and piperidines

Zhao-Fei Zhang [a, b], Zhong-Hua Gao [a, b], Chun-Lin Zhang [a, **], Song Ye [a, b, *]

[a] Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China
[b] University of Chinese Academy of Sciences, Beijing, 100049, China

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ABSTRACT

N-heterocyclic carbene-catalyzed intramolecular aza-Michael addition of alkyl amines to α,β-unsaturated carboxylic acid has been realized. The corresponding pyrrolidine and piperidine derivatives can be obtained in good to excellent yields. Reaction using chiral NHC catalyst showed promising enantioselectivities up to 55% ee. Further chemical transformations of the products provided carboxylic acids, alcohols, and unprotected amines.

1. Introduction

N-containing heterocycles, especially those containing a C2 acetic acid unit, are privileged structure motifs, and widely present in natural products and pharmaceuticals (Scheme 1) [1]. One of the most direct methods to construct these heterocycles is the intramolecular aza-Michael addition [2]. The intramolecular aza-Michael addition to α,β-unsaturated carbonyl compounds, including aldehydes [3], ketones [4], amides [5] and activated esters [6] have been well developed. However, very few examples of the aza-Michael addition to α,β-unsaturated carboxylic acid are reported [7], due to the weak electrophilicity of the β-carbon atom of α,β-unsaturated carboxylic acid and the formation of inert salts of carboxylic acid in the presence of bases.

In the past decades, N-heterocyclic carbenes (NHCs) emerged as efficient organocatalysts for the synthesis of carbo- and heterocyclic compounds [8]. As an important 1,3-biselectrophile intermediate, the NHC-catalyzed generation of α,β-unsaturated acyl azoliums from enals [9], ynals [10], α-bromoenals [11], α,β-unsaturated acyl fluorides [12], and α,β-unsaturated esters [13] has been well established. In 2014, our group reported the NHC catalyzed [3 + 2] and [3 + 3] cyclocondensation of α,β-unsaturated carboxylic acids with α-amino ketones and imines, affording the corresponding annulation products in good yields with high to excellent enantioselectivities [14]. In 2016, Yao and co-workers reported the NHC-catalyzed enantioselective [3 + 3] annulation of cinnamic acid with 1,3-dicarbonyl compounds [15].

The addition of N-centered nucleophiles to α,β-unsaturated acyl azoliums has attracted much more attention for the past few years. The addition of (hetero)aromatic amine to α,β-unsaturated acyl azoliums has been well established by Hui [16], Chi [17], Biju [18], Du [19], and Wang groups (Scheme 2a) [20]. Furthermore, Wang and co-workers disclosed the NHC-catalyzed [3 + 3] annulations of amidines with α-bromoenals (Scheme 2b) [21]. Recently, Chi and co-workers developed the oxidative NHC-catalyzed enantioselective cascade reactions of α-amino ketones with enals for the synthesis of fused pyrrolidines and β-lactones (Scheme 2c) [22]. The intermolecular NHC-catalyzed addition of alcohols and amines

* Corresponding author. Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, CAS Research/Education Center for Excellence in Molecular Sciences, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, China.
** Corresponding author.
E-mail addresses: zhangchunlin@iccas.ac.cn (C.-L. Zhang), songye@iccas.ac.cn (S. Ye).

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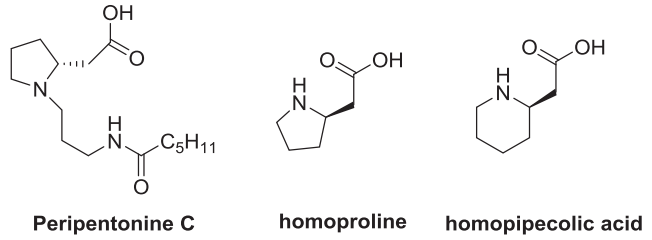
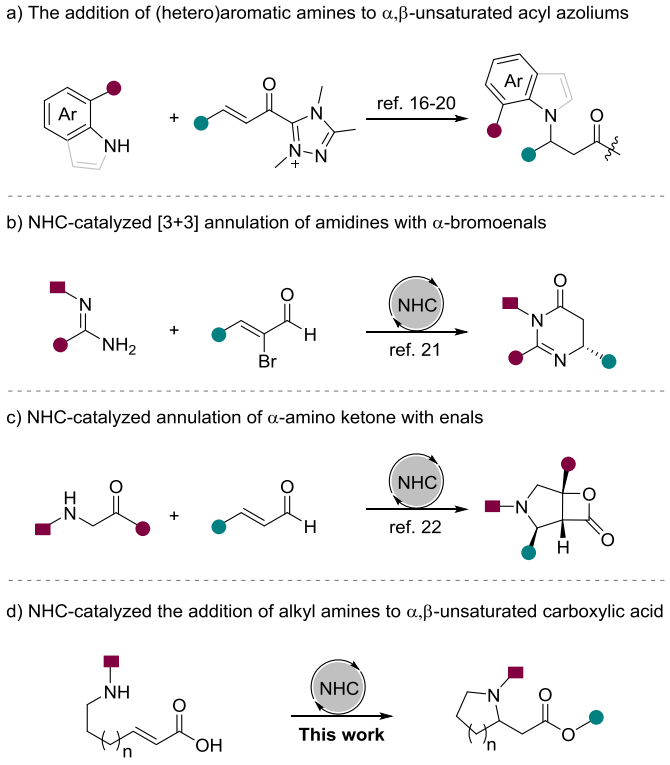


Scheme 1. Selected examples containing a C2 acetic acid unit.



Scheme 2. NHC-catalyzed aza-Michael additions.

to ketones were developed by Scheidt, Zhang et al. [23] To the best of our knowledge, the aza-Michael addition of alkyl amines to α,β-unsaturated acyl azoliums has not been developed. Herein, we report an intramolecular aza-Michael addition of α,β-unsaturated carboxylic acids providing the corresponding N-heterocycles in good to excellent yields (Scheme 2d).

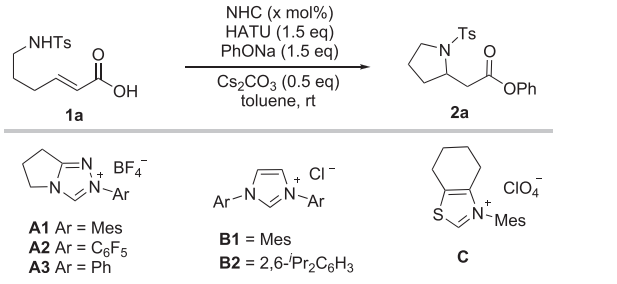
2. Results and discussion

Initially, the model intramolecular aza-Michael addition of 6-amino-α,β-unsaturated carboxylic acid **1a** with 2-(7-aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) as the coupling reagent [24] was investigated under NHC catalysis. We were encouraged to find that the reaction catalyzed by bicyclic *N*-mesityl triazolium NHC precursor **A1** gave the desired pyrrolidine derivative **2a** in 48% yield in the presence of Cs_2CO_3 as the base with sodium phenoxide as the nucleophile (entry 1). The yield was increased when *N*-phenyl or *N*-pentafluorophenyl triazolium NHC precursor **A2** or **A3** was used (entries 2 and 3). The imidazolium *N*-mesityl NHC precursor **B1** performed better than that with *N*-2,6-diisopropylphenyl (**B2**) (entries 4 and 5). The yield dropped when thiazolium NHC precursor **C** was used (entry 6). Using DBU as the base instead of Cs_2CO_3 resulted in low yield (entry 7). Using DCM or THF as the solvent didn't improve the yield (entries 8 and 9). Increasing the loading of Cs_2CO_3 to 1.5 eq led to better yield (entry 10). Reducing the loading of NHC to 10 mol% or 5 mol% resulted in some loss of yield (entries 11 and 12). Interestingly, the reaction without the addition of NHC could give the desired product but in much lower yield (entry 13).

With the optimized conditions in hand, we proceeded to investigate the application of this protocol for the synthesis of other pyrrolidines **2** from 6-amino-α,β-unsaturated carboxylic acids **1** (Table 2). It was found that the substrates bearing N-sulfonyl analogues worked well to give the desired products (**2a**-**2c**) in good to high yields. A variety of aryl esters (**2d-2j)** could be obtained when a series of substituted phenoxides were used for the reaction. The reaction of 6-amino-4-methyl- α,β-unsaturated carboxylic acid gave 2,3-disubstituted pyrolidine **2k** in 81% yield with high diastereoselectivity. Allylic was also tolerated to afford pyrrolidine **2l** in 50% yield with 4:1 dr. The reaction of cyclohexane-derived 6-amino-α,β-unsaturated acid afforded the corresponding spirocyclic products **2m** and **2n** in good yields. Silyl ether was also tolerated to give the desired products **2o** and **2p** in good yields with varied diastereoselectivities depending on the position of the silyl ether. In addition, the reaction of aniline or benzylamine-derived α,β-unsaturated acid afforded the indoline (**2q**) and isoindoline (**2r**) in high yields.

The intramolecular aza-Michael addition was further extended for the synthesis of the piperidine derivatives from 7-amino-α,β-unsaturated carboxylic acids **3** (Table 3). We were happy to find that the piperidinylacetate **4a** was obtained in 82% yield when 7-amino-α,β-unsaturated carboxylic acid was subjected under the same reaction conditions as for 6-amino ones. The 3- and 4-substituted-piperidinylacetate products **4b**-**4d** were isolated in good yields when the proper starting materials were used. In addition, the reaction of aniline benzylamine -derived α,β-unsaturated acid afforded the tetrahydroquinolines (**4e-4g**) and tetrahydroisoquinoline

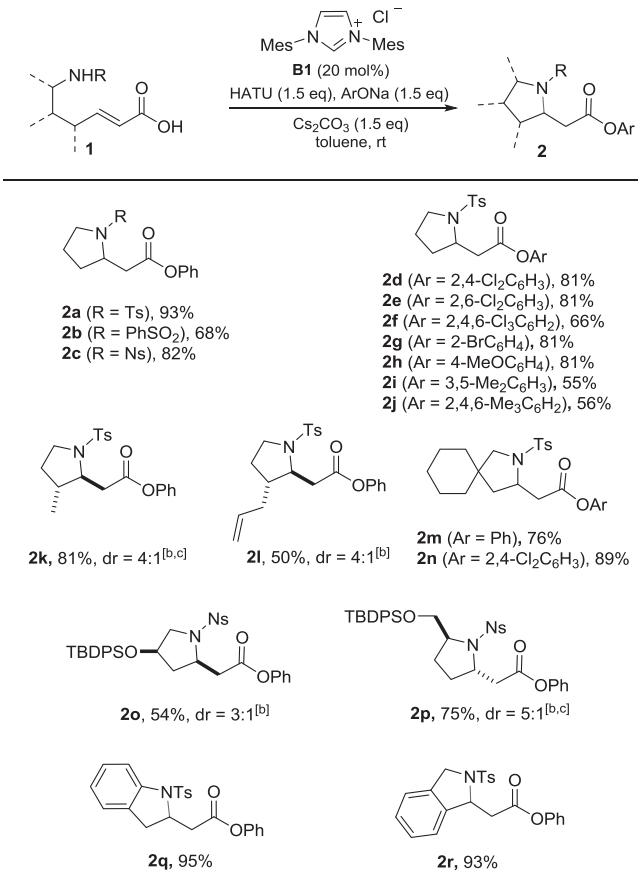
Table 1
Screening of reaction conditions.



entry	NHC	x	base	Solvent	yield[a]
1	**A1**	20	Cs_2CO_3	toluene	48
2	**A2**	20	Cs_2CO_3	toluene	60
3	**A3**	20	Cs_2CO_3	toluene	61
4	**B1**	20	Cs_2CO_3	toluene	78
5	**B2**	20	Cs_2CO_3	toluene	53
6	**C**	20	Cs_2CO_3	toluene	38
7	**B1**	20	DBU	toluene	37
8	**B1**	20	Cs_2CO_3	THF	70
9	**B1**	20	Cs_2CO_3	DCM	42
10	**B1**	20	Cs_2CO_3 [b]	toluene	93
11	**B1**	10	Cs_2CO_3 [b]	toluene	82
12	**B1**	5	Cs_2CO_3 [b]	toluene	79
13	**B1**	0	Cs_2CO_3 [b]	toluene	49

[a] isolated yield.
[b] 1.5 eq Cs_2CO_3 was used. DBU = 1,8-Diazabicyclo-[5.4.0] undec-7-ene.

Table 2
NHC-catalyzed synthesis of pyrrolidines.



[a] NS = 4-$NO_2C_6H_4SO_2$,TBDPSO = *tert*-butyldipropylsilyloxyl. [b] Dr was determined by the ^{1}H NMR spectra. [c] The cis/trans-configurations were assigned by NOESY spectra.

(**4h**) in good to high yields.

The enantioselective reaction catalyzed by chiral NHCs was then briefly investigated. It was found that the reaction of 6-amino-α,β-unsaturated carboxylic acid **1a** using chiral bifunctional triazolium NHC precursor **D,** derived from L-pyroglutamic acid [8h], afforded the desired product (*R*)-**2a** in moderate to good yield with promising enantioselectivity (Scheme 3). The background reaction without the involvement of the NHC catalyst may result in low enantioselectivity (Table 1, entry 13).

Several chemical transformations of the N-heterocycles were carried out (Scheme 4). Pyrolidinylacetate **2a** could be reduced with $LiAlH_4$ to give the corresponding alcohol **5** in 91% yield (reaction a). Hydrolysis of esters (**2a** and **4h**) afforded the corresponding acids (**6** [25] and **7**) in high yields (reaction b and c). The *N*-tosyl group of the tetrahydroquinoline **4h** could be removed under reductive condition to give corresponding product (**8**) in 71% yield (reaction d).

A plausible catalytic cycle of the NHC-catalyzed aza-Michael addition is depicted in Fig. 1. The addition of NHC to ester **1a'**, which is generated in situ from the carboxylic acid, gives the corresponding NHC-bounded LUMO-activation adduct **I**. Then the intramolecular aza-Michael addition of adduct **I** under basic condition furnishes pyrolidine to give intermediate **II**. The substitution of phenyloxide at the acyl imidazolium **II** affords the final product **2a** and regenerates the NHC catalyst.

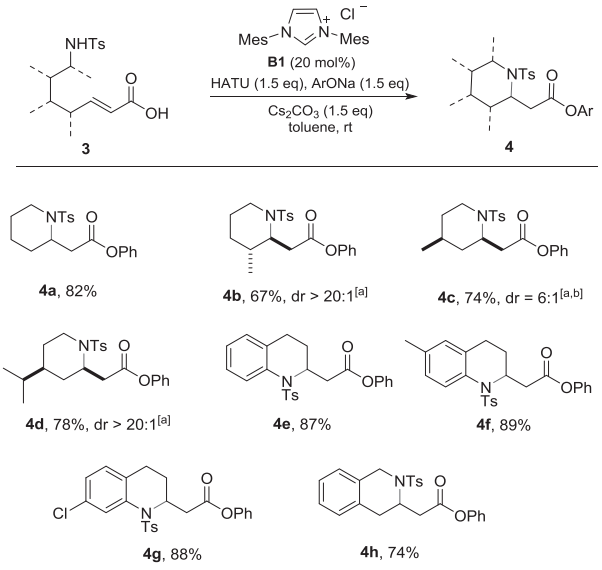
3. Conclusion

In conclusion, the NHC-catalyzed intramolecular aza-Michael addition of amino-tethered α,β-unsaturated carboxylic acid was developed. The corresponding pyrrolidine and piperidine derivatives were obtained in good to excellent yields with good to high diastereoselectivities. Reaction using chiral NHC catalyst showed promising enantioselectivities.

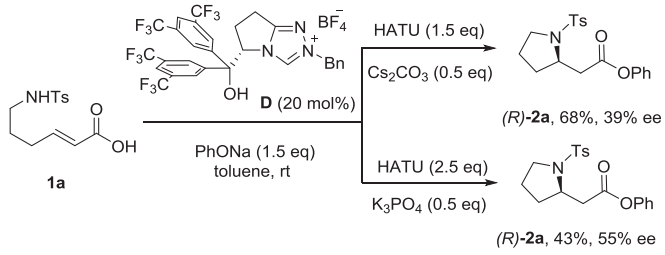
4. Experimental section

Unless otherwise indicated, all reactions were carried out under N_2 atmosphere at room temperature with magnetic stirring. Anhydrous THF and toluene were distilled from sodium and benzophenone. Anhydrous CH_2Cl_2 was distilled from CaH_2. α,β-unsaturated carboxylic acids [7c,26] and sodium phenoxide [27] were prepared according to literatures. Column chromatography was performed on silica gel 200–300 mesh. All ^{1}H NMR (400 and 500 MHz), ^{13}C NMR (100 and 125 MHz) spectra were recorded on a Bruker Avance 400 and Bruker Avance 500 spectrometer in $CDCl_3$, with tetramethylsilane as an internal standard and reported in parts per million (ppm, δ). ^{1}H NMR Spectroscopy splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). Infrared spectra

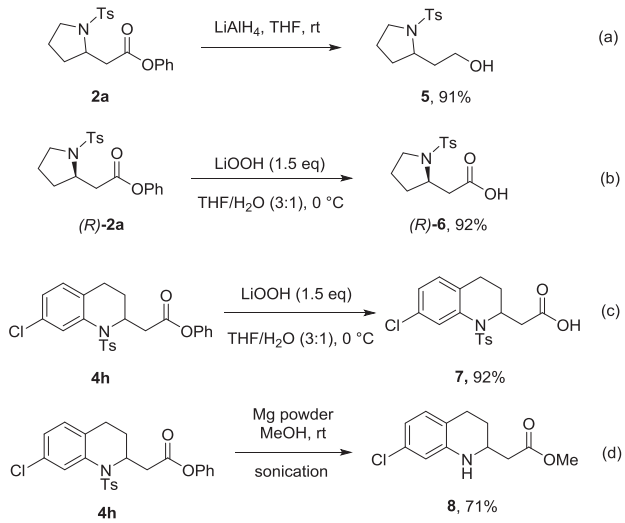
Table 3
NHC-catalyzed Synthesis of piperidines.



[a] Dr was determined by the ^{1}H NMR spectra. [b] The cis-configuration was assigned by its NOESY spectrum.



Scheme 3. Reaction catalyzed by chiral pre-NHC catalyst.



Scheme 4. Chemical transformations.

were recorded on a JASCO FT/IR-480 spectrophotometer and reported as wave number (cm^{-1}). Optical rotations were measured

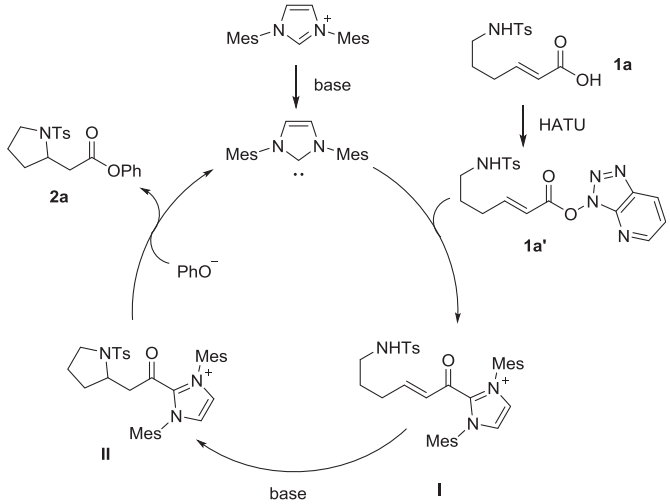


Fig. 1. Plausible catalytic cycle.

on Perkin Elmer/Model-343 digital polarimeter operating at the sodium D line with a 100 mm path cell, and are reported as follows: $[\alpha]^T{}_D$ (concentration (g/100 mL), solvent).

4.1. General procedure of NHC-catalyzed reaction of Aza-Michael addition of α,β-unsaturated carboxylic acid

An oven-dried 50 mL Schlenk tube was charged with unsaturated carboxylic acid (0.20 mmol), NHC precursor **A** (14.0 mg, 0.05 mmol), Cs_2CO_3 (97.6 mg, 0.30 mmol), HATU (114 mg, 0.30 mmol) and PhONa (34.8 mg, 0.30 mmol), then freshly distilled toluene (2.0 mL) was added to this mixture. The reaction mixture was stirred at room temperature until the full consumption of the carboxylic acid (typically, 12–24 h). The reaction mixture was concentrated under reduced pressure and the residue was purified

by column chromatography on silica gel (petroleum ether/EtOAc as the eluent, typically 4:1 to 6:1) to furnish the corresponding products **2** or 4.

*4.1.1. Phenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2a**)*

66.8 mg, 93% yield; White solid, m.p. = 91–92 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 4.10–4.01 (m, 1H), 3.54–3.44 (m, 1H), 3.33 (dd, J = 16.4, 4.0 Hz, 1H), 3.23–3.13 (m, 1H), 2.77 (dd, J = 16.4, 9.5 Hz, 1H), 2.43 (s, 3H), 1.91–1.81 (m, 2H), 1.77 (dt, J = 15.8, 7.9 Hz, 1H), 1.60–1.50 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 150.5, 143.6, 134.0, 129.8, 129.4, 129.2, 127.6, 125.9, 121.6, 56.4, 49.3, 41.4, 31.8, 23.8, 21.6. IR (KBr) 1770, 1473, 1349, 1164, 669; HRMS (ESI) calcd for $C_{19}H_{21}NNaSO_4$ $[M+Na]^+$: 382.1084, found 382.1080.

*4.1.2. Phenyl 2-(1-(phenylsulfonyl)pyrrolidin-2-yl)acetate (**2b**)*

47.1 mg, 68% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91–7.87 (m, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 7.38 (q, J = 7.6 Hz, 2H), 7.24 (t, J = 7.5 Hz, 1H), 7.14–7.08 (m, 2H), 4.08 (m, 1H), 3.56–3.47 (m, 1H), 3.34 (dd, J = 16.4, 4.1 Hz, 1H), 3.19 (dt, J = 10.2, 7.2 Hz, 1H), 2.78 (dd, J = 16.4, 9.4 Hz, 1H), 1.92–1.82 (m, 2H), 1.82–1.74 (m, 2H), 1.60–1.51 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 150.4, 137.0, 132.8, 129.4, 129.2, 127.6, 125.9, 121.6, 77.2, 77.0, 76.8, 56.5, 49.3, 41.4, 31.9, 23.8. IR (KBr) 1752, 1492, 1163, 1092, 691; HRMS (ESI) calcd for $C_{18}H_{19}NNaSO_4$ $[M+Na]^+$: 368.0927, found 368.0923.

*4.1.3. Phenyl 2-(1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl) acetate (**2c**)*

63.7 mg, 82% yield; White solid, m.p. = 113–114 °C, R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 8.8 Hz, 2H), 8.11–8.04 (m, 2H), 7.40 (dd, J = 10.8, 5.0 Hz, 2H), 7.27–7.22 (m, 1H), 7.13–7.08 (m, 2H), 4.10 (m, 1H), 3.62–3.52 (m, 1H), 3.30 (dd, J = 16.4, 4.3 Hz, 1H), 3.21 (dt, J = 10.1, 7.2 Hz, 1H), 2.81 (dd, J = 16.4, 8.8 Hz, 1H), 1.93 (m, 2H), 1.88–1.80 (m, 1H), 1.69–1.59 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 150.4, 142.9, 129.5, 128.8, 126.1, 124.4, 121.5, 56.8, 49.4, 41.1, 32.0, 23.9. IR (KBr) 1754, 1531, 1351, 1164, 737; HRMS (ESI) calcd for $C_{18}H_{18}N_2NaSO_6$ $[M+Na]^+$: 413.0775, found 413.0775.

*4.1.4. 2,4-dichlorophenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2d**)*

69.4 mg, 81% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.27 (m, 1H), 7.15 (d, J = 8.7 Hz, 1H), 4.06 (m, 1H), 3.56–3.44 (m, 1H), 3.38 (dd, J = 16.3, 4.1 Hz, 1H), 3.17 (m, 1H), 2.81 (dd, J = 16.3, 9.4 Hz, 1H), 2.44 (s, 3H), 1.91–1.82 (m, 2H), 1.82–1.73 (m, 1H), 1.60–1.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 145.5, 143.7, 133.9, 132.0, 130.0, 129.8, 128., 127.66, 124.7, 56.3, 49.3, 41.1, 31.9, 23.8, 21.57. IR (KBr) 1767, 1474, 1346, 1160, 665; HRMS (ESI) calcd for $C_{19}H_{19}NCl_2NaSO_4$ $[M+Na]^+$: 450.0304, found 450.0300.

*4.1.5. 2,6-dichlorophenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2e**)*

69.5 mg, 81% yield; White solid, m.p. = 149–150 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.1 Hz, 2H), 7.36 (t, J = 5.4 Hz, 2H), 7.34 (d, J = 8.1 Hz, 2H), 7.15 (t, J = 8.1 Hz, 1H), 4.12–3.99 (m, 1H), 3.52 (m, 2H), 3.21–3.09 (m, 1H), 2.86 (dd, J = 16.3, 10.7 Hz, 1H), 2.44 (s, 3H), 1.95–1.86 (m, 2H), 1.82 (t, J = 7.6 Hz, 1H), 1.64–1.55 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7, 143.8, 143.7, 133.9, 129.8, 128.9, 128.7, 127.6, 127.3, 56.3, 49.3, 40.8, 31.7, 23.8, 21.5. IR (KBr)1771, 1448, 1347, 1160, 663; HRMS (ESI) calcd for $C_{19}H_{19}NCl_2NaSO_4$ $[M+Na]^+$: 450.0304, found 450.0299.

*4.1.6. 2,4,6-trichlorophenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2f**)*

61.0 mg, 66% yield; White solid, m.p. = 125–126 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.38 (s, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.26 (s, 1H), 4.05 (m, 1H), 3.58–3.46 (m, 1H), 3.16 (m, 1H), 2.85 (dd, J = 16.4, 10.6 Hz, 1H), 2.44 (s, 3H), 1.93–1.84 (m, 2H), 1.84–1.76 (m, 1H), 1.63–1.54 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 143.7, 142.7, 133.8, 132.2, 129.8, 129.5, 128.6, 127.6, 56.2, 49.3, 40.7, 31.7, 23.8, 21.5. IR (KBr) 1771, 1447, 1348, 1160, 660; HRMS (ESI) calcd for $C_{19}H_{18}NCl_3NaSO_4$ $[M+Na]^+$: 483.9914, found 483.9908.

*4.1.7. 2-bromophenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2g**)*

71.1 mg, 81% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.61 (dd, J = 8.0, 1.1 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.19 (dd, J = 8.0, 1.2 Hz, 1H), 7.16–7.11 (m, 1H), 4.14–4.03 (m, 1H), 3.55–3.47 (m, 1H), 3.42 (dd, J = 16.3, 3.8 Hz, 1H), 3.16 m, 1H), 2.82 (dd, J = 16.3, 9.8 Hz, 1H), 2.44 (s, 3H), 1.92–1.85 (m, 2H), 1.83–1.78 (m, 1H), 1.62–1.52 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 148.0, 143.6, 133.9, 133.3, 129.8, 128.6, 127.6, 127.4, 123.9, 116.1, 56.4, 49.3, 41.3, 31.9, 23.8, 21.5. IR (KBr) 1763, 1471, 1346, 1160, 664; HRMS (ESI) calcd for $C_{19}H_{20}NBrNaSO_4$ $[M+Na]^+$: 460.0189, found 460.0180.

*4.1.8. 4-methoxyphenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2h**)*

63.0 mg, 81% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 7.05–7.00 (m, 2H), 6.90–6.87 (m, 2H), 4.05 (m, 1H), 3.80 (s, 3H), 3.53–3.45 (m, 1H), 3.30 (dd, J = 16.3, 4.1 Hz, 1H), 3.17 (m, 1H), 2.75 (dd, J = 16.3, 9.4 Hz, 1H), 2.43 (s, 3H), 1.90–1.80 (m, 2H), 1.80–1.71 (m, 1H), 1.60–1.50 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 157.3, 144.0, 143.6, 134.0, 129.7, 127.6, 122.3, 114.4, 56.5, 55.6, 49.3, 41.4, 31.8, 23.7, 21.6. IR (KBr) 1754, 1463, 1345, 1160, 662; HRMS (ESI) calcd for $C_{20}H_{23}NNaSO_5$ $[M+Na]^+$: 412.1189, found 412.1186.

*4.1.9. 3,5-dimethylphenyl 2-(1-tosylpyrrolidin-2-yl)acetate (**2i**)*

42.3 mg, 55% yield; White solid, m.p. = 102–103 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.87 (s, 1H), 6.71 (s, 2H), 4.04 (m, 1H), 3.49 (m, 1H), 3.32 (dd, J = 16.4, 3.9 Hz, 1H), 3.17 (m, 1H), 2.74 (dd, J = 16.4, 9.7 Hz, 1H), 2.43 (s, 3H), 2.31 (s, 6H), 1.85 (m, 2H), 1.80–1.72 (m, 1H), 1.59–1.50 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 150.3, 143.6, 139.3, 134.0, 129.8, 127.7, 119.1, 56.5, 49.3, 41.5, 31.8, 23.9, 21.6, 21.3. IR (KBr) 1754, 1450, 1377, 1160, 665; HRMS (ESI) calcd for $C_{21}H_{25}NNaSO_4$ $[M+Na]^+$: 410.1397, found 410.1393.

*4.1.10. mesityl 2-(1-tosylpyrrolidin-2-yl)acetate (**2j**)*

45.2 mg, 56% yield; White solid, m.p. = 125–126 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.1 Hz, 2H), 6.87 (s, 2H), 4.05 (m, 1H), 3.51 (m, 1H), 3.42 (dd, J = 16.4, 3.4 Hz, 1H), 3.17 (m, 1H), 2.80 (dd, J = 16.4, 10.3 Hz, 1H), 2.43 (s, 3H), 2.26 (s, 3H), 2.11 (s, 6H), 1.93–1.81 (m, 2H), 1.81–1.72 (m, 1H), 1.60–1.50 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 145.7, 143.7, 135.4, 133.9, 129.8, 129.6, 129.3, 127.7, 56.5, 49.4, 41.1, 31.9, 23.8, 21.6, 20.8, 16.4. IR (KBr) 1751, 1484, 1347, 1137, 661; HRMS (ESI) calcd for $C_{22}H_{27}NNaSO_4$ $[M+Na]^+$: 424.1553, found 424.1547.

*4.1.11. Phenyl 2-(3-methyl-1-tosylpyrrolidin-2-yl)acetate (**2k**)*

60.4 mg, 81% yield, dr = 4:1; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.12 (d, J = 7.6 Hz, 2H), 3.69–3.57 (m, 1H), 3.51–3.45 (m, 1H), 3.23–3.18 (m, 1H), 2.86–2.76 (dd, J = 16.3, 9.8 Hz 1H), 2.43

(s, 3H), 2.17 (m, 1H), 2.06–1.87 (m, 1H), 1.27 (tt, J = 6.7, 4.9 Hz, 1H), 1.00 (d, J = 6.9 Hz, 1H), 0.62 (d, J = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.0, 150.6, 143.6, 133.7, 129.7, 129.6, 129.4, 127.7, 125.9, 121.6, 63.8, 47.6, 41.0, 39.1, 31.0, 21.5, 18.1. IR (KBr) 1754, 1644, 1344, 1162, 689; HRMS (ESI) calcd for $C_{20}H_{23}NNaSO_4$ $[M+Na]^+$: 396.1240, found 396.1236.

4.1.12. Phenyl 2-(3-allyl-1-tosylpyrrolidin-2-yl)acetate (**2l**)

40.1 mg, 50% yield, dr = 4:1; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (t, J = 6.2 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.33 (t, J = 6.6 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.11 (d, J = 7.7 Hz, 2H), 5.53 (ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 4.91 (d, J = 10.1 Hz, 1H), 4.71 (dd, J = 17.0, 1.4 Hz, 1H), 3.75 (dt, J = 8.9, 3.4 Hz, 1H), 3.55–3.48 (m, 1H), 3.29–3.21 (m, 1H), 3.19 (td, J = 9.3, 7.1 Hz, 1H), 2.87–2.77 (m, 1H), 2.44 (s, 3H), 2.19–2.11 (m, 1H), 2.05–1.95 (m, 1H), 1.67 (dt, J = 14.0, 7.0 Hz, 1H), 1.51 (dd, J = 14.7, 7.5 Hz, 1H), 1.44 (ddd, J = 10.8, 7.4, 4.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 150.5, 143.7, 135.3, 134.0, 129.7, 129.4, 127.6, 125.9, 121.6, 117.0, 61.0, 47.4, 43.8, 41.3, 36.7, 28.4, 21.5. IR (KBr) 1752, 1592, 1344, 1191, 688; HRMS (ESI) calcd for $C_{22}H_{25}NNaSO_4$ $[M+Na]^+$: 422.1397, found 422.1393.

4.1.13. Phenyl 2-(2-tosyl-2-azaspiro[4.5]decan-3-yl)acetate (**2m**)

64.5 mg, 76% yield; White solid, m.p. = 97–98 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.9 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.23 (dd, J = 10.3, 4.6 Hz, 1H), 7.11 (d, J = 7.7 Hz, 2H), 3.98 (m, 1H), 3.54 (dd, J = 16.5, 4.3 Hz, 1H), 3.22 (p, J = 11.0 Hz, 1H), 2.81 (dd, J = 16.5, 8.3 Hz, 1H), 2.42 (s, 3H), 2.01 (dd, J = 12.7, 7.3 Hz, 1H), 1.61–1.52 (m, 1H), 1.42 (m, 2H), 1.36 (m, 2H), 1.32–1.15 (m, 3H), 1.15–1.02 (m, 1H), 0.77 (ddd, J = 13.1, 9.4, 3.7 Hz, 1H), 0.65–0.55 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 150.5, 143.6, 134.1, 129.7, 129.4, 127.6, 125.9, 121.6, 115.2, 55.9, 41.9, 41.2, 36.4, 33.9, 25.8, 23.6, 22.8, 21.6. IR (KBr) 1755, 1493, 1126, 75, 688; HRMS (ESI) calcd for $C_{24}H_{29}NNaSO_4$ $[M+Na]^+$: 450.1710, found 450.1706.

4.1.14. 2,4-dichlorophenyl 2-(2-tosyl-2-azaspiro[4.5]decan-3-yl) acetate (**2n**)

87.7 mg, 89% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 2.4 Hz, 1H), 7.35–7.29 (m, 2H), 7.26 (s, 1H), 7.16 (dd, J = 8.5, 4.5 Hz, 1H), 3.97 (m, 1H), 3.59 (dd, J = 16.5, 4.3 Hz, 1H), 3.22 (q, J = 10.9 Hz, 2H), 2.86 (dd, J = 16.5, 8.2 Hz, 1H), 2.43 (s, 3H), 2.01 (dd, J = 12.8, 7.3 Hz, 1H), 1.64–1.52 (m, 1H), 1.50–1.41 (m, 2H), 1.41–1.32 (m, 2H), 1.33–1.16 (m, 3H), 1.15–1.02 (m, 1H), 0.77 (ddd, J = 13.1, 9.3, 3.8 Hz, 1H), 0.66–0.54 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.1, 145.6, 143.7, 133.9, 132.0, 130.0, 129.6, 128.0, 127.7, 127.7, 124.8, 55.4, 41.6, 41.2, 36.3, 33.9, 25.8, 23.7, 22.8, 21.6. IR (KBr) 1767, 1474, 1160, 1095, 664; HRMS (ESI) calcd for $C_{24}H_{27}NCl_2NaSO_4$ $[M+Na]^+$: 518.0930, found 518.0927.

4.1.15. Phenyl 2-((4R)-4-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)acetate (**2o**)

69.0 mg, 54% yield; dr = 3:1; White solid, m.p. = 163–164 °C; R_f = 0.23 (petroleum ether/ethyl acetate 8:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.2 Hz, 2H), 8.07 (d, J = 8.3 Hz, 2H), 7.48–7.29 (m, 7H), 7.09 (dd, J = 15.0, 7.9 Hz, 5H), 4.33 (d, J = 24.6 Hz, 3H), 4.27 (m, 1H), 3.68–3.56 (m, 1H), 3.39 (dd, J = 17.1, 4.7 Hz, 1H), 3.35 (d, J = 11.7 Hz, 1H), 2.79 (dd, J = 16.8, 6.5 Hz, 1H), 2.06 (d, J = 6.4 Hz, 1H), 1.78 (t, J = 9.2 Hz, 1H), 0.84 (d, J = 28.7 Hz, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 135.5, 135.4, 130.2, 129.5, 129.1, 127.9, 124.4, 121.6, 70.4, 58.1, 55.5, 41.9, 40.7, 26.8, 26.6, 18.8. IR (KBr) 1748, 1646, 1350, 1164, 743; HRMS (ESI) calcd for $C_{34}H_{36}N_2NaSSiO_7$ $[M+Na]^+$: 667.1905, found 667.1900.

4.1.16. Phenyl 2-((5S)-5-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-yl)acetate (**2p**)

99.1 mg, 75% yield, dr = 5:1; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 7.4 Hz, 4H), 7.51–7.46 (m, 2H), 7.46–7.39 (m, 5H), 7.37 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.8 Hz, 2H), 4.04–3.96 (m, 1H), 3.90 (dd, J = 10.4, 3.7 Hz, 1H), 3.73 (dt, J = 12.8, 6.3 Hz, 1H), 3.63 (m, 1H), 3.30 (dd, J = 16.5, 4.7 Hz, 1H), 2.76 (dd, J = 16.5, 8.5 Hz, 1H), 1.85 (m 1H), 1.74 (m, 1H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.7, 150.4, 150.2, 142.8, 135.7, 135.7, 135.5, 133.3, 132.9, 129.9, 129.7, 129.5, 128.9, 127.8, 126.0, 124.4, 121.5, 115.3, 65.9, 62.6, 58.3, 41.6, 30.6, 26.9, 26.8, 26.6, 19.3. IR (KBr) 1755, 1531, 1350, 1164, 703; HRMS (ESI) calcd for $C_{35}H_{38}N_2NaSSiO_7$ $[M+Na]^+$: 681.2061, found 681.2058.

4.1.17. Phenyl 2-(1-tosylindolin-2-yl)acetate (**2q**)

75.7 mg, 93% yield; Colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.2 Hz, 2H), 7.34–7.25 (m, 3H), 7.18–7.14 (m, 2H), 7.11 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 7.8 Hz, 1H), 6.99 (dd, J = 16.8, 7.8 Hz, 4H), 4.61 (ddd, J = 13.0, 9.3, 3.7 Hz, 1H), 3.25 (dd, J = 16.4, 4.3 Hz, 1H), 2.99–2.92 (m, 1H), 2.86 (dd, J = 16.4, 9.6 Hz, 1H), 2.69–2.62 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 150.4, 144.1, 141.1, 134.6, 131.1, 129.7, 129.5, 129.2, 128.0, 127.2, 126.0, 125.3, 121.6, 117.3, 58.6, 41.6, 34.8, 21.6. IR (KBr) 1755, 1722, 1384, 1168, 754; HRMS (ESI) calcd for $C_{23}H_{21}NNaSO_4$ $[M+Na]^+$: 430.1084, found 430.1087.

4.1.18. Phenyl 2-(2-tosylisoindolin-1-yl)acetate (**2r**)

75.3 mg, 93% yield; White solid, m.p. = 101–102 °C; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.33–7.26 (m, 2H), 7.22–7.19 (m, 2H), 7.19–7.13 (m, 4H), 7.11–7.06 (m, 1H), 6.98 (d, J = 7.9 Hz, 2H), 5.32 (m, 1H), 4.71 (dd, J = 13.8, 2.2 Hz, 1H), 4.51 (d, J = 13.8 Hz, 1H), 3.44 (dd, J = 16.6, 4.2 Hz, 1H), 3.13 (dd, J = 16.6, 6.7 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 150.6, 143.9, 139.2, 135.7, 134.0, 129.9, 129.4, 128.3, 128.0, 127.6, 125.9, 122.7, 122.6, 121.6, 62.0, 53.9, 42.8, 21.5. IR (KBr) 1753, 1724, 1346, 1164, 754; HRMS (ESI) calcd for $C_{23}H_{21}NNaSO_4$ $[M+Na]^+$: 430.1084, found 430.1086.

4.1.19. Phenyl 2-(1-tosylpiperidin-2-yl)acetate (**4a**)

61.1 mg, 82% yield; Colorless oil; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2 Hz, 2H), 7.40–7.34 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.22 (dd, J = 13.0, 5.6 Hz, 1H), 7.10–7.06 (m, 2H), 4.68 (m, 1H), 3.84 (dd, J = 13.8, 4.0 Hz, 1H), 3.12–2.98 (m, 2H), 2.88–2.75 (m, 2H), 2.42 (s, 3H), 1.66 (d, J = 5.3 Hz, 1H), 1.59 (m, 2H), 1.57 (m, 1H), 1.41–1.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 150.5, 143.2, 138.1, 129.8, 129.4, 127.1, 125.9, 121.8, 121.6, 49.8, 41.0, 35.4, 27.8, 24.5, 21.5, 18.4. IR (KBr) 1755, 1493, 1338, 1193, 652; HRMS (ESI) calcd for $C_{20}H_{23}NNaSO_4$ $[M+Na]^+$: 396.1240, found 396.1239.

4.1.20. Phenyl 2-(3-methyl-1-tosylpiperidin-2-yl)acetate (**4b**)

60.0 mg, 78% yield, dr > 20:1; Colorless oil; R_f = 0.33 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2H), 7.37 (t, J = 7.9 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 7.23 (t, J = 7.4 Hz, 1H), 7.11–7.04 (m, 2H), 4.71 (dd, J = 13.2, 6.7 Hz, 1H), 3.87 (dd, J = 14.0, 3.1 Hz, 1H), 3.04 (td, J = 13.8, 2.7 Hz, 1H), 2.86–2.72 (m, 2H), 2.42 (s, 3H), 1.80–1.69 (m, 1H), 1.64 (dd, J = 14.5, 12.9 Hz, 1H), 1.60–1.50 (m, 1H), 1.25–1.16 (m, 1H), 1.05–0.93 (m, 1H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 150.5, 143.2, 138.1, 129.7, 129.4, 127.1, 125.9, 121.5, 50.0, 40.9, 36.3, 35.9, 33.0, 24.9, 22.0, 21.5. IR (KBr) 1755, 1493, 1338, 1155, 697; HRMS (ESI) calcd for $C_{21}H_{25}NNaSO_4$ $[M+Na]^+$: 410.1397, found 410.1393.

*4.1.21. Phenyl 2-(4-methyl-1-tosylpiperidin-2-yl)acetate (**4c**)*

52.1 mg, 67% yield; dr = 6:1; White solid, m.p. = 109–110 °C; R_f = 0.23 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.22–7.18 (m, 1H), 7.10–7.06 (m, 2H), 4.68 (m, 1H), 3.81 (dd, *J* = 21.7, 7.8 Hz, 1H), 3.06–2.95 (m, 1H), 2.66 (dd, *J* = 15.3, 7.1 Hz, 1H), 2.42 (s, 0.78), 2.40 (s, 2.22H), 1.81 (m, 1H), 1.59–1.49 (m, 2H), 1.49–1.34 (m, 1H), 1.34–1.18 (m, 2H), 1.02 (d, *J* = 6.9 Hz, 0.43 H), 0.89 (d, *J* = 6.9 Hz, 2.57 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 150.6, 143.09, 138.3, 129.7, 129.4, 129.3, 129.2, 127.1, 125.8, 121.6, 121.4, 54.7, 40.3, 33.6, 31.6, 26.9, 24.7, 21.5, 18.5. IR (KBr) 1755, 1493, 1338, 1153, 688; HRMS (ESI) calcd for $C_{21}H_{25}NNaSO_4$ $[M+Na]^+$: 410.1397, found 410.1394.

*4.1.22. Phenyl 2-(4-isopropyl-1-tosylpiperidin-2-yl)acetate (**4d**)*

61.0 mg, 74% yield; dr > 20:1Colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.6 Hz, 2H), 4.75 (m, 1H), 3.91 (d, *J* = 14.2 Hz, 1H), 3.03 (td, *J* = 13.8, 2.6 Hz, 1H), 2.84–2.71 (m, 2H), 2.42 (s, 3H), 1.67 (d, *J* = 13.0 Hz, 1H), 1.62–1.51 (m, 1H), 1.45–1.35 (m, 1H), 1.31 (dd, *J* = 13.3, 6.0 Hz, 1H), 1.24 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.03 (ddd, *J* = 25.0, 12.9, 4.7 Hz, 1H), 0.79 (dd, *J* = 6.6, 1.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 150.5, 143.2, 138.1, 129.7, 129.4, 127.1, 125.9, 121.5, 50.1, 41.1, 36.0, 35.9, 32.2, 31.43, 27.9, 21.5, 19.4, 19.2. IR (KBr) 1755, 1493, 1158, 931, 656; HRMS (ESI) calcd for $C_{23}H_{29}NNaSO_4$ $[M+Na]^+$: 438.1710, found 438.1707.

*4.1.23. Phenyl 2-(1-tosyl-1,2,3,4-tetrahydroquinolin-2-yl)acetate (**4e**)*

73.1 mg, 87% yield; White solid, m.p. = 104–105 °C; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 17.6, 8.5 Hz, 4H), 7.22–7.12 (m, 3H), 7.12–7.06 (m, 3H), 7.02 (d, *J* = 7.9 Hz, 2H), 6.92 (d, *J* = 7.3 Hz, 1H), 4.75–4.62 (m, 1H), 3.02–2.96 (m, 1H), 2.66 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.33 (dd, *J* = 13.1, 6.6 Hz, 1H), 2.30 (s, 3H), 1.98 (td, *J* = 12.4, 6.1 Hz, 1H), 1.75–1.62 (m, 1H), 1.54–1.41 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 150.5, 143.7, 135.8, 134.9, 133.6, 129.6, 129.4, 128.0, 127.9, 127.2, 127.0, 126.17, 125.9, 121.6, 53.1, 40.8, 28.3, 24.5, 21.5. IR (KBr) 1756, 1723, 1387, 1166, 771; HRMS (ESI) calcd for $C_{24}H_{23}NNaSO_4$ $[M+Na]^+$: 444.1240, found 444.1243.

*4.1.24. Phenyl 2-(6-methyl-1-tosyl-1,2,3,4-tetrahydroquinolin-2-yl) acetate (**4f**)*

75.3 mg, 89% yield; Colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.29 (dt, *J* = 14.3, 7.3 Hz, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 7.03–6.99 (m, 2H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 11.4 Hz, 1H), 4.71–4.60 (m, 1H), 2.97 (dd, *J* = 15.3, 6.0 Hz, 1H), 2.63 (dd, *J* = 15.3, 8.0 Hz, 1H), 2.29 (s, 3H), 2.25 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.23 (s, 3H), 1.93 (td, *J* = 12.9, 6.4 Hz, 1H), 1.70–1.56 (m, 1H), 1.42 (td, *J* = 13.6, 7.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 150.6, 143.6, 135.9, 135.9, 133.2, 132.2, 129.5, 129.4, 128.5, 127.8, 127.7, 127.2, 125.9, 121.6, 53.0, 40.8, 28.2, 24.4, 21.5, 20.9. IR (KBr) 1756, 1724, 1348, 1167, 753; HRMS (ESI) calcd for $C_{25}H_{25}NNaSO_4$ $[M+Na]^+$: 458.1397, found 458.1400.

*4.1.25. Phenyl 2-(7-chloro-1-tosyl-1,2,3,4-tetrahydroquinolin-2-yl) acetate (**4g**)*

79.8 mg, 88% yield; Colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.7 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.30 (t, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 12.8, 5.3 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.07–6.99 (m, 3H), 6.86 (d, *J* = 8.1 Hz, 1H), 4.76–4.62 (m, 1H), 2.96 (dd, *J* = 15.5, 5.9 Hz, 1H), 2.65 (dd, *J* = 15.4, 8.0 Hz, 1H), 2.38–2.32 (m, 1H), 2.31 (s, 3H), 1.91 (td, *J* = 13.2, 6.3 Hz, 1H), 1.78–1.65 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 150.5, 144.1, 136.0, 135.5, 132.2, 131.4, 129.7, 129.4, 129.0, 127.6, 127.2, 126.2, 125.9, 121.6, 52.9, 40.5, 27.7, 23.9, 21.6. IR (KBr) 1755, 1384, 1166, 754; HRMS (ESI) calcd for $C_{24}H_{22}NClNaSO_4$ $[M+Na]^+$: 478.0850, found 478.0855.

*4.1.26. Phenyl 2-(2-tosyl-1,2,3,4-tetrahydroisoquinolin-3-yl)acetate (**4h**)*

62.2 mg, 74% yield; Colorless oil; R_f = 0.43 (petroleum ether/ethyl acetate 4:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 2H), 7.20–7.14 (m, 3H), 7.13–7.08 (m, 2H), 7.05–6.94 (m, 4H), 4.75–4.66 (m, 1H), 4.61 (d, *J* = 16.2 Hz, 1H), 4.33 (d, *J* = 16.2 Hz, 1H), 2.86 (dd, *J* = 16.1, 5.3 Hz, 1H), 2.74–2.64 (m, 2H), 2.55 (dd, *J* = 15.6, 9.0 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 150.4, 143.6, 136.3, 131.6, 131.5, 129.8, 129.4, 129.4, 127.3, 127.3, 126.7, 126.2, 125.9, 121.5, 49.0, 43.8, 37.6, 32.6, 21.5. IR (KBr) 1755, 1722, 1338, 1161, 772; HRMS (ESI) calcd for $C_{24}H_{23}NNaSO_4$ $[M+Na]^+$: 444.1240, found 444.1244.

4.2. Chiral NHC-catalyzed reaction of Aza-Michael addition of α,β-unsaturated carboxylic acid

General procedure: An oven-dried 50 mL Schlenk tube was charged with unsaturated carboxylic acid (0.2 mmol), NHC precursor **D** (29.7 mg, 0.04 mmol), Cs_2CO_3 (97.6 mg, 0.30 mmol) or K_3PO_4 (22.2 mg, 0.1 mmol), HATU (114 mg, 0.3 mmol or 194 mg, 0.5 eq) and PhONa (34.8 mg, 0.3 mmol)), then freshly distilled toluene (2 mL) was added to this mixture. The reaction mixture was stirred at room temperature for 12. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc as the eluent, typically 4:1) to furnish the corresponding product. ee values were determined by chiral HPLC (IB column, ^{i}PrOH:^{n}Hexane = 10:90, 1.0 ml/min, 210 nm).

*4.2.1. Phenyl (R)-2-(1-tosylpyrrolidin-2-yl)acetate ((R)-**2a**)*

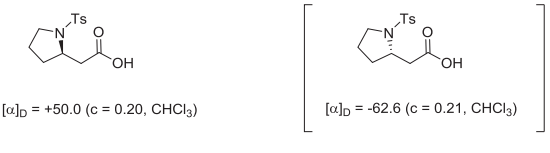
48.1 mg, 68% yield; HPLC analysis: 36% ee [Daicel CHIRALPAK IB column, 20 °C, 210 nm, hexane/*i*-PrOH = 90:10, 1.0 mL/min, 210 nm, 16.7 min (minor), 21.8 min (major)]

*4.2.2. Phenyl (R)-2-(1-tosylpyrrolidin-2-yl)acetate ((R)-**2a**) zzf-1158*

31.0 mg, 43% yield; $[\alpha]_{25}{}^{D}$ = + 30.5 (c = 0.63, $CHCl_3$); HPLC analysis:55% ee [Daicel CHIRALPAK IA column, 20 °C, 210 nm, hexane/*i*-PrOH = 90:10, 1.0 mL/min, 210 nm, 16.9 min (minor), 22.0 min (major)]

*4.3. Determination of the absolute configuration of compound **2a***

The absolute configuration of compound **2a** was determined to be *R* by the comparison of its optical rotation value with the reported one [28].



4.4. Chemical transformations

4.4.1. 2-(1-tosylpyrrolidin-2-yl)ethan-1-ol (**5**)

2a (562 mg, 1 mmol, 1 equiv.) was dissolved in 5 mL THF in an RB flask. $LiAlH_4$ was carefully added in small portions. The mixture was stirred at rt for 30 min and was quenched carefully by addition of saturated aqueous potassium sodium tartrate solution. The mixture was stirred vigorously at for 1 h, separated, and extracted with EtOAc three times. The combined organic phase was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography (eluent: EA: PE = 2:1) to give the alcohol product **5** (245 mg, 91% yield) as colorless oil; $R_f = 0.2$ (petroleum ether/ethyl acetate 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.05–3.93 (m, 2H), 3.70 (m, 1H), 3.40 (m, 1H), 3.19 (m, 1H), 2.82–2.72 (m, 1H), 2.44 (s, 3H), 1.87–1.75 (m, 1H), 1.68 (m, 2H), 1.57 (m, 1H), 1.49 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 134.3, 129.8, 127.6, 59.1, 57.3, 48.6, 38.7, 31.2, 24.1, 21.6. IR (KBr) 1451, 1338, 1158, 1050, 664; HRMS (ESI) calcd for $C_{13}H_{19}NNaSO_3$ $[M+Na]^+$: 292.0978, found 292.0977.

4.4.2. (R)-2-(1-tosylpyrrolidin-2-yl)acetic acid (**6**)

To the solution of (*R*)-**2a** (0.1 mmol, 36 mg, 1.0 equiv) in THF/H_2O (3:1, 4 mL), LiOOH (6.9 mg, 1.5 equiv, 0.15 mmol) was added at 0 °C. After being stired for 2 h, The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (DCM/Methanol = 100:1 as the eluent) to furnish the acid (*R*)-**6** (25.8 mg, 92% yield) as a white solid, m.p. = 113–114 °C; $R_f = 0.2$ (DCM/Methanol = 100:1); $[\alpha]^{25}_D$ = + 50.0 (c 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 3.94 (m, 1H), 3.55–3.40 (m, 1H), 3.14 (dt, J = 17.0, 6.9 Hz, 1H), 2.56 (dd, J = 16.4, 10.0 Hz, 1H), 2.44 (s, 3H), 1.90–1.74 (m, 1H), 1.73–1.62 (m, 1H), 1.60–1.48 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.6, 143.6, 134.1, 129.8, 127.6, 56.3, 49.2, 41.1, 31.7, 23.7, 21.5. IR (KBr) 1711, 1338, 1158, 1092, 662; HRMS (ESI) calcd for $C_{13}H_{17}NNaSO_4$ $[M+Na]^+$: 306.0771, found 306.0769.

4.4.3. 2-(7-chloro-1-tosyl-1,2,3,4-tetrahydroquinolin-2-yl)acetic acid (**7**)

To the solution of **4h** (0.15 mmol, 65.8 mg, 1.0 equiv) in THF/H_2O (3:1, 6.4 mL), LiOOH (11.6 mg, 1.5 equiv, 0.225 mmol) was added at 0 °C. After being stired for 4.5 h, The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (DCM/Methanol = 100:1 as the eluent) to furnish the acid **7** (38.4 mg, 70%) as a white solid, m.p. = 185–186 °C; R_f = 0.4 (DCM/Methanol = 100:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 1.8 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.13 (d, J = 8.1 Hz, 2H), 7.04 (dd, J = 8.1, 1.9 Hz, 1H), 6.85 (d, J = 8.1 Hz, 1H), 4.60–4.47 (m, 1H), 2.83 (dd, J = 15.9, 5.1 Hz, 1H), 2.44 (dd, J = 15.9, 8.9 Hz, 1H), 2.32 (s, 3H), 2.31–2.24 (m, 1H), 1.89 (td, J = 13.2, 6.1 Hz, 1H), 1.74–1.64 (m, 1H), 1.40 (td, J = 13.5, 7.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2, 144.1, 136.0, 135.5, 132.2, 131.5, 129.69, 129.0, 127.5, 127.2, 126.1, 52.6, 40.1, 27.7, 23.9, 21.6. IR (KBr) 1755, 1471, 1195, 1162, 703; HRMS (ESI) calcd for $C_{18}H_{18}NClNaSO_4$ $[M+Na]^+$: 402.0537, found 402.0540.

4.4.4. methyl 2-(7-chloro-1,2,3,4-tetrahydroquinolin-2-yl)acetate (**8**)

To a dry Schlenk tube equipped with a magnetic stir bar, was added **4h** (91.0 mg, 0.2 mmol) and Mg-powder (57.6 mg, 12 equiv.). The tube was capped with a septum, evacuated and refilled with Ar for 3 times. Then, absolute MeOH (4 mL) was added and the reaction was sonicated at room temperature until no more starting material remained monitored by TLC (around 4 h). The solution was cooled to 0 °C and slowly quenched with saturated NH_4Cl. The aqueous phases were extracted with DCM (3 × 10 mL). The combined organic phases were washed with saturated brine, then dried over $MgSO_4$, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EA = 20:1) to afford **8** (34.0 mg, 71%) as light yellow oil; $R_f = 0.2$ (petroleum ether/ethyl acetate 20:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, J = 8.0 Hz, 1H), 6.50 (dd, J = 7.9, 1.3 Hz, 1H), 6.43 (s, 1H), 4.66 (s, 1H), 3.64 (m, 1H), 3.65 (s, 3H), 2.72 (dd, J = 8.6, 4.5 Hz, 1H), 2.68 (dd, J = 9.8, 5.7 Hz, 1H), 2.63 (t, J = 5.3 Hz, 1H), 2.59 (dd, J = 13.4, 8.1 Hz, 1H), 2.45 (m, 1H), 2.44 (d, J = 5.1 Hz, 1H), 1.88 (ddd, J = 13.8, 8.7, 5.3 Hz, 1H), 1.67–1.56 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 144.8, 132.1, 130.2, 119.2, 117.2, 114.1, 51.8, 47.6, 40.4, 27.6, 25.0. IR (KBr) 1737, 1374, 1158, 1092, 710; HRMS (ESI) calcd for $C_{12}H_{15}NClO_2$ $[M+H]^+$: 240.0786, found 240.0786.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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