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Triflic Acid-Catalyzed Cycloisomerization of 1,6-enynes: Facile Access to Carbo- and Azaheterocycles

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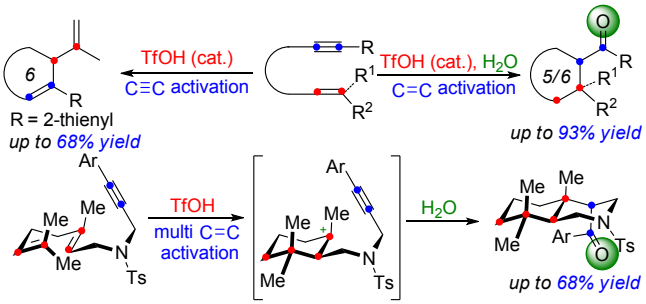
ABSTRACT: A new and efficient strategy for enynes cyclization catalyzed by triflic acid has been described. Various valuable carbocycle-fused and heterocycle-fused ketones were easily accessed by the formation of new C-C and C-O bond under benign reaction conditions. This protocol also provides another opportunity to construct polycyclic single-nitrogen ketones via a cation-induced cascade cyclization of polyenynes. Furthermore, antiviral bioassays revealed that a few compounds exhibited good antiviral activity against tobacco mosaic virus (TMV) at a concentration of 200 μg mL^{-1}.



INTRODUCTION

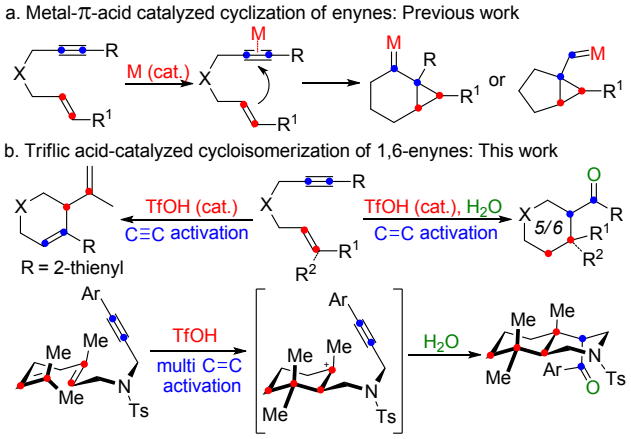
The carbocycle-fused and heterocycle-fused ketones are fundamental and ubiquitous skeletons in biologically active molecules and synthetic pharmaceuticals.[1] Considerable attentions have been devoted to the synthesis of such carbo- and azaheterocycles. Among

these exquisite protocols, metal-π-acid catalyzed cyclization of enynes by the formation of new C-C bond have exhibited powerful advantages in building functionalized cyclic compounds quickly from relatively simple unsaturated substrate (Scheme 1a).[2-4] Particularly, Lewis acidic gold catalysts have been demonstrated to activate the alkyne unit by the manner of coordination with electrophile-π and a myriad of transformations have been reported in this approach.[5] However, these methods usually need to use expensive even toxic noble metals, and relative long reaction times. Thus, the development of metal-free strategy for efficient and direct synthesis of functionalized carbo- and azaheterocycles from enynes is highly desirable.

Brønsted acid catalysis has emerged as a powerful tool in modern organic synthesis.[6-9] Its utilization was limited to the formation and cleavage of C−O bonds, such as hydrolysis and formation of esters and acetals in the early stage.[10] In order to enrich the reaction types, super strong Brønsted acid triflic acid (TfOH) was developed, which is 100 times stronger than sulfuric acid.[11] With the rapidly development of various super strong acid, the application of Brønsted acids as catalysts to activate carbonyl, imine, alkene, alkyne, hydroxyl groups have appeared in the past decades.[12] Particularly, Brønsted acids catalysis proved their unique privilege for the construction of carbo- and heterocycles framework by the formation of new carbon-carbon bond. For example, the groups of Clark, Balamurugana, Niggemann, Zhang, and Yamamoto reported acid-catalyzed cycloisomerization reactions via the activation of isopropen moiety or enones.[7,13] Although these seminal works for the synthesis of cyclic molecules catalyzed by Brønsted acid have been

documented, it has not been successfully applied to the preparation of six members carbocycle-fused and heterocycle-fused ketones as well as polycyclic single-nitrogen ketones. As a continuation of our interest in the synthesis of heterocyclic compounds,[14] we report our discovery that enynes could be selectively activated and converted to functionated carbo- and azaheterocycles in the presence of catalytic amount of triflic acid (Scheme 1b).

Scheme 1. Cycloisomerization of Enynes for the Synthesis of Carbo- and Azaheterocycles

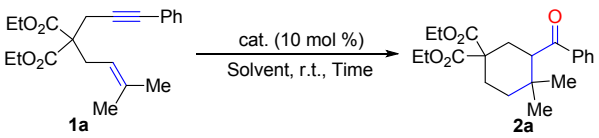


RESULTS AND DISCUSSION

We began our study of cycloisomerization of enynes with compound **1a** as the model substrate. A variety of Lewis acids were first utilized for this cyclization reaction. When **1a** was treated with 10 mol% $ZnCl_2$ catalyst in wet dichloromethane, none of the desired product was detected after 12 h (Table 1, entry 1). Catalytic amount of $AlCl_3$ could not initiate the reaction in the same conditons (entry 2). Weak Brønsted acid acetic acid (AcOH) and trifluoroacetic acid (TFA) were useless to the

transformation as well (entries 3-4). To our delight, carbocyclic molecule **2a** was formed in 55% yield when using $BF_3 \cdot OEt_2$ as catalyst (entry 6). In order to increase the yield, stronger acid trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triflic acid (TfOH) were tested for the reactions (entries 7 and 8). It was found that TfOH were more effective leading to 88% yield of **2a**, which indicate that the acidity of the Brønsted acid is vital to this transformation. In fact, the transformation was fast and the enyne substrate could be nearly converted fully just in 2 h, affording the product **2a** in 87% isolated yield (entry 9). Shortening the reaction time to 30 min led to a slightly decreased yield (entry 10). We then investigated the effects of different solvents to this cycloisomerization. It appeared that replacing solvent DCM with $Cl(CH_2)_2Cl$ delivered 85% yield of desired product (entry 11). And the reaction did not work well in toluene, which may result from the low solubility of TfOH in toluene (entry 12). Solvents such as CH_3CN, THF, and MeOH gave bad results compared with CH_2Cl_2 and no desired cyclic product was observed (entries 13-15). Therefore, in the presence of 10 mol% TfOH in wet DCM to react for 2 h at room temperature could afford the product **2a** in 87% yield, which were the optimal reaction conditions. And it should be noted that the stoichiometric amount of H_2O for cycloisomerization reactions with the hydration of alkynes come from wet solvent.

Table 1. Optimization of Reaction Conditions[a]



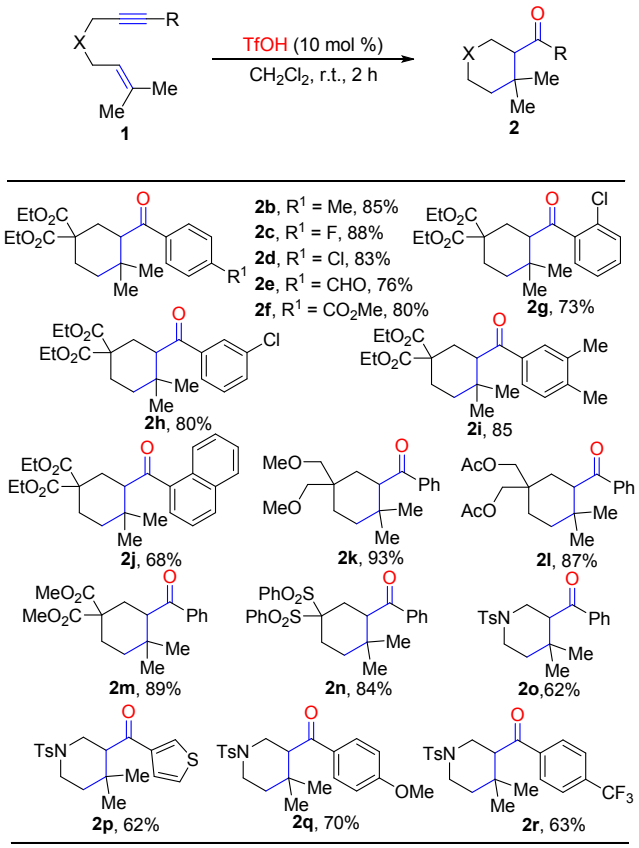
entry	cat.	solvent	time	yield (%)[b]
1	$ZnCl_2$	CH_2Cl_2	12 h	nd
2	$AlCl_3$	CH_2Cl_2	12 h	nd
3	AcOH	CH_2Cl_2	12 h	nd
4	TFA	CH_2Cl_2	12 h	nd
5	MsOH	CH_2Cl_2	12 h	trace
6	$BF_3{\cdot}OEt_2$	CH_2Cl_2	12 h	55
7	TMSOTf	CH_2Cl_2	12 h	80
8	TfOH	CH_2Cl_2	12 h	88
9	TfOH	CH_2Cl_2	2 h	88(87)
10	TfOH	CH_2Cl_2	30 min	82
11	TfOH	$Cl(CH_2)_2Cl$	2 h	85
12	TfOH	toluene	2 h	22
13	TfOH	CH_3CN	2 h	nd
14	TfOH	THF	2 h	nd
15	TfOH	MeOH	2 h	nd

[a]Reaction condition: **1a** (0.05 mmol, 1.0 equiv), catalyst (0.005 mmol, 10 mol %), solvent (1.0 mL, 0.05M), r.t.. [b]Refers to NMR yield using benzyl benzoate as the internal standard. Isolated yield is in the parenthesis in 0.1 mmol scale.

With the optimal conditions in hand, the scope of cycloisomerization of various enynes catalyzed by triflic acid was evaluated (Scheme 2). Enynes substrates bearing *para*- substituent on the phenyl ring could efficiently undergo cycloisomerization to produce the cyclization products in good yields (e.g. **2b**-**2f**, 76-88%). It proved that even highly reactive groups such as aldehydes were found to interfere by no means with the desired reaction approach. The substrate with a chlorine group at the ortho position on the phenyl ring lead to a slightly drop yield, which may be attributed to the steric hindrance of the aryl group (**2g**, 73%). The *meta*-chlorine group and dimethyl substituent on the phenyl ring was well-tolerated under the optimized conditions (**2h**, 80%; **2i**, 85%). Electron-rich naphthyl-substituted enyne could also proceed the cyclization and give the final product **2j** in 68% yield. Substrates **1k**-**1n**

could convert to the correspounding cyclization products in good yield at the same conditions. This triflic acid-catalyzed cycloisomerization of enynes not only provide a direct method to synthesize functionated carbocyclic molecules, but also show a facile access to azaheterocycles. For example, single-nitrogen enyne was subjected to the cascade cyclization under the optimal condition, the corresponding azaheterocyclic product **2o** could be afforded in 62% yield. We were delighted to find that the electron-rich 3-thiophenyl on the enyne was also tolerated under the strong acidity conditions (**2p**, 62%). Furthermore, the effect of electron density of aryl group on enyne was studied. It was found that trifluoromethyl and methoxy group installed at the *para* positions of the phenyl ring could smoothly undergo the cyclization to deliver the corresponding azaheterocyclic products (**2q**, 70%; **2r**, 63%). Based on these results, our method provides an efficient and direct pathway for the activate double bonds and achieves the carbon-carbon bond and carbon-oxygen bond formation in one step.

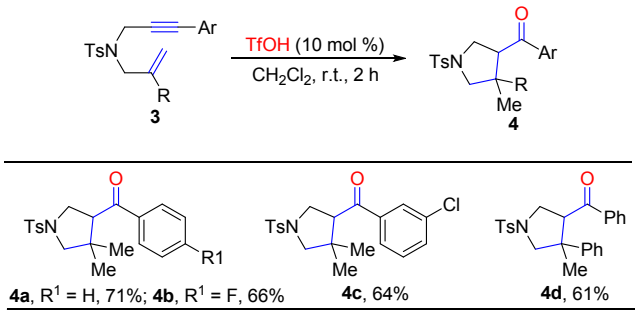
Scheme 2. Substrate Scope of Cycloisomerization[a]



[a]Conditions: **1** (0.1 mmol, 1.0 equiv), TfOH (0.9 μL, 0.01 mmol, 10 mol %), CH_2Cl_2 (2.0 mL, 0.05M), r.t., 2 h. Isolated yield.

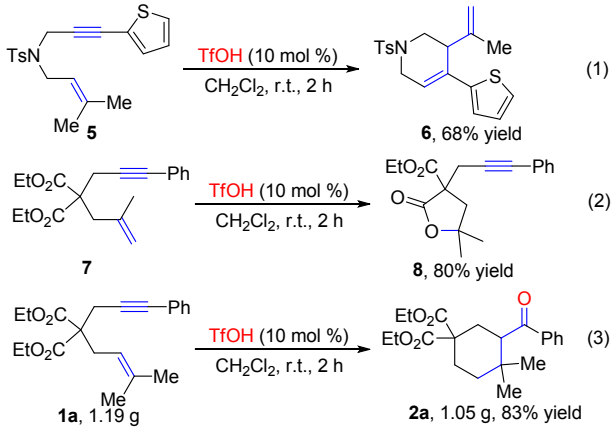
In additon, the method could also be applied to prepare five members azaheterocycle-fused ketones by adjusting to operate the enynes containing a 1,1-disubstituent alkene under the same conditons. We executed the cyclization using enynes **3** as the substrate, five members azaheterocycle-fused ketones **4** could be generated in good yields (Scheme 3). For example, desired product **4a** was formed in the presence of 10 mol% TfOH in 71% yield. When the electron-withdrawing group such as –Cl and –Br was put on the phenyl ring of substrates (**3b** and **3c**), the cyclization also proceeded to give the corresponding products with a slightly decrease of isolated yield. Pleasingly, this method was also suitable for the alkene furnished an aryl substitutent affording the desired product **4d** in 61% yield. From the above results, it was concluded that the catalytic system was applicable to both five and six members azaheterocycle compounds.

Scheme 3. Cycloisomerization of 1,6-enynes[a]



[a]Conditions: **3** (0.1 mmol, 1.0 equiv), TfOH (0.9 μL, 0.01 mmol, 10 mol %), CH_2Cl_2 (2.0 mL, 0.05M), r.t., 2 h. Isolated yield.

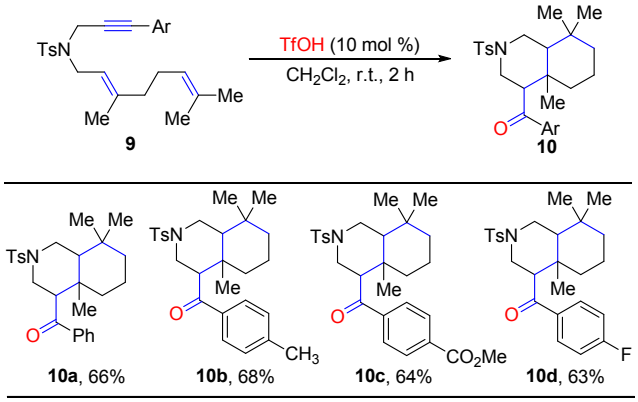
As we all known that the noble metals could serve as π-acid and exhibit powerful ability for carban-carban triple bonds activation, and a wide range of derived new reaction has been discovered. In contrast, the Brønsted acid catalysis usually preferred to activate carban-carban double bond in enynes to generate carbocation, which could be attacked by various nucleophiles. Interestingly, when the enyne **5** with an electron-rich 2-thiophenyl was employed to this transformation, a new cyclization product **6** was obtained in 68% yield (eq. 1). Owing to the subtle difference of electron property on unsaturated bonds between substrate **5** and **1p**, different cyclization products could be produced in the presence of catalytic amount of triflic acid. The substrate **7** was also performed under the optimized conditons, lactonisation product **8** was detected in 80% yield but no cycloisomerization product formed (eq. 2). To confirm reaction efficiency, we carried out gram-scale reaction using enyne **1a** as the substrate in the presence of 10 mol% catalyst TfOH. The carbocyclic product could still be obtained in 83% yield (eq. 3).



To extend this method to more challenging substrates, polyenynes was examined. To our delight, numbers of polycyclic single-nitrogen ketones could be synthesized via a cation-induced cascade cyclization of polyenynes in good yields (Scheme 4).

Substrate **9a** underwent cascade cyclization to afford product **10a** in 66% yield. This method has good functional tolerance as well. A variety of substituents, such as 4-Me, 4-CO_2Me, and 4-F, on the phenyl ring of polyenyne were worked well under the same acid-catalyzed conditions and gave the corresponding polycyclic single-nitrogen ketones (**10b-d**, 63-68%). The structure of **10b** was also confirmed by X-ray crystal structure analysis (see the Supporting Information (SI)).

Scheme 4. Triflic Acid-Catalyzed Cascade Cyclization[a]



[a]Conditions: **9** (0.1 mmol, 1.0 equiv), TfOH (0.9 μL, 0.01 mmol, 10 mol %), CH_2Cl_2 (2.0 mL, 0.05M), r.t., 2 h. Isolated yield.

In order to test the antiviral activity of the compound synthesized by this method, we conducted bioassays against tobacco mosaic virus (TMV) at a concentration of 200 μg mL^{-1}. These data are summarized in Table 2 and Figure 1. The results indicated that **10a** showed a good therapeutic effect on TMV, the percentage inhibition was 54.2%, which even exceeded that of ningnanmycin (48.5%). The above biological activity study results demonstrate that the polycyclic single-nitrogen

derivative has good biocontrol activity, though the detail effect on TMV of the molecule structure need to be further studied.

Table 2. Antiviral activities of the target compounds against TMV[a]

compound	percentage inhibition	toxic regression equation	R	EC_{50} (μg mL^{-1})
10a	54.2%	Y=0.8122X + 3.2188	0.9918	155.99
2c	45.2%	Y=1.0717X + 2.3804	0.9958	278.23
2r	32.1%	Y=1.4216X + 1.3442	0.9933	372.93
Ningnanmycin	48.5%	--	--	--

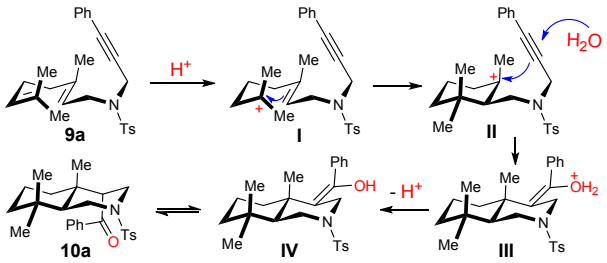
[a]Conditions: Tested and calculated at the drug test concentrations of 200 μg mL^{-1}. The data are average of three replicates. Agents ningnanmycin is commercial.

Figure 1. The test of antiviral activity against TMV

Right half leaves treated with the solution of **10a**

A plausible mechanism that is consistent with the experimental results mentioned above is proposed in Scheme 5. Protonation of the terminal trisubstituent alkene moiety in the presence of triflic acid leads to the relative stable carbocation **I**. Active carbocation **I** was attacked by another intramolecular nucleophilic group trisubstituent alkene, meanwhile the cationic cascade process is terminated by intermolecular H_2O capture to afford the intermediate **Ⅲ**. Then, enol intermediate **Ⅳ** was formed after a proton loss. Subsquently, enol isomerisation of **Ⅳ** to give fanal product.

Scheme 5. Possible Mechanism.



In summary, we have developed an efficient and straightforward triflic acid catalysis system to synthesize a variety of carbocycle-fused and heterocycle-fused ketones under mild reaction conditions. This catalytic reaction proceeds in a broad scope and good functional group tolerance, and can be easily scaled up. In addition, this method was also successfully applied to construct polycyclic single-nitrogen ketones via a cation-induced cascade cyclization of polyenynes. Antiviral bioassays revealed that compound **10a** exhibited good antiviral activity against TMV at a concentration of 200 μg mL^{-1}. A further investigation of potential bioactivity of these carbons and azaheterocyclic molecules are ongoing in our laboratory.

EXPERIMENTAL SECTION

General Methods

Unless otherwise noted, commercial reagents were purchased from Macklin, Energy, Aladdin, Adamas and so on. The solvents used in the reaction, such as dichloromethane, THF, and so on, are all analytical pure, and their water content is 0.03% - 0.05%. All reactions were carried out using oven-dried glassware and all catalytic reactions proceeded without special care. Analytical thin layer chromatography was carried out using silica gel GF254, and visualized under 254 nm

UV light or by staining with potassium permanganate. Column chromatography was performed on 200-300 mesh silica gel (Huanghai, China).

^{1}H, ^{19}F and $^{13}C\{^{1}H\}$ NMR spectra were recorded on an Bruker Ascend 400MHz spectrometer at ambient temperature. ^{1}H NMR spectra are referred to the TMS signal (δ = 0 ppm) and ^{13}C NMR spectra are referred to the residual solvent signal (δ = 77.16 ppm). Data for ^{1}H NMR are reported as follows: chemical shifts (δ ppm), multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz), integration. Data for $^{13}C\{^{1}H\}$ NMR and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (q = quartet), coupling constant (Hz).

Preparation of enyne substrates: The procedure for the synthesis of enyne substrates was based on the known procedure.[15a] Compounds **1b**, **1f-1j**, **1p**, **1r**, and **9** are new and their characterization data are as follows. Other starting compounds are known and their spectral data are in accordance with those reported in the literature.[15]

Diethyl 2-(3-methylbut-2-en-1-yl)-2-(3-(p-tolyl)prop-2-yn-1-yl)malonate (1b):

Colorless oil. IR (KBr): 2984, 2930, 1731, 1471, 1223, 1195, 660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, 2H), 7.06 (d, J = 7.9 Hz, 2H), 4.97 (ddd, J = 7.6, 4.4, 1.3 Hz, 1H), 4.26 – 4.15 (m, 4H), 2.97 (s, 2H), 2.83 (d, J = 8.4 Hz, 2H), 2.31 (s, 3H), 1.71 (s, 3H), 1.68 (s, 3H), 1.25 (t, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.3, 137.9, 136.5, 131.5, 129.0, 120.4, 117.5, 84.2, 83.3, 61.5, 57.4, 30.9, 26.1, 26.1, 23.4, 21.4, 18.1, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{22}H_{28}NaO_4$ $[M+Na]^+$: 379.1880, found: 379.1879.

Diethyl 2-(3-(4-(methoxycarbonyl)phenyl)prop-2-yn-1-yl)-2-(3-methylbut-2-en-1-yl)malonate (1f):

Colorless oil. IR (KBr): 2984, 2925, 1727, 1440, 1278, 1175, 1108 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 2H), 4.97 (t, *J* = 7.7 Hz, 1H), 4.32 – 4.14 (m, 4H), 3.91 (s, 3H), 3.02 (s, 2H), 2.84 (d, *J* = 7.6 Hz, 2H), 1.72 (s, 3H), 1.69 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.2, 166.7, 136.8, 131.6, 129.5, 129.3, 128.2, 117.3, 88.6, 82.7, 61.7, 57.4, 52.3, 31.0, 26.2, 23.5, 18.1, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{23}H_{28}NaO_6$ $[M+Na]^+$: 423.1778, found: 423.1771.

Diethyl 2-(3-(2-chlorophenyl)prop-2-yn-1-yl)-2-(3-methylbut-2-en-1-yl)malonate (1g):

Colorless oil. IR (KBr): 2984, 2925, 1731, 1471, 1223, 1195, 1061 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddd, *J* = 16.7, 7.4, 1.4 Hz, 2H), 7.23 – 7.10 (m, 2H), 5.04 – 4.92 (m, 1H), 4.31 – 4.11 (m, 4H), 3.06 (s, 2H), 2.87 (d, *J* = 7.7 Hz, 2H), 1.70 (d, *J* = 11.8 Hz, 6H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.2, 136.8, 135.9, 133.6, 129.2, 129.0, 126.4, 123.3, 117.4, 90.7, 80.1, 61.7, 57.5, 30.9, 26.2, 23.7, 18.2, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{25}ClNaO_4$ $[M+Na]^+$: 399.1334, found: 399.1332.

Diethyl 2-(3-(3-chlorophenyl)prop-2-yn-1-yl)-2-(3-methylbut-2-en-1-yl)malonate (1h):

Colorless oil. IR (KBr): 2984, 2933, 1735, 1451, 1294, 1195, 1057 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 7.28 – 7.16 (m, 3H), 5.02 – 4.86 (m, 1H), 4.32 – 4.14 (m, 4H), 2.98 (s, 2H), 2.82 (d, *J* = 7.7 Hz, 2H), 1.72 (s, 3H), 1.68 (s, 3H), 1.26

(tt, *J* = 6.5, 3.2 Hz, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.2, 136.8, 134.1, 131.5, 129.89, 129.5, 128.5, 128.3, 125.1, 117.3, 86.6, 82.0, 61.7, 57.4, 30.9, 26.2, 23.4, 18.1, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{25}ClNaO_4$ $[M+Na]^+$: 399.1334, found: 399.1331.

Diethyl 2-(3-(3,4-dimethylphenyl)prop-2-yn-1-yl)-2-(3-methylbut-2-en-1-yl)malonate (1i): Colorless oil. IR (KBr): 2930, 1737, 1461, 1223, 1195, 766, 657 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.06 (m, 1H), 7.05 – 6.96 (m, 1H), 6.92 – 6.79 (m, 1H), 4.92 – 4.80 (m, 1H), 4.20 – 4.07 (m, 4H), 2.93 (s, 2H), 2.74 (d, *J* = 7.7 Hz, 2H), 1.63 (s, 3H), 1.62 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.2, 136.8, 131.6, 126.9, 126.5, 123.5, 117.4, 89.2, 76.4, 61.7, 57.4, 31.0, 26.2, 23.8, 18.2, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{23}H_{30}NaO_4$ $[M+Na]^+$: 393.2036, found: 393.2036.

Diethyl 2-(3-methylbut-2-en-1-yl)-2-(3-(naphthalen-1-yl)prop-2-yn-1-yl)malonate (1j):

Colorless oil. IR (KBr): 2930, 1731, 1471, 1223, 1195, 765, 660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.58 – 7.52 (m, 1H), 7.49 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.38 (dt, *J* = 8.2, 5.6 Hz, 1H), 5.03 (t, *J* = 8.3, 7.0 Hz, 1H), 4.30 – 4.19 (m, 4H), 3.16 (s, 2H), 2.93 (d, *J* = 7.6 Hz, 2H), 1.73 (s, 3H), 1.69 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 6H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 170.4, 136.8, 133.5, 133.2, 130.5, 128.4, 128.3, 126.7, 126.4, 126.4, 125.3, 121.2, 117.5, 90.0, 81.4, 61.7, 57.6, 31.1, 26.2, 23.9, 18.2, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{25}H_{28}NaO_4$ $[M+Na]^+$: 415.1880, found: 415.1881.

4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(thiophen-3-yl)prop-2-yn-1-yl)benzenesulfonamide (1p):

White solid. mp: 84.4–85.0 °C. IR (KBr): 3114, 2921, 1345, 1164, 1089, 903 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.21 (dt, *J* = 8.4, 4.2 Hz, 1H), 7.13 (dd, *J* = 3.0, 1.0 Hz, 1H), 6.79 (dd, *J* = 5.0, 1.1 Hz, 1H),

5.26 – 5.12 (m, 1H), 4.27 (s, 2H), 3.88 (d, *J* = 7.3 Hz, 2H), 2.37 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 143.4, 139.2, 136.1, 129.6, 129.5, 128.8, 128.0, 125.3, 121.5, 118.1, 81.1, 80.6, 44.2, 36.4, 26.0, 21.6, 18.0. HR-MALDI-MS *m/z* calcd. for $C_{19}H_{21}NNaO_2S_2$ $[M+Na]^+$: 382.0906, found: 382.0900.

4-Methyl-*N*-(3-methylbut-2-en-1-yl)-*N*-(3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-yl)benzenesulfonamide (1r):

White solid. mp: 65.1–65.7 °C. IR (KBr): 2976, 2925, 1617, 1325, 1160, 1120, 655 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.73 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.34 – 7.22 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 5.19 (dddd, *J* = 7.3, 6.0, 2.7, 1.4 Hz, 1H), 4.31 (s, 2H), 3.90 (d, *J* = 7.3 Hz, 2H), 2.35 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 143.5, 139.4, 136.1, 131.8, 130.1, 129.6, 128.0, 126.5 (q, *J* = 263.2 Hz), 126.2 (q, *J* = 1.4 Hz), 125.25 (q, *J* = 3.9 Hz), 117.98, 85.14, 84.12, 44.39, 36.33, 26.06, 21.53, 18.04. ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.91. HR-MALDI-MS *m/z* calcd. for $C_{22}H_{22}F_3NNaO_2S$ $[M+Na]^+$: 444.1216, found: 444.1215.

(*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-4-methyl-*N*-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (9a):

White solid. 539.6 mg, 64% total yield. mp: 74.2–75.1 °C. IR (KBr): 2930, 2900, 1634, 1465, 910, 766, 660 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (t, *J* = 7.1 Hz, 2H), 7.32 – 7.18 (m, 5H), 7.08 – 6.99 (m, 2H), 5.20 – 5.13 (m, 1H), 5.09 – 5.00 (m, 1H), 4.28 (s, 2H), 3.89 (d, *J* = 7.3 Hz, 2H), 2.32 (s, 3H), 2.04 (ddd, *J* = 18.0, 14.7, 4.7 Hz, 4H), 1.68 (s, 6H), 1.59 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 143.4, 142.6, 136.1, 132.0, 131.5, 129.5, 128.4, 128.2, 128.0, 123.9, 122.4, 118.0, 85. 5,

82.3, 44.2, 39.8, 36.2, 26.3, 25.8, 21.5, 17.8, 16.3. HR-MALDI-MS *m/z* calcd. for $C_{26}H_{31}NNaO_2S$ $[M+Na]^+$: 444.1968, found: 444.1959.

(*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-4-methyl-N-(3-(*p*-tolyl)prop-2-yn-1-yl)benzenesulfonamide (9b):

White solid. 548.9 mg, 63% total yield. mp: 75.9–76.2 °C. IR (KBr): 2927, 2908, 1465, 1330, 1155, 911, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.19 – 7.13 (m, 2H), 6.95 (d, *J* = 7.9 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 5.07 (td, *J* = 7.2, 1.0 Hz, 1H), 4.96 (ddd, *J* = 6.7, 5.4, 1.2 Hz, 1H), 4.19 (s, 2H), 3.81 (d, *J* = 7.3 Hz, 2H), 2.24 (d, *J* = 6.3 Hz, 6H), 2.08 – 1.92 (m, 4H), 1.59 (s, 6H), 1.51 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 143.3, 142.5, 138.5, 136.1, 131.9, 131.4, 129.5, 128.9, 127.9, 123.9, 119.4, 118.1, 85. 6, 81.6, 44.1, 39.7, 36.3, 26.4, 25.8, 21.5, 17.8, 16.3. HR-MALDI-MS *m/z* calcd. for $C_{27}H_{33}NNaO_2S$ $[M+Na]^+$: 458.2124, found: 458.2124.

4-(3-(*N*-(3,7-dimethylocta-2,6-dien-1-yl)-4-methylphenylsulfonamido)prop-1-yn-1-yl)benzoate (9c):

White solid. 565.9 mg, 59% total yield. mp: 87.3–88.9 °C. IR (KBr): 2913, 1600, 1515, 1327, 1150, 913, 845, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.13 – 7.05 (m, 2H), 5.18 – 5.12 (m, 1H), 5.08 – 4.99 (m, 1H), 4.29 (s, 2H), 3.92 (s, 3H), 3.89 (d, *J* = 7.3 Hz, 2H), 2.33 (s, 3H), 2.11 – 2.02 (m, 4H), 1.68 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 166.5, 143.6, 142.8, 136.1, 132.1, 131.4, 129.6, 129.4, 128.0, 127.8, 127.1, 123.8, 117. 9, 85.6, 84.7, 52.4, 44.3, 39.8, 36.2, 26.3, 25.9, 21.6, 17.8,

16.3, 16.3. HR-MALDI-MS *m/z* calcd. for $C_{28}H_{33}NNaO_4S$ $[M+Na]^+$: 502.2023, found: 502.2022.

(*E*)-*N*-(3,7-Dimethylocta-2,6-dien-1-yl)-*N*-(3-(4-fluorophenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide (9d):

White solid. 526.8 mg, 60% total yield. mp: 71.3–71.9 °C. IR (KBr): 2910, 2855, 1515, 1330, 1155, 843, 650 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.25 (t, *J* = 6.5 Hz, 2H), 7.07 – 6.98 (m, 2H), 6.98 – 6.86 (m, 2H), 5.15 (td, *J* = 7.3, 1.0 Hz, 1H), 5.04 (td, *J* = 5.4, 2.6 Hz, 1H), 4.26 (s, 2H), 3.88 (dj, *J* = 8.2 Hz, 2H), 2.33 (s, 3H), 2.11 – 2.01 (m, 4H), 1.68 (s, 6H), 1.59 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 249.8 Hz), 143.4, 142.6, 136.2, 133.4 (d, *J* = 8.4 Hz), 132.0, 129.5, 128.0, 123.8, 118.5 (d, *J* = 3.5 Hz), 118.0, 118.5 (d, *J* = 3.5 Hz), 84.3, 82.1, 82.1, 44.2, 39.7, 36.2, 26.2, 25.8, 21.5, 17.8, 16.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ -110.63. HR-MALDI-MS *m/z* calcd. for $C_{26}H_{30}FNNaO_2S$ $[M+Na]^+$: 462.1874, found: 462.1873.

(*E*)-Methyl

General procedure for triflic acid-catalyzed cyclization of enynes: To a solution of enyne substrate (0.1 mmol, 1.0 equiv) in wet CH_2Cl_2 (2 mL, 0.05M) at room temperature was added TfOH (0.9 μL, 0.01 mmol, 0.1 equiv). The resultant mixture was stirred at room temperature for 2 h. Next the mixture was concentrated *in vacuo* and purified by preparative TLC (eluent: PE/EtOAc = 10/1, v/v) to yield the corresponding cyclization product.

Diethyl 3-benzoyl-4,4-dimethylcyclohexane-1,1-dicarboxylate (2a):

Colorless oil. 31.4 mg, 87% yield. IR (KBr): 2925, 2846, 1731, 1522, 1239, 545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.51 – 7.43 (m, 1H), 7.43 – 7.34 (m, 2H), 4.28 – 4.15 (m, 2H), 4.12 – 4.03 (m, 2H), 3.61 (dd, *J* = 12.7, 3.3 Hz, 1H), 2.24 – 2.11 (m, 2H), 2.09 – 1.96 (m, 2H), 1.39 – 1.29 (m, 2H), 1.22 (t, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 3H), 0.75 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.3, 171.9, 171.5, 138.9, 133.0, 128.7, 128.3, 61.6, 61.5, 54.8, 48. 6, 38.7, 33.3, 31.3, 30.2, 26.8, 20.3, 14.3, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{28}NaO_5$ $[M+Na]^+$: 383.1829, found: 383.1822.

Diethyl 4,4-dimethyl-3-(4-methylbenzoyl)cyclohexane-1,1-dicarboxylate (2b):

Colorless oil. 31.8 mg, 85% yield. IR (KBr): 3460, 2961, 2929, 2862, 1727, 1672, 1243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 9.6 Hz, 2H), 4.36 – 4.22 (m, 2H), 4.20 – 4.08 (m, 2H), 3.64 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.41 (s, 3H), 2.24 (ddd, *J* = 16.5, 5.5, 2.4 Hz, 2H), 2.15 – 2.04 (m, 2H), 1.46 – 1.35 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H), 0.82 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 202.8, 171.9, 171.5, 143.7, 136.4, 129.4, 128.5, 61.6, 61. 5, 54.8, 48.3, 38.7, 33.2, 31.3, 30.2, 26.8, 21.7, 20.3, 14.3, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{22}H_{30}NaO_5$ $[M+Na]^+$: 397.1985, found: 397.1989

Diethyl 3-(4-fluorobenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2c):

Colorless oil. 33.3 mg, 88% yield. IR (KBr): 2972, 2933, 1731, 1684, 1589, 1227, 1156 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H), 7.09 – 7.00 (m, 2H), 4.29 – 4.15 (m, 2H), 4.14 – 4.02 (m, 2H), 3.57 (dd, *J* = 12.7, 3.3 Hz, 1H), 2.23 – 2.10 (m, 2H), 2.09 – 1.96 (m, 2H), 1.40 – 1.26 (m, 2H), 1.22 (t, 3H), 1.15 (t, *J* = 7.1 Hz,

3H), 1.00 (s, 3H), 0.76 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 201. 7, 171.8, 171.5, 165.8 (d, J = 254.5 Hz), 135.2 (d, J = 2.9 Hz), 131. 0 (d, J = 9.3 Hz), 115. 8 (d, J = 21.8 Hz), 61.7, 61.5, 54.8, 48.5, 38.7, 33.3, 31.2, 30.3, 26.7, 20.2, 14.3, 14.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.84. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{27}FNaO_5$ $[M+Na]^+$: 401.1735, found: 401.1731.

Diethyl 3-(4-chlorobenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2d):

Colorless oil. 32.8 g, 83% yield. IR (KBr): 2968, 1735, 1684, 1589, 1250, 1093, 848 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.47 – 7.39 (m, 2H), 4.35 – 4.21 (m, 2H), 4.21 – 4.10 (m, 2H), 3.63 (dd, J = 12.7, 3.3 Hz, 1H), 2.24 (ddt, J = 14.1, 9.3, 2.9 Hz, 2H), 2.14 – 2.03 (m, 2H), 1.46 – 1.34 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H), 1.06 (s, 3H), 0.82 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 202.1, 171.8, 171.5, 139.4, 137.1, 129.7, 129.0, 61.7, 61.5, 54.7, 48.6, 38.6, 33.3, 31.2, 30.2, 26.7, 20.2, 14.3, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{27}ClNaO_5$ $[M+Na]^+$: 417.1439, found: 417.1434.

Diethyl 3-(4-formylbenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2e):

Colorless oil. 29.5 mg, 76% yield. IR (KBr): 2980, 1727, 1290, 1250, 1160, 1045, 864 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.13 (d, J = 8.2 Hz, 2H), 7.98 (d, J = 8.2 Hz, 2H), 4.38 – 4.23 (m, 2H), 4.23 – 4.10 (m, 2H), 3.71 (dd, J = 12.7, 3.2 Hz, 1H), 2.34 – 2.19 (m, 2H), 2.16 – 2.04 (m, 2H), 1.48 – 1.35 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 12.1, 5.0 Hz, 3H), 1.07 (s, 3H), 0.82 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.0, 191.8, 171.7, 171.5, 143.3, 138.9, 130.0, 128.8, 61.8, 61.6, 54.7, 49.4, 38.6, 33.4, 31.3, 30.1, 26.7, 20.2, 14.3, 14.2. HR-MALDI-MS *m/z*

calcd. for $C_{22}H_{28}NaO6$ $[M+Na]^+$: 411.1778, found: 411.1773.

Diethyl

3-(4-(methoxycarbonyl)benzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2f):

Colorless oil. 33.5 mg, 80% yield. IR (KBr): 2956, 2862, 1731, 1684, 1282, 1246, 1160 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2H), 7.96 (d, 2H), 4.29 – 4.16 (m, 2H), 4.14 – 4.04 (m, 2H), 3.88 (s, 3H), 3.61 (dd, *J* = 12.7, 3.3 Hz, 1H), 2.27 – 2.12 (m, 2H), 2.09 – 1.97 (m, 2H), 1.39 – 1.28 (m, 2H), 1.23 (t, *J* = 8.5, 5.7 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 3H), 0.74 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.0, 171.8, 171.4, 166.4, 142.2, 133.7, 130.0, 128.2, 61.7, 61.6, 54.7, 52. 6, 49.2, 38.6, 33.3, 31.3, 30.1, 26.7, 20.2, 14.3, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{23}H_{30}NaO_7$ $[M+Na]^+$: 441.1884, found: 441.1875.

Diethyl 3-(2-chlorobenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2g):

Colorless oil. 28.8 mg, 73% yield. IR (KBr): 2972, 2870, 1735, 1680, 1570, 1467, 1049 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 7.4, 1.8 Hz, 1H), 7.40 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38 – 7.29 (m, 2H), 4.29 – 4.21 (m, 2H), 4.21 – 4.13 (m, 2H), 3.49 (dd, *J* = 12.8, 3.3 Hz, 1H), 2.42 – 2.33 (m, 1H), 2.24 – 2.15 (m, 2H), 2.06 – 1.93 (m, 1H), 1.41 – 1.34 (m, 2H), 1.31 – 1.21 (m, 6H), 1.04 (s, 3H), 0.83 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 205.4, 172.0, 171.2, 141.5, 131.6, 130.9, 130.8, 129.1, 126.9, 61. 7, 61.5, 54.7, 53.7, 38.7, 33.8, 31.1, 29.4, 26.7, 20.3, 14.2, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{27}ClNaO_5$ $[M+Na]^+$: 417.1439, found: 417.1433.

Diethyl 3-(3-chlorobenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2h):

Colorless oil. 31.6 mg, 80% yield. IR (KBr): 2980, 1727, 1688, 1471, 1243, 1156,

758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J* = 1.8 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.53 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 4.38 – 4.25 (m, 2H), 4.20 – 4.10 (m, 2H), 3.60 (dd, *J* = 12.7, 3.2 Hz, 1H), 2.35 – 2.17 (m, 2H), 2.18 – 2.02 (m, 2H), 1.49 – 1.36 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 3H), 0.83 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 202.1, 171.8, 171.4, 140.4, 135.1, 132.9, 130.1, 128.3, 126.5, 61.7, 61.6, 54.7, 48.9, 38.6, 33.3, 31.2, 30.1, 26.7, 20.2, 14.3, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{27}ClNaO_5$ $[M+Na]^+$: 417.1439, found: 417.1436.

Diethyl 3-(3,4-dimethylbenzoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2i):

Colorless oil. 33.0 mg, 85% yield. IR (KBr): 2925, 2862, 1680, 1349, 1160, 722, 545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.61 (m, 2H), 7.14 (d, *J* = 7.7 Hz, 1H), 4.28 – 4.16 (m, 2H), 4.12 – 4.03 (m, 2H), 3.55 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 2.21 – 2.10 (m, 2H), 2.09 – 1.96 (m, 2H), 1.37 – 1.29 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 3H), 0.75 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.1, 172.0, 171.5, 142.5, 137.1, 136.8, 129.9, 129.4, 126.2, 61.6, 61. 5, 54.8, 48.3, 38.7, 33.2, 31.3, 30.2, 26.8, 20.4, 20.1, 20.0, 14.3, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{23}H_{32}NaO_5$ $[M+Na]^+$: 411.2142, found: 411.2137.

Diethyl 3-(1-naphthoyl)-4,4-dimethylcyclohexane-1,1-dicarboxylate (2j):

Colorless oil. 27.9 mg, 68% yield. IR (KBr): 2984, 1727, 1684, 1459, 1246, 1156, 793 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 8.5 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.93 – 7.84 (m, 2H), 7.62 – 7.48 (m, 3H), 4.37 – 4.24 (m, 2H), 4.24 – 4.14 (m, 2H), 3.70 (dd, *J* = 12.8, 3.3 Hz, 1H), 2.50 – 2.34 (m, 1H), 2.31 – 2.18 (m, 2H), 2.11

(td, J = 13.6, 4.7 Hz, 1H), 1.44 – 1.33 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.25 (t, 3H), 1.14 (s, 3H), 0.74 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 207.3, 172.0, 171.5, 139.0, 134.2, 132.3, 129.8, 128.6, 127.9, 127.2, 126.5, 125.8, 124.6, 61.7, 61.5, 54.9, 53.2, 38.9, 33.9, 31.4, 30.1, 26.8, 20.2, 14.3, 14.2. HR-MALDI-MS *m/z* calcd. for $C_{25}H_{30}NaO_5$ $[M+Na]^+$: 433.1985, found: 433.1978.

(5,5-Bis(methoxymethyl)-2,2-dimethylcyclohexyl)(phenyl)methanone (2k):

Colorless oil. 28.3 mg, 93% yield. IR (KBr): 2921, 2866, 1680, 1451, 1112, 689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 5.2, 3.4 Hz, 2H), 7.52 – 7.43 (m, 1H), 7.41 – 7.33 (m, 2H), 3.43 – 3.35 (m, 3H), 3.33 (s, 3H), 3.24 (s, 3H), 3.13 – 3.06 (m, 2H), 1.62 (q, J = 14.3 Hz, 2H), 1.55 – 1.35 (m, 2H), 1.26 – 1.15 (m, 1H), 1.24 – 1.12 (m, 2H), 0.99 (s, 3H), 0.80 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 204.0, 139.0, 132.7, 128.6, 128.2, 79.8, 72.9, 59.5, 59.5, 47.7, 38.8, 37.8, 33. 9, 31.4, 29.3, 25.8, 20.2. HR-MALDI-MS *m/z* calcd. for $C_{19}H_{28}NaO_3$ $[M+Na]^+$: 327.1931, found: 327.1933.

(3-Benzoyl-4,4-dimethylcyclohexane-1,1-diyl)bis(methylene) diacetate (2l):

Colorless oil. 31.3 mg, 87% yield. IR (KBr): 2925, 2854, 1735, 1680, 1231, 1037, 691 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 10.9, 3.7 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.45 – 7.35 (m, 2H), 4.27 (d, J = 11.4 Hz, 1H), 4.05 (d, J = 11.4 Hz, 1H), 3.95 – 3.76 (m, 2H), 3.46 (dd, J = 13.1, 3.2 Hz, 1H), 1.99 (s, 3H), 1.98 (s, 3H), 1.85 – 1.75 (m, 1H), 1.45 (dtd, J = 16.3, 13.6, 6.7 Hz, 4H), 1.24 (dd, J = 10.4, 7.7 Hz, 1H), 0.94 (s, 3H), 0.79 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.5, 171.3, 171.2, 138. 9, 133.0, 128.8, 128.3, 70.1, 63.4, 47.0, 37.2, 37.1, 33.9, 31.6, 28.5, 25.3, 21.0,

20.1. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{28}NaO_5$ $[M+Na]^+$: 383.1829, found: 383.1826.

Dimethyl 3-benzoyl-4,4-dimethylcyclohexane-1,1-dicarboxylate (2m):

Colorless oil. 29.6 mg, 89% yield. IR (KBr): 3458, 2960, 2930, 2865, 1727, 1243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (dt, *J* = 8.6, 1.7 Hz, 2H), 7.61 – 7.52 (m, 1H), 7.51 – 7.41 (m, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.65 (dd, *J* = 12.6, 3.3 Hz, 1H), 2.33 – 2.20 (m, 2H), 2.20 – 2.06 (m, 2H), 1.47 – 1.32 (m, 2H), 1.07 (s, 3H), 0.83 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 203.2, 172.3, 171.9, 138.9, 133.0, 128.7, 128.3, 54.9, 52.9, 52.8, 48.6, 38.7, 33.2, 31.3, 30.3, 26.9, 20.3. HR-MALDI-MS *m/z* calcd. for $C_{19}H_{24}NaO_5$ $[M+Na]^+$: 355.1516, found: 355.1517.

2,2-Dimethyl-5,5-bis(phenylsulfonyl)cyclohexyl)(phenyl)methanone (2n):

White solid. 41.7 mg, 84% yield. mp: 147.4–147.8 °C. IR (KBr): 2933, 2854, 1448, 1341, 1156, 923, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.4 Hz, 2H), 8.07 – 8.02 (m, 2H), 8.01 – 7.96 (m, 2H), 7.71 (dt, *J* = 10.1, 7.1 Hz, 2H), 7.63 – 7.56 (m, 5H), 7.47 (t, *J* = 7.6 Hz, 1H), 4.45 (dd, *J* = 12.7, 3.6 Hz, 1H), 2.89 (dd, *J* = 15.5, 12.8 Hz, 1H), 2.65 – 2.53 (m, 1H), 2.34 – 2.17 (m, 3H), 1.50 – 1.39 (m, 1H), 0.87 (s, 3H), 0.83 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 202.6, 138.5, 136.3, 135.9, 134.8, 134.7, 133. 5, 131.7, 131.3, 128.9, 128.8, 128.8, 128.4, 87.5, 46.5, 36.8, 32.8, 31.0, 26.4, 22.1, 19.6. HR-MALDI-MS *m/z* calcd. for $C_{27}H_{28}NaO_5S_2$ $[M+Na]^+$: 519.1270, found: 519.1270.

(4,4-Dimethyl-1-tosylpiperidin-3-yl)(phenyl)methanone (2o):

White solid. 24.3 mg, 65% yield. mp: 120.4–120.9 °C. IR (KBr): 2925, 1787, 1353,

1160, 742, 553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.68 – 7.63 (m, 2H), 7.62 – 7.55 (m, 1H), 7.51 – 7.43 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.75 – 3.59 (m, 3H), 2.82 – 2.72 (m, 1H), 2.55 – 2.47 (m, 1H), 2.46 (s, 3H), 1.77 (td, *J* = 13.2, 4.6 Hz, 1H), 1.46 (dt, *J* = 13.5, 2.7 Hz, 1H), 0.86 (s, 3H), 0.83 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 201.5, 143.8, 138.3, 133.5, 133.3, 129.9, 128.8, 128.4, 127. 8, 50.9, 44.6, 42. 6, 40.1, 32. 6, 31.3, 21.7, 19.9. HR-MALDI-MS *m/z* calcd. for $C_{21}H_{25}NNaO_3S$ $[M+Na]^+$: 394.1447, found: 394.1443.

(4,4-Dimethyl-1-tosylpiperidin-3-yl)(thiophen-3-yl)methanone (2p):

Colorless oil. 23.4 mg, 62% yield. IR (KBr): 2925, 2580, 1664, 1357, 1164, 1093, 955 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.46 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.32 – 7.23 (m, 3H), 3.68 – 3.53 (m, 2H), 3.33 (dd, *J* = 11.5, 3.7 Hz, 1H), 2.67 (t, *J* = 11.8 Hz, 1H), 2.49 – 2.32 (m, 4H), 1.75 – 1.63 (m, 1H), 1.38 (ddd, *J* = 9.0, 5.9, 2.2 Hz, 1H), 0.87 (s, 3H), 0.77 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 195.1, 143.8, 143.5, 133.3, 133.2, 130.0, 127. 8, 127.3, 126.8, 53.3, 44.5, 42.5, 40.1, 32.5, 31.4, 21.7, 19.8. HR-MALDI-MS *m/z* calcd. for $C_{19}H_{23}NNaO_3S_2$ $[M+Na]^+$: 400.1012, found: 400.1007.

(4,4-Dimethyl-1-tosylpiperidin-3-yl)(4-methoxyphenyl)methanone (2q):

White solid. 28.1 mg, 70% yield. mp: 137.4–137.9 °C. IR (KBr): 2956, 2925, 2854, 1455, 1337, 1164, 545 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 6.98 – 6.95 (m, 1H), 6.81 (d, *J* = 2.3 Hz, 1H), 6.68 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.80 – 3.76 (m, 2H), 3.74 (s, 3H), 3.73 – 3.69 (m, 1H), 3.30 (t, *J* = 5.7 Hz, 2H), 2.50 – 2.44 (m, 2H), 2.35 (s, 3H), 1.13 (s, 6H). ^{13}C {1H} NMR (101

MHz, $CDCl_3$) δ 158.3, 155.3, 143. 7, 142.3, 134.7, 134.1, 130.7, 129.9, 127.7, 118.8, 111.2, 108.5, 55.7, 48.7, 43.3, 43.0, 24. 5, 22.6, 21. 7. HR-MALDI-MS *m/z* calcd. for $C_{22}H_{27}NNaO_4S$ $[M+Na]^+$: 424.1553, found: 424.1547.

(4,4-Dimethyl-1-tosylpiperidin-3-yl)(4-(trifluoromethyl)phenyl)methanone (2r):

White solid. 27.6 mg, 63% yield. mp: 140.4–140.9 °C. IR (KBr): 2958, 2931, 1447, 1344, 1161, 1093, 907, 759, 553 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.2 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.59 (d, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 3.67 – 3.52 (m, 3H), 2.72 (t, *J* = 12.4 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.39 (s, 3H), 1.77 – 1.64 (m, 1H), 1.41 (dt, *J* = 13.7, 2.8 Hz, 1H), 0.79 (s, 3H), 0.75 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 200.8, 143.9, 141.0, 133.3, 130.0, 128.7, 128.5 (q, *J* = 413.0 Hz), 127.8, 126.0 (q, *J* = 3.7 Hz), 51.5, 44.4, 42.5, 40.0, 32.8, 31.4, 21.7, 19.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.13. HR-MALDI-MS *m/z* calcd. for $C_{22}H_{24}F_3NNaO_3S$ $[M+Na]^+$: 462.1321, found: 462.1321.

(4,4-Dimethyl-1-tosylpyrrolidin-3-yl)(phenyl)methanone (4a):

Colorless oil. 25.4 mg, 71% yield. IR (KBr): 2968, 2882, 1676, 1345, 1160, 1101, 663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.68 (m, 4H), 7.54 – 7.47 (m, 1H), 7.43 – 7.36 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 3.73 (t, *J* = 7.6 Hz, 1H), 3.60 (ddd, *J* = 28.4, 10.0, 7.6 Hz, 2H), 3.16 (d, *J* = 9.5 Hz, 1H), 3.04 (d, *J* = 9.5 Hz, 1H), 2.39 (s, 3H), 1.04 (s, 3H), 0.62 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 199.1, 143.6, 137.8, 134.0, 133.6, 129.8, 128.9, 128.5, 127.8, 61.0, 53.2, 49.7, 42.5, 27.6, 22.4, 21.7. HR-MALDI-MS *m/z* calcd. for $C_{20}H_{23}NNaO_3S$ $[M+Na]^+$: 380.1291, found: 380.1289.

(4,4-Dimethyl-1-tosylpyrrolidin-3-yl)(4-fluorophenyl)methanone (4b):

White solid. 24.8 mg, 66% yield. mp: 79.8–80.5 °C. IR (KBr): 2930, 2854, 1545, 1156, 1015, 927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.75 (m, 2H), 7.73 – 7.67 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.10 – 7.00 (m, 2H), 3.67 (dd, *J* = 14.2, 6.6 Hz, 1H), 3.62 – 3.51 (m, 2H), 3.16 (d, *J* = 9.5 Hz, 1H), 3.04 (d, *J* = 9.5 Hz, 1H), 2.39 (s, 3H), 1.06 (s, 3H), 0.62 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 197.5, 166.1 (d, *J* = 260.0 Hz), 143.7, 134.2 (d, *J* = 3.1 Hz), 134.0, 131.2 (d, *J* = 9.4 Hz), 129.8, 127.8, 116.0 (d, *J* = 21.9 Hz) 61.0, 53.2, 49.8, 42.6, 27.7, 22.5, 21.8. ^{19}F NMR (377 MHz, $CDCl_3$) δ -104.28. HR-MALDI-MS *m/z* calcd. for $C_{20}H_{22}FNNaO_3S$ $[M+Na]^+$: 398.1197, found: 398.1192.

(4-Chlorophenyl)(4,4-dimethyl-1-tosylpyrrolidin-3-yl)methanone (4c):

White solid. 25.0 mg, 64% yield. mp: 78.4–79.0 °C. IR (KBr): 2965, 2925, 2865, 1345, 1015, 670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 3H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.36 – 7.26 (m, 3H), 3.71 – 3.48 (m, 3H), 3.15 (d, *J* = 9.5 Hz, 1H), 3.04 (d, *J* = 9.5 Hz, 1H), 2.40 (s, 3H), 1.04 (s, 3H), 0.63 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 198.0, 143.7, 139.3, 135.3, 133.9, 133.5, 130.2, 129.9, 128.5, 127.8, 126.6, 60.9, 53.4, 49.6, 42.7, 27.6, 22. 5, 21.8. HR-MALDI-MS *m/z* calcd. for $C_{20}H_{22}ClNNaO_3S$ $[M+Na]^+$: 414.0901, found: 414.0896.

(4-Methyl-4-phenyl-1-tosylpyrrolidin-3-yl)(phenyl)methanone (4d):

Colorless oil. 25.6 mg, 61% yield. IR (KBr): 2916, 1599, 1451, 1333, 1156, 1108, 908, 754, 563 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 2H), 7.58 – 7.46 (m, 3H), 7.38 – 7.30 (m, 4H), 7.11 – 7.03 (m, 3H), 6.95 – 6.88 (m, 2H), 4.18 (dd, J =

7.7, 3.2 Hz, 1H), 4.11 – 4.03 (m, 1H), 3.91 (dd, J = 10.7, 7.7 Hz, 1H), 3.70 (d, J = 8.7 Hz, 1H), 3.55 (dt, J = 16.2, 8.1 Hz, 1H), 2.44 (s, 3H), 1.47 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 199.4, 143.6, 143.1, 137.3, 134.3, 133.2, 129.9, 128. 7, 128.4, 128.1, 127.6, 126.6, 125.9, 57.9, 53.4, 50.2, 50.1, 30.1, 21.7. HR-MALDI-MS *m/z* calcd. for $C_{25}H_{25}NNaO_3S$ $[M+Na]^+$: 442.1447, found: 442.1447.

3-(Prop-1-en-2-yl)-4-(thiophen-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (6):

White solid. 24.4 mg, 68% yield. mp: 142.4–143.1 °C. IR (KBr): 3075, 2854, 1471, 1333, 1156, 663 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.04 (dd, *J* = 3.8, 2.4 Hz, 1H), 6.88 – 6.80 (m, 2H), 6.06 – 5.99 (m, 1H), 4.87 (s, 1H), 4.79 (s, 1H), 4.04 – 3.94 (m, 1H), 3.66 (dt, *J* = 33.0, 16.5 Hz, 1H), 3.32 (ddd, *J* = 13.3, 6.6, 4.2 Hz, 1H), 3.21 (s, 1H), 2.75 (dd, *J* = 11.6, 4.1 Hz, 1H), 2.36 (s, 3H), 1.77 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 143.9, 143.8, 143. 7, 133.4, 131.9, 129. 8, 127.9, 127. 5, 123.9, 123.3, 119.6, 115.1, 47.3, 45.7, 45.0, 29.8, 21. 7, 21.6. HR-MALDI-MS *m/z* calcd. for $C_{19}H_{21}NNaO_2S_2$ $[M+Na]^+$: 382.0906, found: 382.0904.

Ethyl

5,5-dimethyl-2-oxo-3-(3-phenylprop-2-yn-1-yl)tetrahydrofuran-3-carboxylate

(8):

Colorless oil. 24.0 mg, 80% yield. IR (KBr): 2935, 2854, 1355, 1165, 758, 655, 541 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.1, 2.6 Hz, 2H), 7.33 – 7.20 (m, 2H), 4.37 – 4.17 (m, 2H), 3.24 – 3.10 (m, 1H), 3.05 (d, *J* = 16.9 Hz, 1H), 2.66 (t, *J* = 14.6 Hz, 1H), 2.57 (t, *J* = 18.4 Hz, 1H), 1.61 (s, 6H), 1.33 (t, 3H). ^{13}C {1H} NMR

(101 MHz, $CDCl_3$) δ 173.2, 169. 8, 131.8, 128.4, 122.9, 84.4, 84.0, 83.0, 62.8, 56.9, 43.2, 29.9, 28.9, 26.5, 14.1. HR-MALDI-MS *m/z* calcd. for $C_{18}H_{20}NaO_4$ $[M+Na]^+$: 323.1254, found: 323.1256.

Phenyl(4a,8,8-trimethyl-2-tosyldecahydroisoquinolin-4-yl)methanone (10a):

White solid. 29.0 mg, 66% yield. mp: 124.4–125.0 °C. IR (KBr): 3445, 2925, 2854, 1633, 1160, 714, 549 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.51 (m, 1H), 7.44 (dd, *J* = 10.5, 4.7 Hz, 2H), 7.29 (t, *J* = 6.7 Hz, 2H), 3.72 – 3.65 (m, 2H), 3.22 (dd, *J* = 4.7, 2.0 Hz, 1H), 3.11 (dd, *J* = 12.9, 4.8 Hz, 1H), 2.62 – 2.53 (m, 2H), 2.43 (s, 3H), 1.59 – 1.53 (m, 1H), 1.47 (dd, *J* = 12.6, 3.1 Hz, 1H), 1.37 (ddd, *J* = 13.4, 10.6, 5.7 Hz, 2H), 1.31 – 1.22 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.81 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 200.5, 143.4, 138.4, 134.5, 133.0, 129.7, 128.8, 128.2, 127.8, 51.6, 44.2, 43.2, 42.3, 41.7, 36.5, 36.3, 33.0, 32.5, 22.3, 21.7, 21.0, 18.6. HR-MALDI-MS *m/z* calcd. for $C_{26}H_{33}NNaO_3S$ $[M+Na]^+$: 462.2073, found: 462.2073.

***p*-Tolyl(4a,8,8-trimethyl-2-tosyldecahydroisoquinolin-4-yl)methanone (10b)**:

White solid. 30.8 mg, 68% yield. mp: 154.4–154.9 °C. IR (KBr): 2921, 2854, 1522, 1160, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 3.71 – 3.60 (m, 2H), 3.20 (dd, *J* = 4.7, 2.1 Hz, 1H), 3.11 (dd, *J* = 12.9, 4.7 Hz, 1H), 2.69 – 2.53 (m, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 1.62 – 1.50 (m, 1H), 1.45 (dd, *J* = 12.6, 3.2 Hz, 1H), 1.41 – 1.32 (m, 2H), 1.30 – 1.20 (m, 2H), 1.11 (s, 3H), 0.94 (s, 3H), 0.80 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 200.1, 143.8, 143.3, 135.6, 134.6, 129.6, 129. 5, 128.3,

127.8, 51.4, 44.2, 43.2, 42.3, 41.7, 36.5, 36.3, 33.0, 32.5, 22.3, 21.7, 21.7, 21.1, 18.6. HR-MALDI-MS *m/z* calcd. for $C_{27}H_{35}NNaO_3S$ $[M+Na]^+$: 476.2230, found: 476.2228.

Methyl 4-(4a,8,8-trimethyl-2-tosyldecahydroisoquinoline-4-carbonyl)benzoate (10c):

White solid. mp: 188.7–189.1 °C. 31.8 mg, 64% yield. IR (KBr): 2925, 2854, 1727, 1282, 1156, 1105, 730 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.06 (m, 2H), 7.90 – 7.81 (m, 21H), 7.69 – 7.63 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.95 (s, 3H), 3.72 – 3.63 (m, 2H), 3.19 (dd, *J* = 4.6, 2.0 Hz, 1H), 3.09 (dd, *J* = 12.8, 4.7 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.43 (s, 3H), 1.64 – 1.59 (m, 2H), 1.49 – 1.39 (m, 2H), 1.27 (ddd, *J* = 15.5, 11.7, 3.5 Hz, 2H), 1.11 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 200.1, 166.3, 143.5, 141.7, 134.5, 133.7, 130.0, 129.7, 128.0, 127.8, 52.6, 52.2, 44.3, 43.1, 42.4, 41.7, 36.5, 36.4, 33.0, 32.5, 22.3, 21.7, 21.0, 18.6. HR-MALDI-MS *m/z* calcd. for $C_{28}H_{35}NNaO_5S$ $[M+Na]^+$: 520.2128, found: 520.2128.

(4-Fluorophenyl)(4a,8,8-trimethyl-2-tosyldecahydroisoquinolin-4-yl)methanone (10d):

White solid. mp: 166.5–167.0 °C. 28.8 mg, 63% yield. IR (KBr): 2929, 2854, 1546, 1156, 1014, 927 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (ddd, *J* = 8.3, 5.2, 2.5 Hz, 2H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.16 – 7.06 (m, 2H), 3.70 – 3.60 (m, 2H), 3.16 (dd, *J* = 4.6, 1.9 Hz, 1H), 3.12 – 3.05 (m, 1H), 2.62 – 2.50 (m, 2H), 2.43 (s, 3H), 1.64 – 1.56 (m, 2H), 1.46 – 1.36 (m, 2H), 1.30 – 1.21 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.81 (s, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$) δ 198.8, 165.6 (d, *J* = 254.8 Hz), 143.4, 134.7 (d, *J* = 17.4 Hz), 130.8 (d, *J* = 9.2 Hz), 129.7, 127.8,

115.9 (d, J = 21.8 Hz), 51.6, 44.2, 43.2, 42.3, 41.7, 36.6, 36.3, 33.0, 32.5, 22.3, 21.7, 21.1, 18.6. ^{19}F NMR (377 MHz, $CDCl_3$) δ -105.69. HR-MALDI-MS *m/z* calcd. for $C_{26}H_{32}FNNaO_3S$ $[M+Na]^+$: 480.1979, found: 480.1976.

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SUPPORTING INFORMATION

Copies of ^{1}H and ^{13}CNMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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