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Article

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Stereospecific Synthesis of *cis*-2,5-disubstituted pyrrolidines via *N,O*-acetals Formed by Hydroamination Cyclization-Hydroalkoxylation of Homopropargylic Sulfonamides in HFIP

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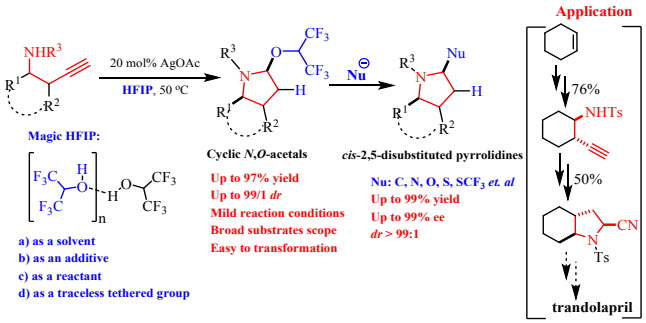


KEYWORDS: HFIP, Hydroamination cyclization-hydroalkoxylation, 2,5-*cis*-Disubstituted pyrrolidine, *Formal* nucleophilic substitution

ABSTRACT

We reported a novel two-step stereoselective synthesis of functionalized pyrrolidines from homopropargylic sulfonamides and nucleophiles via an isolable *N*,*O*-acetals intermediates. This reaction features mild conditions and good scope of substrates. And the use of hexafluoroisopropanol, acting as a solvent, an additive, a weak nucleophile and a good leaving group, is pivotal to the success of the method. Moreover, reactions of chiral homopropargylic sulfonamides afford only 2,5-*cis*-disubstituted pyrrolidines with high diastereoselectivity (up to >99:1 *dr*) and enantioselectivity (up to >99% ee). The overall reaction constitutes a *formal* 1,1-bifunctionalization of terminal alkynes, which has hitherto been reported only rarely. Additionally, this method provides an efficient access to pharmaceutical intermediate and to carry out post-modification of natural products.

INTRODUCTION

The pyrrolidines are ubiquitous building blocks in natural products, pharmaceuticals and materials.[1] Thus the development of effective methods for accessing pyrrolidines has been a focus of research by synthetic chemists. And many successful synthetic methods have been reported up to date.[2] Among them, the intramolecular hydroamination cyclization reaction of homoallylic amines is the most significant.[3] In contrast, there have been few reports about the synthesis of pyrrolidines by means of intramolecular hydroamination cyclization reactions of homopropargylic amines, a strategy that is commonly used to generate dihydropyrroles and pyrrolidinone derivatives.[4] Recently, Zhu and his coworkers described a three-component cyclizative 1,1-aminoacylation of terminal alkynes. In their report, a part of multiple substituted pyrrolidine products were obtained in relatively low diastereoselectivities (Scheme 1a).[5] Ye's research group developed a method to prepare various enantioenriched 2,5-disubstituted pyrrolidines from chiral homopropargylic

sulfonamides (Scheme 1b).[6] They used the structurally elaborate Au complexes and Et_3N for the intramolecular hydroamination cyclization cascade reaction. And the low diastereoselectivities were generated in the cases of allylsilane as a strong carbon nucleophile in this cascade cyclization. Therefore, developing high efficient methodology for the synthesis of 2, 5-disubstituted pyrrolidines with high diastereoselectivity is desirable and more challenging.

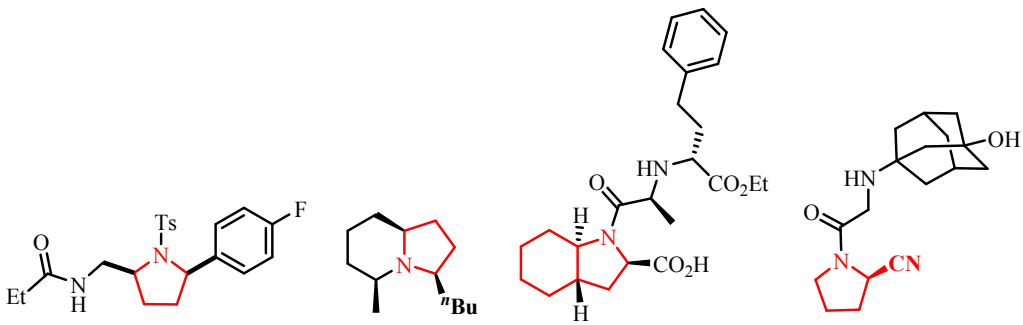
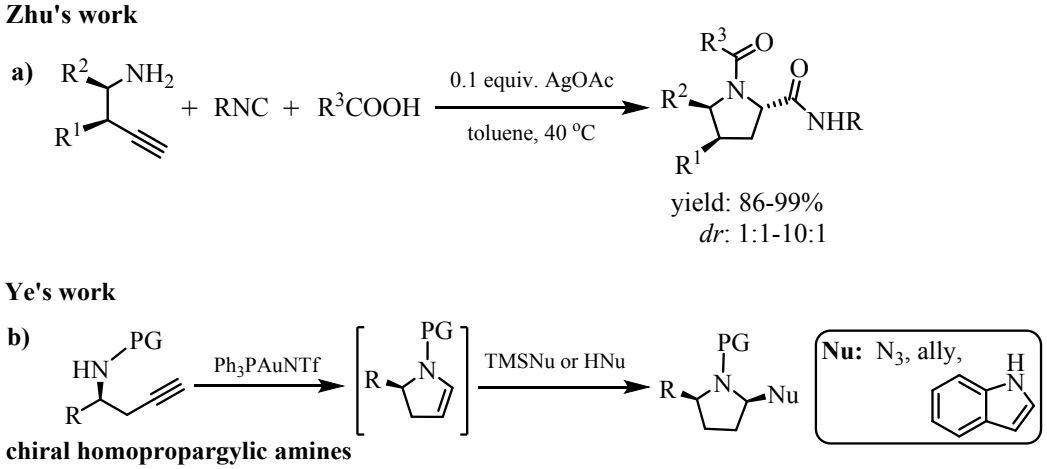


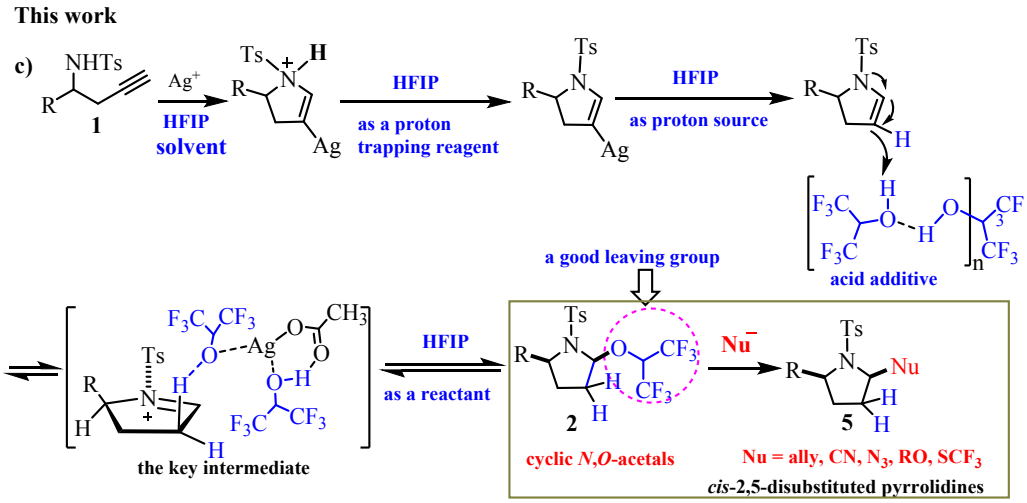
Figure 1. Drugs and natural products containing unsymmetrical 2, 5-disubstituted pyrrolidines moieties.

On the other hand, the 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) displays unique properties (weak acidity (pKa 9.3) and nucleophilicity (N -4.23), strong polarity (ENT 1.068) and ionizing power (Y 3.82), etc.) because of its strong electron-withdrawing nature in many organic reactions.[7] Moreover, there have been an increasing reports on the ability of HFIP to promote organic reactions as an acid component or interaction with reactants by hydrogen-bonded cluster.[8]

In light of the existing work on the synthesis of pyrrolidines and as part of ongoing work in our research group,[9] we herein explored the use of HFIP as a solvent for the construction of 2,5-bifunctionalized pyrrolidines and developed a simple two-step method. This method involves an intramolecular hydroamination cyclization-hydroalkoxylation reaction of

homopropargylic sulfonamides to give *N*,*O*-acetals **2**, which were followed by a *formal* intermolecular nucleophilic substitution. The whole reaction constitutes a 1,1-bifunctionalization of terminal alkynes.[10] Moreover, we found that the HFIP played multiple roles in this process: it acted as not only a solvent, but also an additive, a reactant and a good leaving group (Scheme 1c). More importantly, the obtained *N*,*O*-acetals **2** could be facilely transformed to other diverse stereodefined *cis*-2,5-disubstituted pyrrolidines derivatives **5**, especially for the formation of C-X bonds (X = O, S, N etc.), whereas previous studies pay more attention to the linear *N*,*O*-acetals and their application for the construction of C-C bond.[11] Therefore, these results are significant and this method provides an efficient synthetic strategy for the access to stereospecific 2,5-disubstituted pyrrolidines.[12]





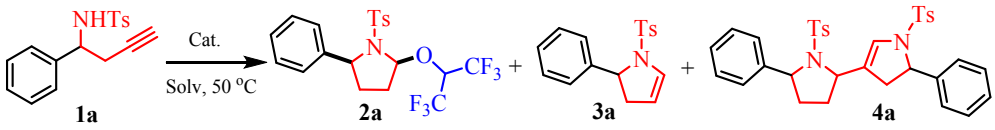
Scheme 1. The synthesis of multisubstituted pyrrolidines

RESULTS AND DISCUSSION

In our initial study, the elegant Ph_3PAuCl (5 mol%) was chose to catalyze the possible intramolecular hydroamination cyclization reaction of the homopropargylic sulfonamide with HFIP (20 equiv.) as an additive at 50 °C in 1,2-dichloroethane (DCE) for 48 h. To our delight, a new *N*,*O*-acetal **2a** was unexpectedly obtained as a minor product, along with *N*-Ts dihydropyrrolidine **3a** as the major product (entry 1, Table 1). When DCE was replaced with DMF, no reaction occurred with the great amount of starting material recovered (entry 2). And the similar results were obtained when trifluoroethanol (TFE) or MeOH was used as an additive (entries 3 and 4). These results demonstrated that HFIP and the solvent had significant effects on the reaction. Therefore, we carried out the reaction of homopropargylic sulfonamide in HFIP slovent in the absence of any additives and found that under these conditions, the reaction smoothly delivered desired product **2a** in 80% yield after 48 h (entry 5). The addition of KF to the reaction mixture did not improve the results (entry 6). However, attempting to use a combination of Ph_3PAuCl and $AgNTf_2$

catalysts, dimer **4a** was obtained in 75% yield (entry 7). Other metal salts, AgOAc, $Cu(OAc)_2$ and $FeCl_3$ were also examined as catalysts, and AgOAc showed a slight advantage over the Cu and Fe salts at a loading of 5 mol% (entries 8-10). Surprisingly, increasing the amount of AgOAc to 10 mol% resulted in a 75% yield of **2a** after only 18 h (entry 11). Intrigued by this result, we increased the amount of AgOAc even further and found that 20 mol% was optimal, giving **2a** in 93% yield (entries 12 and 13). Furthermore, the reaction time could be reduced to 8 h with 95% yield of desired product generated (entry 14). Nevertheless, only a trace amount of desired product **2a** was detected when the reaction was carried out at room temperature (entry 15). And in isopropanol solvent, the homopropargylic sulfonamide **1a** delievered the dihydropyrrole **3a** in 80% yield (Table 1, entry 16). Based on the above all results, the optimal reaction conditions were determined as follows: homopropargylic sulfonamide **1** (0.2 mmol), AgOAc (20 mol%) or Ph_3PAuCl (5 mol%) at 50 °C in HFIP (1 mL) for 8 h or 48 h. It should be noted that all the 2-hexafluoroisopropxy pyrrolidines products were in a *cis* configuration.

Table 1. Optimization of reaction conditions [a]



Entry	Cat. (mol%)	Add. (mol%)	Solv.	Time (h)	Yield (%)[b]
1	Ph_3PAuCl (5)	HFIP (20)	DCE	48	**2a**+**3a**/95[c]
2	Ph_3PAuCl (5)	HFIP (20)	DMF	48	**2a**/0
3	Ph_3PAuCl (5)	TFE (20)	DCE	24	**2a**/0
4	Ph_3PAuCl (5)	MeOH (20)	DCE	24	**2a**/0
5	Ph_3PAuCl (5)	-	HFIP	48	**2a**/80

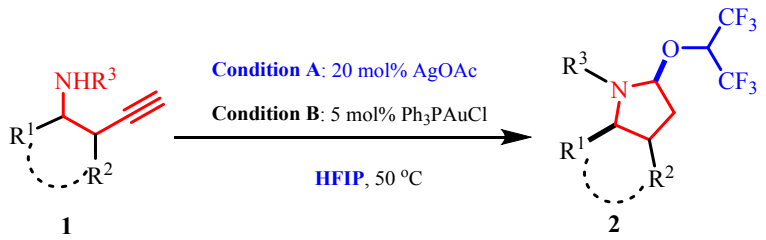
6	Ph_3PAuCl (5)	KF (5)	HFIP	48	**2a**/79
7	Ph_3PAuCl/ $AgNTf_2$ (5)	-	HFIP	10 mins	**4a**/75[d]
8	AgOAc (5)	-	HFIP	48	**2a**/32
9	$Cu(OAc)_2$ (5)	-	HFIP	48	**2a**/19
10	FeCl (5)	-	HFIP	48	**2a**/0
11	AgOAc (10)	-	HFIP	18	**2a**/75
12	AgOAc (20)	-	HFIP	12	**2a**/93
13	AgOAc (50)	-	HFIP	13	**2a**/76
14	AgOAc (20)	-	HFIP	8	**2a**/95
15	AgOAc (20)	-	HFIP	24	Trace[e]
16	AgOAc (20)	-	iPrOH	18	**3a**/80[f]

[a] Standard procedure: The reaction was carried out with **1a** (0.2 mmol) and catalyst at 50 °C. [b] Isolated yield of **2a**. [c] The total yield of the mixture **2a** and **3a** (1:5.5). [d] The yield of **4a** (*cis* : *trans* = 1:1). [e] room temperature. [f] The isolated yield of **3a**.

With the optimized reaction conditions in hand, the scope of the reaction was then investigated with either 20 mol% AgOAc (condition A) or 5 mol% Ph_3PAuCl (condition B) as catalyst (Table 2). Remarkably, most of homopropargylic sulfonamides we tested were competent, affording the corresponding 2-hexafluoroisopropoxy pyrrolidines derivatives in good to excellent yields with excellent diastereoselectivities. For example, homopropargylic sulfonamides in which R^1 was a phenyl group with one or two electron-withdrawing or electron-donating substituents rendered the corresponding 1,2,5-trisubstituted pyrrolidines (**2b-2j)** in good to excellent yields under the reaction condition A. When R^1 was a naphthyl group or a thiophenyl group, the reaction also proceeded

smoothly to generate **2k** and **2l** in 91% and 75% yields, respectively, under the reaction condition B. Howerver, 3-pyridinyl homopropargylic sulfonamide (**1m**) failed to produce **2m**, for reasons that remain unclear. To our delight, when R^1 was H, a benzyl (Bn) or cyclohexyl group (R^2 = H), the corresponding products (**2n**-**2p**) were obtained in moderate to high yields, as was also the case for a fused cyclohexyl substrate (R^1, R^2 = cyclohexyl, **2q**). In addition, when R^3 was changed from tosyl to methanesulfonyl, benzenesulfonyl, *p*-nitrophenylsulfonyl, or *p*-methoxylphenylsulfonyl, good yields of the desired products (**2r-2u**) were all obtained. However, the diastereoselectivity for 2-hexafluoroisopropoxy pyrrolidines **2t** was unsatisfactory with *trans*-configuration as a major (*cis/trans* = 1:6.6). It was speculated that electron effect on the sulfonyl aromatic ring affected the diastereoselectivity of this reaction. Reaction of a phenyl substituted internal homopropargylic sulfonamide only gave the 2,3-dihydropyrrole **3v** in 89% yield without further HFIP adduct. We surmised that the steric hindrance of 5-phenyl of **3v** inhibited the addition of hexafluoroisopropoxy group. Interestingly, the γ-sulfonaminoalkyne gave dimer **4w** in 95% yield. Changing the *N*-tosyl group to a *t*-butylsulfinamide group (**1x)**, a benzoylamine (**1y**) or an *n*-butylamine group (**1z**), no desired product was generated whether under reaction condition A or B. Benzoylamine **1y** afforded compound **5y**, which was generated by reaction of the benzoyl group attacking the alkynyl group. The **1z** with *n*-butyl substituted homopropargylic amine decomposed. These results indicated the sulfonyl group played a crucial role in this reaction. In other words, this reaction occurrence depends on the acidity of NH on the substrates. The absolute structure of **2e** was unambiguously determined by single crystal X-ray diffraction analysis (Figure S1).[13]

Table 2. Substrate scope of the intramolecular hydroamination cyclization-hydroalkoxylation reaction[a,b,c]



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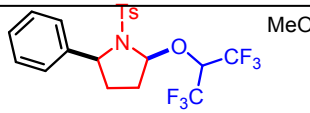
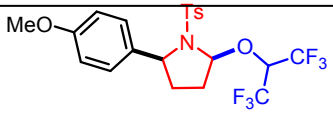
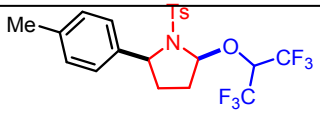


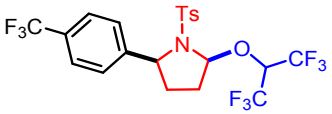
2a, Yield 95%[a]



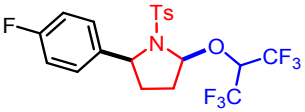
2b, Yield 93%[a]



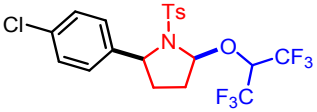
2c, Yield 94%[a]



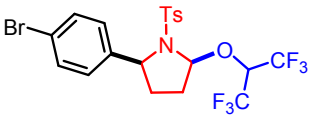
2d, Yield 81%[a,c]



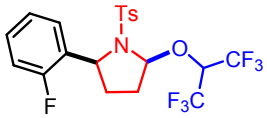
2e, Yield 97%[a]



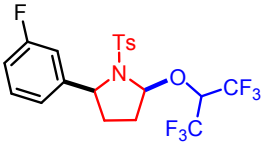
2f, Yield 90%[a]



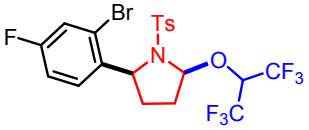
2g, Yield 85%[a]



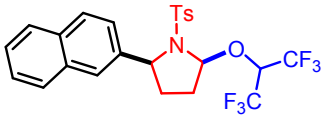
2h, Yield 85%[b]



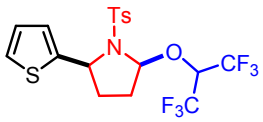
2i, Yield 81%[b]



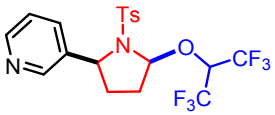
2j, Yield 79%[a,d]



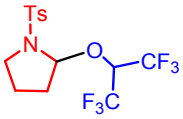
2k, Yield 91%[b]



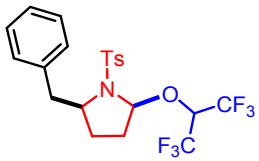
2l, Yield 75%[b]



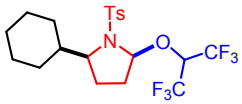
2m, N.R.[a,b,e]



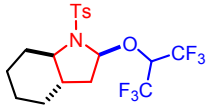
2n, Yield 97%[a]



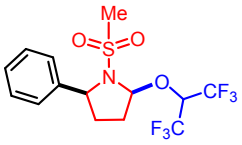
2o, Yield 83%[b]



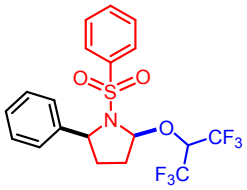
2p, Yield 57%[b]



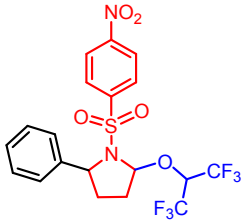
2q, Yield 51%[b]



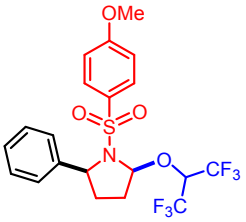
2r, Yield 90%[a]



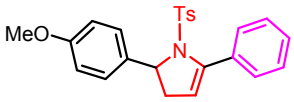
2s, Yield 88%[a]



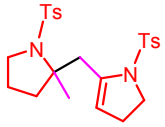
2t, Yield 75%[a,f]
cis:trans = 1:6.6



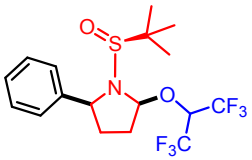
2u, Yield 95%[a]



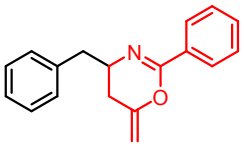
3v, Yield 89%[a,g]



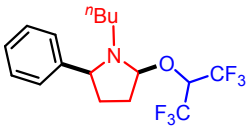
4w, Yield 95%[b,g]



2x, Yield 0%, N.R.[a,h]



5y, Yield 80%[a]



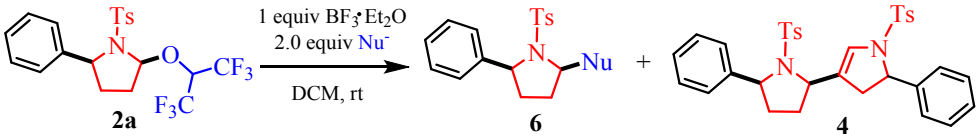
2z, Yield 0%, N.D.[a,i]

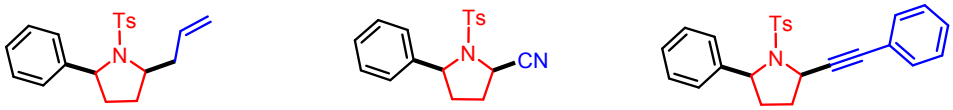
[a] Method A: The reaction was carried out with **1a** (0.2 mmol) and AgOAc (0.04 mmol, 20 mol%) in HFIP (1 mL) at 50 °C for 8 h. [b] Method B: The reaction was carried out with **1a** (0.2 mmol) and Ph_3PAuCl (0.01 mmol, 5 mol%) in HFIP (1 mL) at 50 °C for 48 h. [c] Isolated yield. [d] Reaction time, 12 h. [e] No reaction. [f] The mixture of *cis/trans* = 1/6.6, reaction time, 36 h. [g] Reaction time, 3 h. [h] N.R. = no reaction. [i] N. D. = Not determined.

The *N,O*-acetals can be readily transformed to a variety of useful compounds. Therefore, further reactions of the five-membered cyclic *N,O*-acetals obtained by means of hydroamination cyclization-hydroalkoxylation were investigated with the goal of constructing new C−C or C−X bonds (X = *N, O, S*) (Table 3). It should be noted that previous reports pay more attention to the formation of C-C bond from *N,O*-acetals. In comparison, there are few researches on the construction of C-X bonds from *N,O*-acetals. Herein, we chose compound **2a** as a model substrate for reactions with several representative nucleophiles. As shown in Table 3, carbon nucleophiles (allyltrimethylsilane, trimethylsilyl cyanide and acetylene), oxygen nucleophiles (3-butyn-1-ol, water, MeOH,

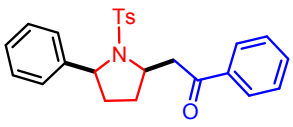
EtOH, ^{i}PrOH, CF_3CH_2OH), sulfur nucleophiles (2-Mercaptothiazole, benzyl mercaptan and $AgSCF_3$) and a nitrogen nucleophile ($TMSN_3$), all smoothly and stereospecifically produced the corresponding *cis*-2, 5-disubstituted pyrrolidines (**6a-6c**, **6e-6g**, **6i-6n**, **6o**) in good to high yields. Among them, the reaction of **2a** with CF_3CH_2OH produced an inseparable mixture of trifluoroethoxy pyrrolidine **6i** and hexafluoroisopropoxy pyrrolidine **2a** (**6i** : **2a** = 25 : 4). And we obtained no target compound **6h** when using ^{i}PrOH as an oxygen nucleophile. In spite of this, the direct nucleophilic substitution of the hexafluoroisopropoxy with other different alkoxy groups is very important and will have potential application in the aspect of carbohydrate chemistry. The ketone **6d** was obtained as a side product of the reaction between **2a** and acetylene. Additionally, the hexafluoroisopropoxy-pyrrolidine could be reduced to 2-substituted pyrrolidine **6q** in the presence of $NaBH_4$. The products **6l** and **6m** were unstable and readily decomposed at room temperature. Unfortunately, other amines (aniline or benzylamine or *N*-methlybenzylamine) were not applicable in this *formal* nucleophilic substitution reaction at present.

Table 3. Reactions of hexafluoroisopropoxyl pyrrolidine 2a with nucleophiles[a]

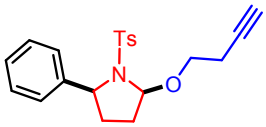




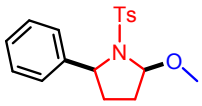
6a, Yield 90%[b] **6b**, Yield 98%, *dr* = 1.2/1[b] **6c**, Yield 60%[c]



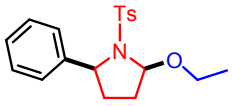
6d, Yield <10%[c,h]



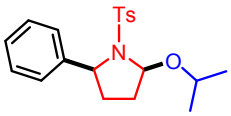
6e, Yield 81%[d]



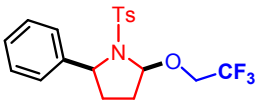
6f, Yield 91%[e]



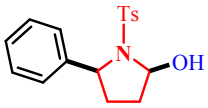
6g, Yield 90%[e]



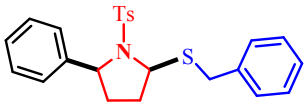
6h, **ND** [e]



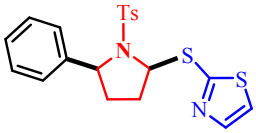
6i, Yield 85%[e]



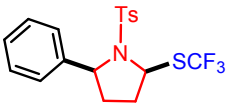
6j, Yield 40%[f], *dr* = 6/1



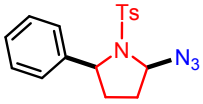
6k, Yield 95%[d]



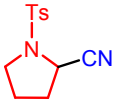
6l, Yield 51%[d]
unstable



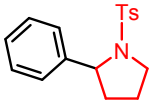
6m, Yield 57%[g]
unstable



6n, Yield 99%[b]



6o, Yield 98%



6q, Yield 66%[i]

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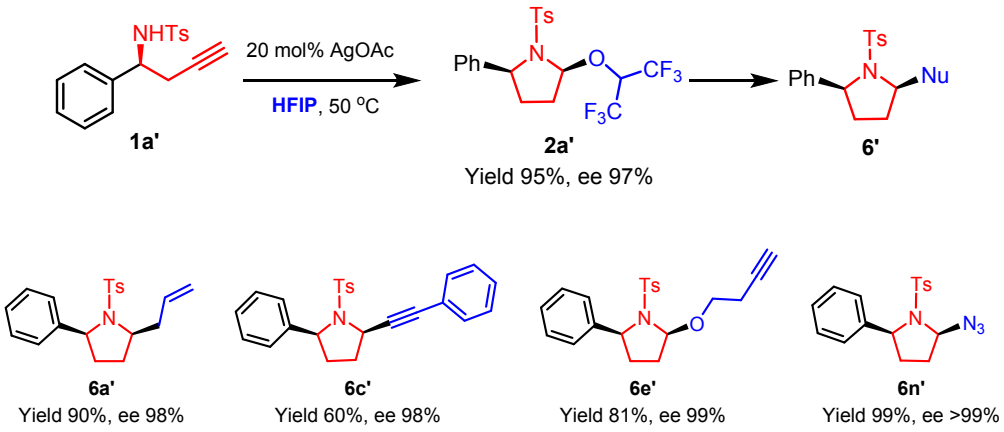
[a] Isolated yields. [b] Reaction with 2.0 equiv allyltrimethylsilane or TMSCN or $TMSN_3$ and 2.0 equiv KF. [c] Reaction with 2.0 equiv acetylene, 2.0 equiv KF, 2.0 equiv CuI. [d] Reaction with 2.0 equiv 3-butyn-1-ol or 2-mercaptothiazole or benzyl mercaptan. [e] Reaction with 4.0 equiv MeOH or EtOH or ^{i}PrOH or CF_3CH_2OH. [f] Reaction with 2.0 equiv H_2O in 2:1 DCM/CH_3CN. [g] Reaction with 4.0 equiv $AgSCF_3$ in 1:1 DCM/CH_3CN. [h] This compound was a byproduct of the reaction between **2a** and acetylene. [i] Reaction with 8.0 equiv $NaBH_4$ in HFIP solvent.

Encouraged by the high diastereoselectivity of this hydroamination cyclization-hydroalkoxylation reaction, we were interested in exploiting chirality transfer from a pre-existing stereogenic center, such as that in an enantiopure homopropargylic sulfonamide **1a'** (Scheme 2). As expected, the reaction of enantiopure **1a'** afforded enantiopure *N*, *O*-acetal **2a'** with almost complete retention of chirality under the above standard conditions.

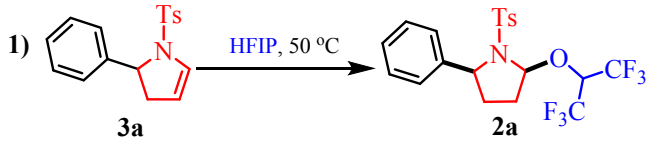
Next, we carried out reactions of **2a'** with several typical nucleophiles. Specifically, enantiopure 2,5-disubstituted pyrrolidines **6a', 6c'**, **6e'** and **6n'** were obtained with excellent enantioselectivities, as shown in Scheme 2.



Scheme 2. The enantioselective transformation

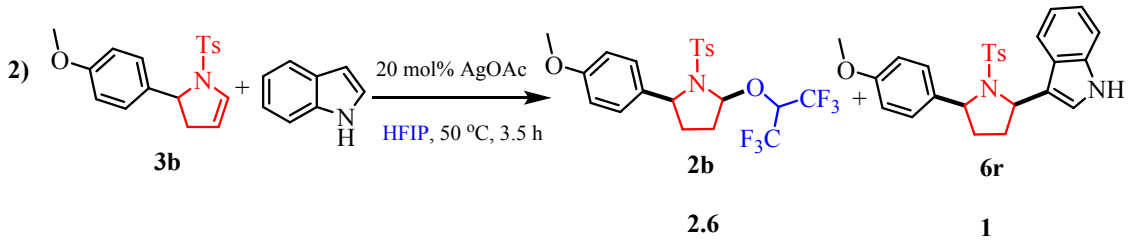
To shed light on this reaction mechanism, we carried out some controll experiments (Scheme 3) and monitoring reaction by ^{1}H NMR spectroscopy. Treatment of *N*-tosyl-2, 3-dihydropyrrole **3a** with HFIP at 50 °C afforded **2a** in 91% or 95% yield in the absence or presence of AgOAc for 48 h or 3.5 h (Scheme 3, eq.1a and 1b). From these two results we could conclude that: 1) the reaction of the homopropargylic sulfonamide in HFIP might proceed via dihydropyrrole intermediate **3a**, 2) HFIP served as a hydroalkoxylative reagent in the addition reaction with no requisition of AgOAc catalyst. To further ascertain the nucleophilicity of HFIP, the emulative strong nucleophilicity indole was added into the reaction of dihydropyrrole **3b** in HFIP solvent. Consequently, the **2b** and **6r** were both obtained in 2.6:1 ratio (determined by ^{1}H NMR spectroscopy of crude product) (Scheme 3, eq.2). This result indicated that the HFIP may attack the dihydropyrrole **3b** in a cluster

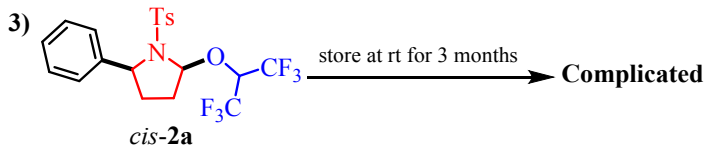
mode, which was superior to the nucleophilic addition of indole. And a slight chemical shift change of protons a, b and c in **3a** was observed with HFIP by ^{1}H NMR spectrum (Figure S2). Monitoring the interaction between HFIP and **2a** by ^{1}H NMR also displayed a little chemical shift change of protons a and b on HFIP (Figure S3). Additionally, we found that *cis*-**2a** decomposed slowly upon storage at room temperature for 3 months (eq.3), as demonstrated that the *N*,*O*-acetals have relative stability. The **1t** was subjected to the optimized conditions for the hydroamination-hydroalkoxylation reaction, the *cis*/*trans* ratio of the corresponding product (**2t**) decreased continuously with prolonging reaction time (Scheme 3, eq.4), as was determined by ^{1}H NMR spectrum of protons b and c in **2t** (Figure S4). This phenomenon demonstrated that the hexafluoroisopropoxy moiety was a good leaving group and that the *trans*-product was more stable than the *cis*-product. Besides, the deuterated HFIP-d_2 was used to ascertain the proton source. As a result, nearly all hydrogen atoms on the 2-site and 3-site of pyrrolidine **2b** come from the HFIP (eq.5).

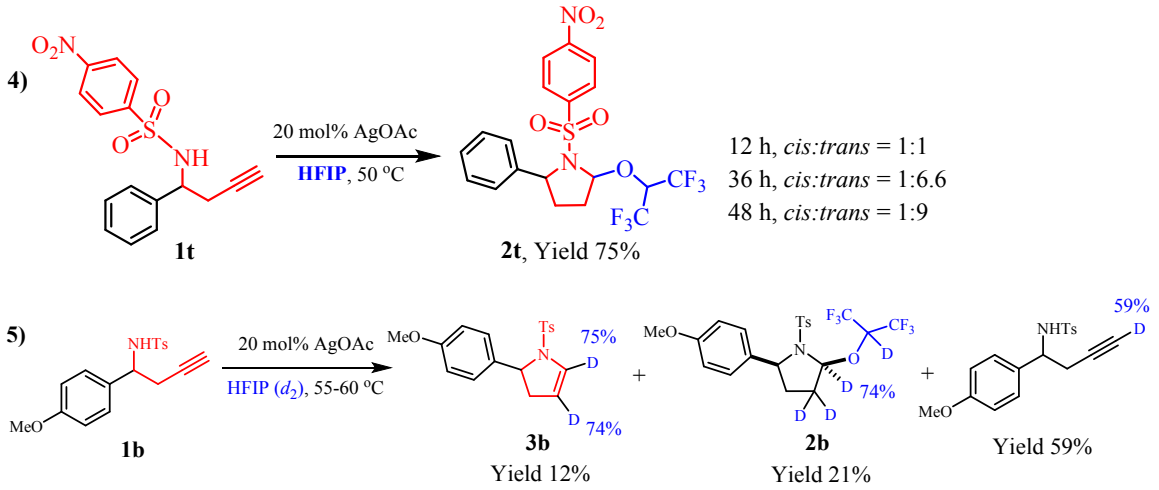


a) Without AgOAc, 48 h, yield 91%;

b) With 20 mol% AgOAc, 3.5 h, yield 95%.







Scheme 3. Mechanistic controll experiments.

To provide further understanding of the mechanism for the reaction catalyzed by AgOAc, quantum chemical investigations based on density functional theory (DFT) were performed. And a possible reaction pathway was proposed (Figure 2). The whole catalytic cycle involves two steps: the Intramolecular cycloaddition of sulfonamide to alkyne group and the stereoselective addition of HFIP to dihydropyrrolidine. In the first reaction step, the AgOAc actives the alkynyl group by forming the π complex **Int-1s** with the substrate **1s** solvated by HFIP. Then, the nitrogen atom attacks the activated alkynyl group to form the **Int-2s** through transition state **TS-1s**. The Gibbs free energy barrier for the whole cyclization process is 25.8 kcal/mol, which is the rate-determing step and is also in accordance with our experimental results, namely, no significant accumulation of **3s** was observed during the reaction process. Subsequently, the proton on the nitrogen is trapped by the assitance of two molecular HFIP as a hydrogen-bond bridge through the **TS-2s** to afford the **Int-3s** and concomitant with delivering the proton of HFIP to the alkenyl carbon to give the stable **Int-4s** (the compund **3s**) through **TS-3s**. After the **Int-4s** is formed, AgOAc will further catalyze the addtion of HFIP to the carbon-carbon double bond. The oxygen atom on HFIP is coordinated to Ag, the acidity of molecule is greatly increased and the energy barrier is decreased to 21.9 kcal/mol (**TS-4s-*cis***). This is consistent with our experimental result that **3a** in HFIP solvent to form **2a** is rather slow without the participation of AgOAc (Scheme 3, eq.1). In addition, we also studied the addition process of **3s** by isopropanol and found that it required a quite

high activation energy (32.9 kcal/mol, see supporting information for details). This result rationalizes why the reaction stays in the process of forming **3s** in isopropanol (Table 1, entry 16). Finally, we search for the key transition states that produce *cis* and *trans* products (Scheme S1). **TS-4s-*cis*** is more stable than other transition states to afford the major product with *cis* configuration. A relative ΔΔG (1.6 kcal/mol) for **TS-4s-*trans*** was obtained to predict the stereoselectivity of product. The predicted value is 95:5 (*cis*:*trans*), which is close to the experimental results. It should be noted that the proton transfer bridge composed with one HFIP or two HFIPs and the corresponding transition states involving one HFIP or two HFIPS in stereoselectivity were also calculated (Figures S5-S6). Moreover, the addition process of HFIP to the dihydropyrrole was nonsynergistic (Figure S7). The Figure S8 described the causes of stereoselectivity with more conformations of the transition states in rate-determining step.

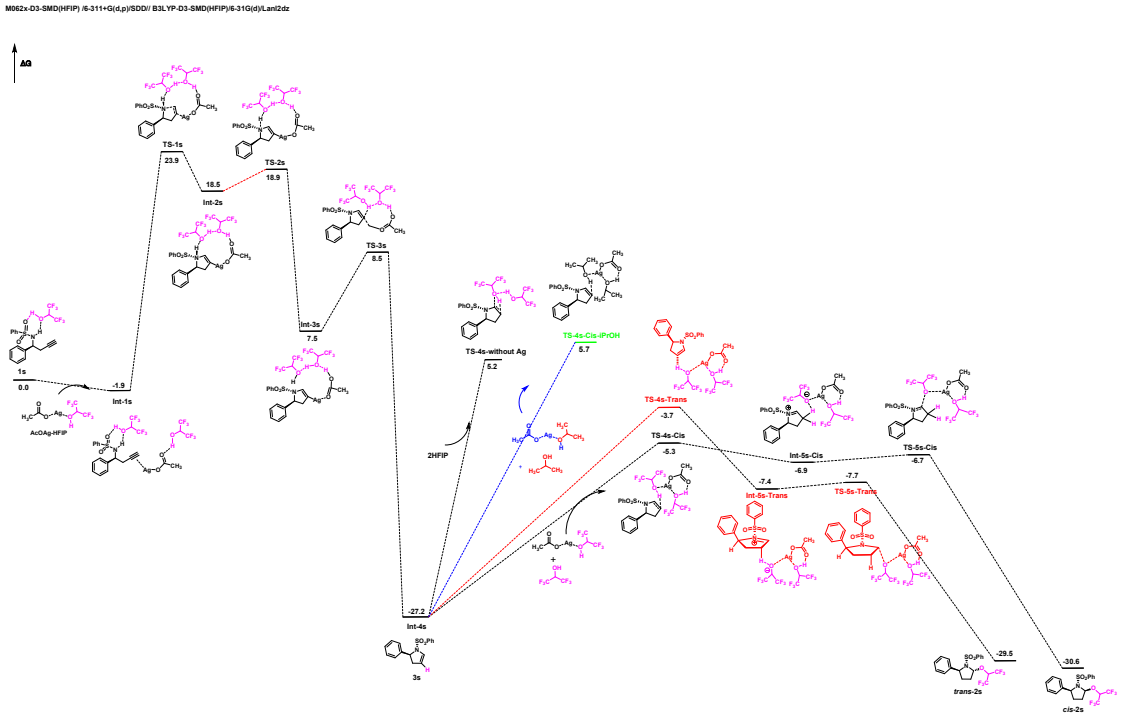
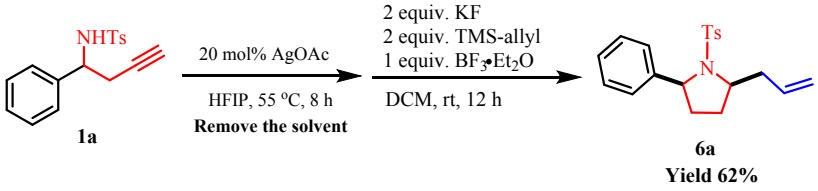


Figure 2. The DFT calculations of the reaction pathways

A one pot reaction was also carried out (Scheme 4). The details were as follows: **1a** (0.2 mmol) and AgOAc (0.04 mmol, 20 mol%) were stirred at 55 °C for 8 h in HFIP (1 mL), then removing the solvent under vacuo, subsequently adding KF (0.4 mmol, 23.2 mg, 2.0

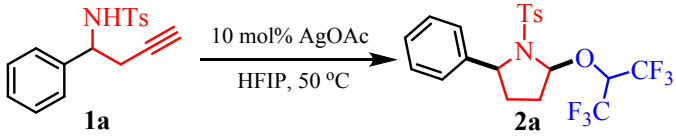
equiv.), TMS-allyl (0.4 mmol, 45.6 mg, 2 equiv.) and $BF_3{\cdot}Et_2O$ (0.2 mmol, 28.4 mg, 1 equiv.) as well as 1 mL DCM, the mixture was stirred for another 12 h. Consequently, the reaction afforded the corresponding *N*-Ts-2-allyl-5-phenyl-pyrrolidine in 62% yield.



Scheme 4. A one pot reaction

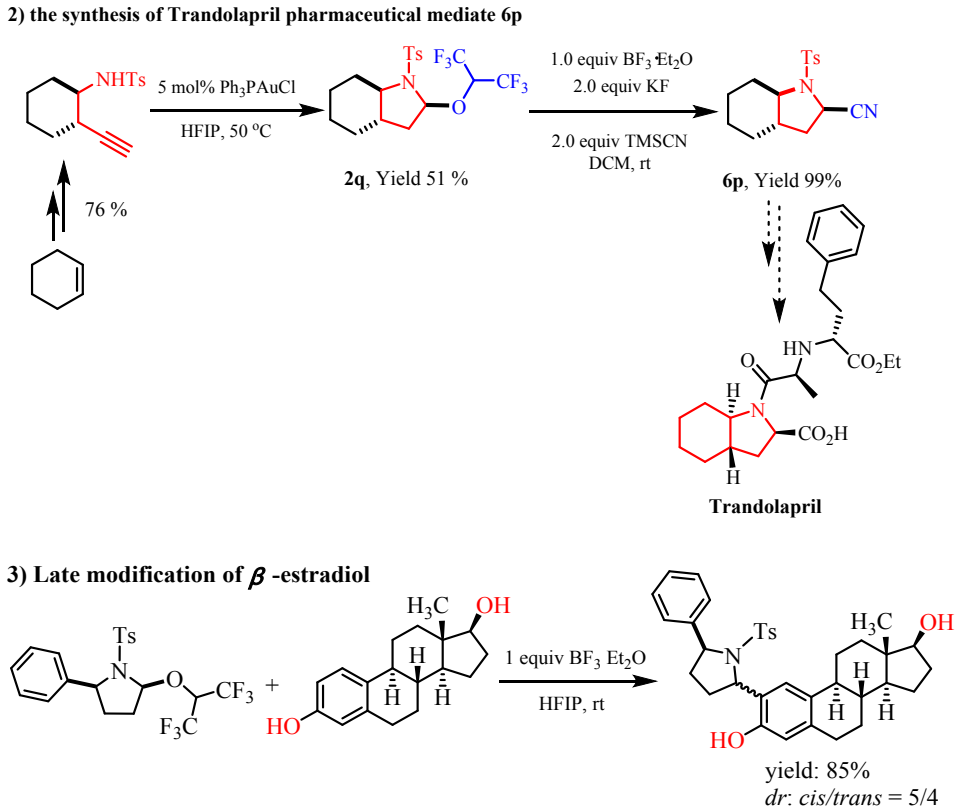
The practical application of our method was finally test (Scheme 5). When the intramolecular hydroamination cyclization-hydroalkoxylation reaction of **1a** was carried out on a 2 mmol scale in the presence of 10 mol% AgOAc, desired product **2a** was generated in 86 % yield (Scheme 5, eq. 1). And the pharmaceutical intermediate of trandolapril could be readily synthesized in good yield from **2q** (eq.2). This synthesis method of trandolapril intermediate **6p** was simpler and more efficient than that of previously reported.[14] Besides, we could also successfully achieved the late functionalization of *β*-Estradiol (Scheme 5, eq.3).

1) the scale-up experiment



2 mmol, 0.6 g

0.81 g, Yield 86%



Scheme 5. The application of this methodology

CONCLUSION

In conclusion, we have developed a simple and highly efficient method for stereoselective synthesis of 1, 2, 5-trisubstituted pyrrolidines via cyclic *N*,*O*-acetals, which were obtained by means of intramolecular hydroamination cyclization- hydroalkoxylation in HFIP. Notably, the cyclic *N*,*O*-acetals could be further facilely used for the formation of various C-C and C-S, C-N and other C-O bonds, thus constructing diverse functionalized multiple substituted pyrrolidines in excellent diastereoselectivity. And we observed that the HFIP played multiple roles, a solvent, an acidic proton source and a nucleophile as well as a good leaving group in this method. The weak nucleophilicity of HFIP is amplified as an advantageous nucleophile by hydrogen-bond cluster and coordination with AgOAc modes, and the hexafluoroisopropoxy group on the resulting *N*,*O*-acetals facilitates late

modification at the 2-site of pyrrolidine due to its good leaving ability. Additionally, enantioenriched products could be obtained from simple chiral starting materials. A possible reaction mechanism was also proposed and DFT study discovered HFIP acting as a proton-bridge deliever and a cocatalyst with AgOAc. Besides, we demonstrated the utility of the method by using it to synthesize pharmaceutical intermediate from simple substrate. From a synthetic viewpoint, the stereospecific cyclic *N*,*O*-acetals would endow themselves diverse reactivity for preparing functionalized stereoselective cyclic amines, as will provide a highly efficient and highly stereoselective protocol for the synthesis of mulitiple substituted pyrrolidines.

EXPERIMENTAL SECTION

1. General Information

The data for NMR spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR) were recorded at 293 K on a Bruker AVANCE AV 400 (400 MHz, 101 MHz and 376 MHz). ^{1}H and ^{13}C NMR Chemical shifts were calibrated to tetramethylsilane as an internal reference. Chemical shifts (δ) were reported with respect to the corresponding solvent residual peak at 7.26 ppm for $CDCl_3$ for ^{1}H NMR. ^{13}C NMR spectra (^{1}H-broadband decoupled) were reported in ppm using the central peak of $CDCl_3$ (77.16 ppm). Chemical shifts are given in (ppm) and coupling constants (J) in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet; High resolution mass spectrometric (HRMS) analyses spectrum was determined on the Varian 7.0T FTMS instrument. Chiral high performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260II with commercial ChiralCel 4.6 × 250 mm (OD - H) column and Chiralpak IC column.

2. Synthesis and characterization

1) Synthesis and characterization of the homopropargylic sulfonamides 1a-1q, 1r-1s, 1v and 4-methyl-*N*-(pent-4-yn-1-yl) benzenesulfonamide 1w

Compounds **1a-1g**, **1n**, **1q**, **1r**, **1s**, **1v** and **1w** were prepared according to the known procedures.[15]

To a solution of aldehyde (20 mmol) in dry DCM (50 mL) was added sulfonamide derivatives (1.0 equiv.) and 4Å molecular sieves (1 g/mmol). The resulting reaction mixture was stirred at 60 ^{o}C on a heating block until the reaction was completed (by TLC). Filtration by flash silical gel chromatography with DCM as eluent and then removal of the solvent under reduced pressure afforded the desired sulfimides **S1** as a white solid, which was used without further purification.[16]

To a solution of imide **S1** (10.0 mmol, 1.0 equiv.) in THF (30 mL) was added the activated zinc (975 mg, 15 mmol, 1.5 equiv.) at 0 °C. Then propargylic bromide (1.7 mL, 15 mmol, 1.5 equiv.) was added at 0 °C and the mixture stirred at room temperature for overnight. Aqueous sat. NH_4Cl (10 mL) was added and the aqueous phase extracted with Et_2O (3 x 30 mL). After the organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, the desired compound **S2** was isolated. The spectral data are in good agreement with previous reports.[17]

***N*-(1-(2-fluorophenyl) but-3-yn-1-yl)-4-methylbenzenesulfonamide** (**1h**). White solid, mp 117.1-118.2 °C, 2.4 g, yield 75 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.62 (d, *J* = 8.0 H z, 2H), 7.22 – 7.14 (m, 4H), 7.00 – 6.96 (t, *J* = 7.6 Hz, 1 H), 6.91 – 6.86 (dd, *J* = 8.4 Hz, 1H), 5.49 – 5.47 (d, *J* = 8.0 Hz, 1H), 4.80 – 4.75 (q, *J* = 6.4 Hz, 1H), 2.66 – 2.64 (q, *J* = 6.0, 2.0 Hz, 2H), 2.35 (s, 3H), 1.95 – 1.94 (t, *J* = 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.1 (d, *J* = 244.4 Hz), 143.5, 137.1, 129.5 (d, *J* = 8.3 Hz), 129.5, 128.8 (d, *J* = 4.0 Hz), 127.2, 126.5 (d, *J* = 12.8 Hz), 124.1 (d, *J* = 3.2 Hz), 115.5 (d, *J* = 21.4 Hz), 78.9, 72.2, 51.2, 26.6, 21.6. HRMS (ESI^{+}) calculated for $C_{17}H_{17}FNO_2S$ (M+H^{+}) 318.0959; found 318.0950.

***N*-(1-(3-fluorophenyl) but-3-yn-1-yl)-4-methylbenzenesulfonamide (1i).** White solid, mp 115.1-116.9 °C, 2.27 g, yield 71 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.61 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.16 (t, *J* = 8.0 Hz, 3H), 6.97 – 6.83 (m, 3H), 5.34 – 5.33 (d, *J* = 7.2 Hz, 1H), 4.53 – 4.48 (q, *J* = 6.4 Hz, 1H), 2.66 – 2.55 (m, 2H), 2.39 (s, 3H), 2.00 (s, 1H). ^{13}C{^{1}H}

NMR (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 245.1 Hz), 143.7, 141.9 (d, *J* = 6.9 Hz), 137.2, 130.1 (d, *J* = 8.1 Hz), 129.6, 127.3, 122.4 (d, *J* = 2.8 Hz), 114.9 (d, *J* = 20.9 Hz), 113.9 (d, *J* = 22.3 Hz), 78.7, 72.7, 55.3, 27.3, 21.6. HRMS (ESI^+) calculated for $C_{17}H_{17}FNO_2S$ ($M+H^+$) 318.0959; found 318.0963.

***N*-(1-(2-bromo-4-fluorophenyl)but-3-yn-1-yl)-4-methylbenzenesulfonamide (1j).** White solid, mp 175.9-177.0 °C, 2.17 g, yield 55 %, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.63 (d, *J* = 8.0 Hz, 2H), 7.29 – 7.27 (t, 1H), 7.20 – 7.18 (d, *J* = 8.0 Hz, 3H), 6.90 – 6.86 (m, 1H), 5.38 – 5.37 (d, *J* = 7.2 Hz, 1H), 4.92 – 4.87 (q, *J* = 6.0 Hz, 1H), 2.69 – 2.50 (m, 2H), 2.38 (s, 3H), 2.00 (s, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.7 (d, *J* = 249.7 Hz), 143.8, 136.7, 134.4, 129.8 (d, *J* = 8.5 Hz), 129.6, 127.3, 122.3 (d, *J* = 9.2 Hz), 119.9 (d, *J* = 24.4 Hz), 114.7 (d, *J* = 20.9 Hz), 78.2, 72.9, 54.1, 26.2, 21.6. HRMS (ESI^+) calculated for $C_{17}H_{16}FBrNO_2S$ ($M+H^+$) 396.0064; found 396.0074.

4-methyl-*N*-(1-(pyridin-3-yl)but-3-yn-1-yl)benzenesulfonamide (1m). Earth yellow solid, 1.11 g, yield 37 %, ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 – 8.43 (t, *J* = 4.8 Hz, 2H), 7.64 – 7.58 (m, 3H), 7.22 – 7.17 (m, 3H), 5.47 – 5.45 (d, *J* = 7.2 Hz, 1H), 4.58 – 4.53 (q, *J* = 6.4 Hz, 1H), 2.71 – 2.58 (m, 2H), 2.39 (s, 3H), 2.04 – 2.03 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.1, 148.3, 143.9, 137.1, 135.1, 134.6, 129.8, 127.3, 123.5, 78.3, 73.2, 53.6, 27.2, 21.7. HRMS (ESI^+) calculated for $C_{16}H_{17}N_2O_2S$ ($M+H^+$) 301.1005; found 301.1013

2) Synthesis and characterization of the homopropargylic sulfonamide 1o

To the solution of phenylacetaldehyde **S3** (1.20 g, 10 mmol) and Zn powder (0.98 g, 15 mmol) was added propargylic bromide (1.77 g, 1.2 mL, 15 mmol) at 0 °C and warm up to room temperature. After the reaction mixture was stirred overnight, it was quenched with saturated aq NH_4Cl (20 mL) and extracted with AcOEt (3 x 30 mL). The organic layer was dried over with anhydrous $MgSO_4$ and filtrated. The filtrate was concentrated under reduced pressure. The residue **S4** was used without extra purification.

To the solution of PPh_3 (1.89 g, 7.2 mmol), *N*-Boc-4-methylbenzene- sulfonamide (1.63 g, 6.0 mmol) and **S4** (754 mg, 6.0 mmol) in THF (43mL) was added DIAD (1.55 mL, 7.2 mmol) at room temperature. After the reaction mixture was stirred for 36 h, it was quenched with saturated $NaHCO_3$ aqueous (10 mL) and extracted with AcOEt (3 x 15 mL). The organic layer was washed with brine, dried over with $MgSO_4$ and filtrated. The filtrate was

concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt and Petroleum (1/5) to give **S5** (1.98 g, 4.8 mmol, 80%).

To the solution of **S5** (1.98 g, 4.8 mmol) in CH_2Cl_2 (10.0 mL) was added TFA (18.0 mL, 24 mmol) at 0 °C and warm up to room temperature. After the reaction mixture was stirred for 24 h, it was quenched with saturated aq. $NaHCO_3$ (5 mL) and extracted with AcOEt (3 x 10 mL). The organic layer was washed with brine, dried over with $MgSO_4$ and filtrated. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with AcOEt and Petroleum (1/5) to give **1o** (689 mg, 2.2 mmol, 45%).

4-methyl-*N*-(1-phenylpent-4-yn-2-yl)benzenesulfonamide(1o). White solid, mp 111.7-113.2 °C, 689 mg, yield 45 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.64 – 7.62 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.19 (m, 5H), 7.06 – 4.04 (d, *J* = 6.0 Hz, 2H), 5.00 – 4.99 (d, *J* = 8.4 Hz, 1H), 3.55 – 3.54 (d, *J* = 6.0 Hz, 1H), 2.90 – 2.76 (m, 2H), 2.40 (s, 3H), 2.29 (s, 2H), 2.06 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.4, 137.4, 136.8, 129.7, 129.3, 128.6, 127.0, 126.8, 79.6, 72.1, 53.3, 39.9, 24.2, 21.6. HRMS (ESI$^+$) calculated for $C_{18}H_{20}NO_2S$ (M+H$^+$) 314.1209; found 314.1201.

3) Synthesis and characterization of the homopropargylic sulfonamides 1t and 1u

4-Nitrobenzenesulfonyl chloride or 4-Methoxybenzenesulfonyl chloride (1.2 mmol) was added to a mixture of 1-phenylbut-3-yn-1-amine **S6**[18] (1 mmol), and Et_3N (2 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at room temperature for overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5 % of aqueous NaOH, brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified through silica gel flash chromatography to give desired homopropargyl amine.

4-nitro-*N*-(1-phenylbut-3-yn-1-yl)benzenesulfonamide (1t). White solid, mp 155.8-157.0 °C, 248 mg, yield 75 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.13 (d, *J* = 8.0 Hz, 2H), 7.81 – 7.79 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.09 (m, 5H), 5.49 – 5.47 (d, *J* = 7.2 Hz, 1H), 4.67 – 4.62 (q, *J* = 6.4 Hz, 1H), 2.77 – 2.61 (m, 2H), 2.06 (s, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.9, 146.3, 138.4, 128.7, 128.5, 126.7, 124.0, 78.7, 72.9, 56.3, 27.6. HRMS (ESI$^+$) calculated for $C_{16}H_{18}N_3O_4S$ (M+NH_4^+) 348.1013; found 348.1012.

4-methoxy-*N*-(1-phenylbut-3-yn-1-yl)benzenesulfonamide (1u). White solid, mp 121.1-122.2 °C, 72 mg, yield 23 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.65 (d, *J* = 9.2

Hz, 2H), 7.21 – 7.13 (m, 5H), 6.84 – 6.82 (d, *J* = 9.2 Hz, 2H), 5.38 – 5.35 (t, *J* = 7.2 Hz, 1H), 4.51 – 4.46 (q, *J* = 6.4 Hz, 1H), 3.82 (s, 3H), 2.65 – 2.62 (q, *J* = 2.4 Hz, 2H), 1.99 – 1.97 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.9, 139.3, 131.9, 129.4, 128.6, 128.0, 126.7, 114.1, 79.3, 72.2, 55.9, 55.7, 27.4. HRMS (ESI^+) calculated for $C_{17}H_{18}NO_3S$ ($M+H^+$) 316.1002; found 316.1004.

***N*-(1-phenylpent-4-yn-2-yl)benzamide (1y).** Compound **1y** was synthesized from the known literature[19]. White solid, mp 112.0-113.0 °C, 144 mg, yield = 87.4 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.72 (d, *J* = 7.2 Hz, 2H), 7.50 – 7.39 (m, 3H), 7.33 – 7.22 (m, 5H), 6.43 – 6.41 (d, *J* = 8 Hz, 1H), 4.55 – 4.47 (m, 1H), 3.10 – 2.96 (m, 2H), 2.56 – 2.37 (m, 2H), 2.14 – 2.13 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 167.0, 137.5, 134.6, 131.6, 129.4, 128.7, 128.7, 127.0, 126.9, 80.3, 71.7, 48.9, 39.1, 22.8. HRMS (ESI^+) calculated for $C_{18}H_{18}NO$ ($M+H^+$) 264.1383; found 264.1386.

4) The synthesis of the chiral homopropargylic sulfonamine 1a'

To a solution of (*R*)-tert-butanesulfinamide (2.42 g, 20 mmol) in DCM (24 mL) was added $Ti(OEt)_4$ (9.12 g, 4.2 mL, 40 mmol) followed by benzaldehyde (2.12 g, 20 mmol). The mixture was stirred at 60 ºC on a heating block overnight. The reaction mixture was washed by a lot of saturated NaCl solution. The aqueous layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated give sulfinimine **S7** (4.0 g, 88%, colorless liquid).[20]

To a solution of the sulfinimine **S7** (1.33 g, 5 mmol) in DCM (50 mL) was added propargylmagnesium bromide ether solution (50 mL, 10 mmol) slowly at -48 ºC. The mixture was stirred at -48 ºC for 2 h and then was allowed to warm to room temperature and stirred overnight. The reaction mixture was quenched with 15 mL of saturated ammonium chloride aqueous solution and the aqueous layer was extracted with DCM.

The combined organic layers were dried over $MgSO_4$ and removed the solvent . The residue was purified through silica gel flash chromatography (eluents: Hexanes: ethyl acetate = 5 : 1) to give desired product **S8** (1.12 g, colorless liquid) in 90% yield.

The above sulfinamide **S8** (249 mg, 1.0 mmol) was dissolved in MeOH (12 mL) and the solution was cooled to 0 ºC. Concentrated hydrochloric acid (2.2 equiv.) was added, and the reaction mixture was stirred at 0 ºC for 30 minutes. The solvent was evaporated, water was added and acid base work up to give pure amine **S6'** (0.142 g, yellow liquid) in 98%

yield.

p-toluenesulfonyl chloride (1.2 mmol) was added to a mixture of **S6'** (1 mmol), and Et_3N (2 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred at room temperature for overnight. The reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with 5 % of aqueous NaOH, brine, dried with anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified through silica gel flash chromatography to give desired pure homopropargyl amine **1a'**.[19]

5) Synthesis and characterization of 2

Condition A:

To a solution of the compound **1** (0.2 mmol) in HFIP (1 mL) was added AgOAc (6.6 mg, 0.04 mmol). The reaction was heated to 50 °C on a heating block and stired until the homopropargylic sulfonamides disappeared. The reaction mixture was purified through silica gel flash chromatography to give desired compound **2**.

Condition B:

To a solution of the homopropargylic sulfonamides (0.2 mmol) in HFIP (1 mL) was added Ph_3PAuCl (5.0 mg, 0.01 mmol). The reaction was heated to 50 °C on a heating block and stired until the homopropargylic sulfonamides disappeared. The reaction mixture was purified through silica gel flash chromatography to give desired compound **2**.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-phenyl-1-tosylpyrrolidine (2a/2a').** Condition A: Colorless solid, mp 57.0 - 58.3 °C, 89 mg, yield 95 %, $[\alpha]_D^{20} = -109.0°$ (c = 0.50, $CHCl_3$), 97.3% ee,^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.56 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.21 (m, 7H), 5.67 – 5.66 (d, *J* = 4.2 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.43 – 4.39 (dd, *J* = 2.8, 9.6 Hz, 1H), 2.41 (s, 3H), 2.26 – 2.08 (m, 3H), 1.60 – 1.51 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.5, 140.6, 134.4, 130.0, 128.4, 127.8, 127.7, 127.0, 93.2, 72.1 (m), 66.7, 34.5, 32.7, 21.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ - 69.0 to - 69.2 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{19}F_6NNaO_3S$ ($M+Na^+$) 490.0882; found 490.0874. HPLC analysis (Chiralpak IC column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 5.99 min (major) and 7.21 min (minor).

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-(4-methoxyphenyl)-1-tosyl pyrrolidine (2b).** Condition A: Colorless viscous liquid, 92 mg, yield 93 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.55 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.19 (dd, *J* = 8.4, 8.8 Hz, 4H), 6.81

– 6.78 (d, *J* = 6.8 Hz, 2H), 5.66 – 5.65 (d, *J* = 4.2 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.40 – 4.36 (q, *J* = 6.8 Hz, 1H), 3.78 (s, 3H), 2.41 (s, 3H), 2.23 – 2.07 (m, 3H), 1.60 – 1.50 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.3, 144.4, 134.6, 132.5, 129.9, 128.3, 127.8, 113.9, 93.2, 72.1 (m), 66.2, 55.4, 34.4, 32.6, 21.6. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ - 68.7 to - 69.1 (m, 6F). HRMS (ESI^+) calculated for $C_{21}H_{21}F_6NNaO_4S$ ($M+Na^+$) 520.0988; found 520.0983.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-(p-tolyl)-1-tosylpyrrolidine (2c).** Condition A: Colorless viscous liquid, 90 mg, yield 94 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.56 (d, *J* = 8.4 Hz, 2H), 7.26 – 7.24 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.17 (d, *J* = 8.0 Hz, 2H), 7.09 – 7.07 (d, *J* = 8.0 Hz, 2H), 5.65 – 5.64 (d, *J* = 4.2 Hz, 1H), 5.24 – 5.15 (m, 1H), 4.39 – 4.34 (q, *J* = 7.2 Hz, 1H), 2.41 (s, 3H), 2.31 (s, 3H), 2.21 – 2.07 (m, 3H), 1.58 – 1.48 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.5, 137.6, 137.5, 134.5, 129.9, 129.2, 127.8, 127.0, 93.2, 72.0 (m), 66.5, 34.4, 32.7, 21.6, 21.2. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ - 68.6 to – 68.9 (m, 6F). HRMS (ESI^+) calculated for$C_{21}H_{21}F_6NNaO_3S$ ($M+Na^+$) 504.1039; found 504.1042.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl-5-(4-(trifluoromethyl)phenyl) pyrrolidine (2d).** Condition A: Colorless viscous liquid, 87 mg, yield 81 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.55 – 7.53 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.49 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.37 (d, *J* = 8.0 Hz, 2H), 7.24 – 7.22 (d, *J* = 8.0 Hz, 2H), 5.72 – 5.71 (d, *J* = 4.2 Hz, 1H), 5.21 – 5.12 (m, 1H), 4.51 – 4.47 (q, *J* = 7.2 Hz, 1H), 2.40 (s, 3H), 2.33 – 2.27 (m, 1H), 2.18 – 2.08 (m, 2H), 1.68 – 1.57 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.9, 144.8 (d, *J* = 1.2 Hz), 134.1, 130.0, 127.8, 127.3, 125.4 (q, *J* = 3.7 Hz), 93.2, 72.2 (m), 65.9, 34.5, 32.8, 21.6. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): δ - 58.2 (s, 3F), - 68.6 to - 69.0 (m, 6F). HRMS (ESI^+) calculated for $C_{21}H_{18}F_9NNaO_3S$ ($M+Na^+$) 558.0756; found 558.0748.

***cis*-2-(4-fluorophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2e).** Condition A: Colorless solid, mp 106.7-108.5 °C, 94 mg, yield 97 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.55 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.24 (m, 4H), 6.98 – 6.93 (m, 2H), 5.66 – 5.65 (d, *J* = 5.6 Hz, 1H), 5.21 – 5.12 (m, 1H), 4.42 – 4.38 (q, *J* = 6.8 Hz, 1H), 2.42 (s, 3H), 2.26 – 2.07 (m, 3H), 1.61 – 1.50 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245 Hz), 144.8, 136.5 (d, *J* = 2.9 Hz), 134.2, 130.0, 128.7 (d, *J* = 8.2 Hz), 127.7, 115.3 (d, *J* = 21.5 Hz), 93.2, 72.0 (m), 65.9, 34.4, 32.6, 21.6. $^{19}F\{^{1}H\}$ NMR (376

MHz, $CDCl_3$): δ - 110.69 to -110.74 (m, 1F), - 68.6 to - 69.0 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{18}F_7NNaO_3S$ ($M+Na^+$) 508.0788; found 508.0793

***cis*-2-(4-chlorophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2f).** Condition A: white solid, mp 100.0-102.3 °C, 90 mg, yield 90 %, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.55 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.22 (t, *J* = 8.0 Hz, 6H), 5.66 – 5.64 (d, *J* = 5.2 Hz, 1H), 5.22 – 5.13 (m, 1H), 4.40 – 4.36 (q, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 2.26 – 2.04 (m, 3H), 1.60 – 1.49 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.8, 139.3, 134.2, 133.5, 130.0, 128.6, 128.4, 127.8, 93.2, 72.1 (m), 65.9, 34.4, 32.7, 21.6. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ - 68.6 to - 68.9 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{18}ClF_6NNaO_3S$ ($M+Na^+$) 524.0492; found 524.0480

***cis*-2-(4-bromophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2g).** Condition A: white solid, mp 98.7-100.3 °C, 92 mg, yield 85 %, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.56 – 7.54 (d, *J* = 8.4 Hz, 2H), 7.39 – 7.37 (d, *J* = 8.4 Hz, 2H), 7.27 – 7.25 (d, *J* = 8.0 Hz, 2H),7.16 – 7.14 (d, *J* = 8.4 Hz, 2H), 5.66 – 5.65 (d, *J* = 4.2 Hz, 1H), 5.20 – 5.12 (m, 1H), 4.39 – 4.35 (q, *J* = 7.2 Hz, 1H), 2.43 (s, 3H), 2.27 – 2.04 (m, 3H), 1.62 – 1.51 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 144.8, 139.8, 134.2, 131.6, 130.0, 128.7, 127.8, 121.7, 93.2, 72.1 (m), 65.9, 34.4, 32.7, 21.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ - 68.8 to - 69.2 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{18}BrF_6NNaO_3S$ ($M+Na^+$) 567.9987; found 567.9980.

***cis*-2-(2-fluorophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2h).** Condition B: Colorless solid, mp 110.3-111.1 °C, 82 mg, yield 85 %, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.66 (d, *J* = 7.6 Hz, 2H), 7.56 – 7.53 (t, *J* = 6.8 Hz, 1H), 7.33 – 7.31 (d, *J* = 7.6 Hz, 2H), 7.24 – 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 – 7.11 (t, *J* = 6.8 Hz, 1H), 7.00 – 6.95 (t, *J* = 9.2 Hz, 1H), 5.59 – 5.58 (d, *J* = 4.4 Hz, 1H), 5.32 – 5.29 (t, 1H), 4.81 – 4.77 (t, *J* = 6.8 Hz, 1H), 2.42 (s, 3H), 2.28 – 2.26 (d, *J* = 6.0 Hz, 1H), 2.10 – 2.07 (d, *J* = 9.2 Hz, 2H), 1.50 – 1.45 (q, *J* = 7.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.1 (d, *J* = 243.6 Hz), 144.9, 133.7, 130.2, 129.1 (d, *J* = 8.3 Hz), 128.5 (d, *J* = 2.5 Hz), 128.0 (d, *J* = 12.3 Hz), 127.9, 124.5 (d, *J* = 3.4 Hz), 115.0 (d, *J* = 21.8 Hz), 93.1, 71.9 (m), 59.0, 33.0, 32.7, 21.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$): δ - 116.7 to -116.8 (m, 1F), - 68.6 to - 68.9 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{18}F_7NNaO_3S$ ($M+Na^+$) 508.0788; found 508.0778.

***cis*-2-(3-fluorophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2i).**

Condition B: Colorless solid, mp 97.0-98.1 °C, 78 mg, yield 81 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.57 (d, *J* = 7.6 Hz, 2H), 7.28 – 7.20 (m, 3H), 7.08 – 7.06 (d, *J* = 7.6 Hz, 1H), 7.00 – 6.97 (d, *J* = 10.0 Hz, 1H), 6.94 – 6.90 (t, *J* = 8.4 Hz, 1H), 5.67 – 5.66 (d, *J* = 5.2 Hz, 1H), 5.22 – 5.15 (m, 1H), 4.42 – 4.39 (t, *J* = 8.4 Hz, 1H), 2.42 (s, 3H), 2.28 – 2.22 (m, 1H), 2.17 – 2.06 (m, 2H), 1.61 – 1.53 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.9 (d, *J* = 244.6 Hz), 144.8, 143.5, 134.2, 130.0, 130.0 (d, *J* = 8.8 Hz), 127.8, 122.6, 114.6 (d, *J* = 21.0 Hz), 113.9 (d, *J* = 22.2 Hz), 93.2, 72.2 (m), 66.0, 34.4, 32.7, 21.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ - 108.98 to -109.04 (m, 1F), - 68.8 to - 69.1 (m, 6F). HRMS (ESI$^+$) calculated for $C_{20}H_{18}F_7NNaO_3S$ (M+Na$^+$) 508.0788; found 508.0787.

***cis*-2-(2-bromo-4-fluorophenyl)-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyl pyrrolidine (2j).** Condition A: Colourless viscous liquid, 89 mg, yield 79 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.67 (d, *J* = 8.0 Hz, 2H), 7.61 – 7.57 (dd, *J* = 6.4 Hz, 1H), 7.34 – 7.32 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.21 (dd, *J* = 2.8 Hz, 1H), 7.04 – 7.00 (m, 1H), 5.62 – 5.61 (d, *J* = 5.6 Hz, 1H), 5.34 – 5.25 (m, 1H), 4.85 – 4.80 (dd, *J* = 6.8 Hz, 1H), 2.44 (s, 3H), 2.41 – 2.35 (m, 1H), 2.12 – 2.07 (dd, *J* = 6.0 Hz, 1H), 1.94 – 1.84 (m, 1H), 1.56 – 1.46 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 161.6 (d, *J* = 250.1 Hz), 145.0, 136.2, 133.4, 130.2, 129.6 (d, *J* = 8.7 Hz), 128.0, 121.9 (d, *J* = 9.6 Hz), 119.5 (d, *J* = 24.3 Hz), 115.5 (d, *J* = 21.0 Hz), 93.4, 72.2 (m), 65.1, 33.0, 32.7, 21.8. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): δ - 108.8 (s, 1F), - 68.7 to - 69.0 (d, 6F). HRMS (ESI$^+$) calculated for $C_{20}H_{17}BrF_7NNaO_3S$ (M+Na$^+$) 585.9893; found 585.9885.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-(naphthalen-2-yl)-1-tosylpyrrolidine (2k).** Condition B: White solid, mp 132.1-133.4 °C, 94 mg, yield 91 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.91 (t, *J* = 2.0, 6.8 Hz, 1H), 7.84 – 7.81 (t, *J* = 2.8, 6.8 Hz, 1H), 7.72 – 7.70 (t, *J* = 6.0, 2.8 Hz, 2H), 7.51 – 7.37 (m, 5H), 7.11 – 7.09 (d, *J* = 8.0 Hz, 2H), 5.83 – 5.82 (d, *J* = 5.2 Hz, 1H), 5.36 – 5.26 (m, 2H), 2.47 – 2.40 (m, 1H), 2.33 (s, 3H), 2.20 – 2.11 (m, 2H), 1.83 – 1.74 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.5, 135.9, 134.0, 133.7, 130.4, 129.7, 129.2, 128.0, 127.9, 126.2, 125.7, 125.5, 124.8, 122.2, 93.4, 72.7 (m), 63.3, 33.8, 32.8, 21.6. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 68.7 to - 69.1 (m, 6F). HRMS (ESI$^+$) calculated for $C_{24}H_{21}F_6NNaO_3S$ (M+Na$^+$) 540.1039; found 540.1037.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-(thiophen-2-yl)-1-tosylpyrrolidine (2l).** Condition A: Colourless viscous liquid, 71 mg, yield 75 %, ^{1}H NMR (400 MHz,

Chloroform-*d*) δ 7.58 – 7.56 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.21 (m, 5H), 5.67 – 5.66 (d, *J* = 5.2 Hz, 1H), 5.23 – 5.15 (m, 1H), 4.43 – 4.39 (q, *J* = 6.8 Hz, 1H), 2.41 (s, 3H), 2.26 – 2.08 (m, 3H), 1.58 – 1.51 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.5, 140.6, 134.4, 130.0, 128.4, 127.8, 127.7, 127.0, 93.2, 72.1 (m), 66.7, 34.5, 32.7, 21.7. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): - 68.9 to - 69.1 (m, 6F). HRMS (ESI^+) calculated for $C_{18}H_{17}F_6NNaO_3S_2$ ($M+Na^+$) 496.0446; found 496.0436.

2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosylpyrrolidine (2n). Condition A: Colourless viscous liquid, 76 mg, yield 97 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 – 7.67 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.34 (d, *J* = 8.0 Hz, 2H), 5.42 – 5.41 (d, *J* = 4.8 Hz, 1H), 5.18 – 5.11 (m, 1H), 3.56 – 3.52 (t, *J* = 8.8 Hz, 1H), 3.15 – 3.08 (q, *J* = 9.6 Hz, 1H), 2.44 (s, 3H), 2.11 – 2.00 (m, 2H), 1.85 – 1.79 (m, 1H), 1.33 – 1.24 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.7, 134.4, 130.2, 127.5, 91.7, 70.6 (m), 69.9, 48.2, 33.1, 22.8, 21.6 .[21]

***cis*-2-benzyl-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosylpyrrolidine (2o).** Condition B: Colourless viscous liquid, 80 mg, yield 83 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.73 – 7.71 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.35 (t, *J* = 8.0 Hz, 2H), 7.32 – 7.28 (t, *J* = 7.2 Hz, 2H), 7.24 – 7.20 (t, *J* = 7.6 Hz, 3H), 5.42 – 5.41 (d, *J* = 5.2 Hz, 1H), 5.23 – 5.14 (m, 1H), 3.71 – 3.66 (dd, *J* = 2.4 Hz, 1H), 3.61 – 3.54 (m, 1H), 2.69 – 2.63 (t, *J* = 12 Hz, 1H), 2.44 (s, 3H), 1.95 – 1.83 (m, 2H), 1.74 – 1.67 (m, 1H), 1.12 – 1.02 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ144.8, 138.5, 134.3, 130.3, 129.2, 128.7, 127.5, 126.7, 93.0, 70.6 (m), 64.4, 43.7, 31.9, 29.8, 21.7. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): - 69.0 to - 69.2 (m, 6F). HRMS (ESI^+) calculated for $C_{21}H_{21}F_6NNaO_3S$ ($M+Na^+$) 504.1039; found 504.1037.

***cis*-2-cyclohexyl-5-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosylpyrrolidine (2p).** Condition B: Colourless viscous liquid, 54 mg, yield 57 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.65 (d, *J* = 6.4 Hz, 2H), 7.35 – 7.33 (d, *J* = 6.4 Hz, 2H), 5.42 (s, 1H), 5.14 (s, 1H), 3.37 (s, 1H), 2.44 (s, 3H), 1.89 – 1.67 (m, 8H), 1.53 – 1.38 (m, 2H), 1.25 – 1.11 (m, 3H), 1.00 – 0.90 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.5, 134.9, 130.2, 127.4, 93.5, 71.7 (m), 67.9, 41.3, 31.9, 31.1, 27.5, 26.6, 26.4, 26.1, 25.8, 21.6. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): - 68.6 to - 68.9 (m, 6F). HRMS (ESI^+) calculated for $C_{20}H_{25}F_6NNaO_3S$ ($M+Na^+$) 496.1352; found 496.1351.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-tosyloctahydro-1H-indole (2q).**

Condition B: Colourless solid, mp 109.3-110.1 °C,40 mg, yield 51 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.67 – 7.66 (d, *J* = 5.2 Hz, 2H), 7.36 – 7.35 (d, *J* = 5.2 Hz, 2H), 5.30 (s, 2H), 2.46 (s, 4H), 1.94 – 1.69 (m, 5H), 1.45 – 1.23 (m, 4H), 0.97 – 0.89 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.7, 133.6, 130.1, 127.8, 91.8, 70.3 (m), 68.1, 42.5, 37.5, 32.4, 29.4, 25.3, 25.0, 21.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 69.2 to - 69.5 (m, 6F). HRMS (ESI$^+$) calculated for $C_{18}H_{21}F_6NNaO_3S$ (M+Na$^+$) 468.1039; found 468.1045.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-(methylsulfonyl)-5-phenylpyrrolidine (2r).** Condition A: Colourless solid, mp 103.0-104.1 °C,70 mg, yield 90 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.46 – 7.31 (m, 5H), 5.86 – 5.85 (d, *J* = 5.2 Hz, 1H), 4.80 – 4.69 (m, 1H), 2.52 – 2.46 (m, 1H), 2.41 (s, 3H), 2.39 – 2.31 (m, 2H), 2.14 – 2.04 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ139.9, 129.1, 128.7, 128.0, 93.4, 73.9 (m), 65.8, 42.2, 34.5, 33.0. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 69.2 to - 69.8 (m, 6F). HRMS (ESI$^+$) calculated for $C_{14}H_{15}F_6NNaO_3S$ (M+Na$^+$) 414.0569; found 414.0560.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-5-phenyl-1-(phenylsulfonyl)pyrrolidine (2s).** Condition A: Colourless viscous liquid, 80 mg, yield 88 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.66 (d, *J* = 7.6 Hz, 2H), 7.57 – 7.54 (t, *J* = 7.2 Hz, 1H), 7.46 – 7.42 (t, *J* = 7.6 Hz, 2H), 7.29 – 7.22 (m, 5H), 5.71 – 5.70 (d, *J* = 4.8 Hz, 1H), 5.17 – 5.12 (m, 1H), 4.48 – 4.44 (m, 1H), 2.28 – 2.09 (m, 3H), 1.62 – 1.54 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 140.4, 137.6, 133.5, 129.3, 128.5, 127.8, 127.7, 127.1, 93.3, 72.2 (m), 66.6, 34.5, 32.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 68.5 to - 68.9 (m, 6F). HRMS (ESI$^+$) calculated for $C_{19}H_{17}F_6NNaO_3S$ (M+Na$^+$) 476.0726; found 476.0720.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-((4-nitrophenyl)sulfonyl)-5-phenylpyrrolidine (2t).** Condition A: Colourless viscous liquid, 74 mg, yield 75 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 8.07 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.59 (d, *J* = 8.8 Hz, 2H), 7.20 – 7.13 (m, 5H), 5.92 – 5.90 (d, *J* = 4.8 Hz, 1H), 4.76 – 4.68 (m, 2H), 2.47 – 2.40 (m, 1H), 2.29 – 2.18 (m, 2H), 1.97 – 1.88 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.0, 144.6, 138.9, 128.9, 128.6, 128.3, 127.8, 123.8, 93.1, 72.7 (m), 66.3, 34.3, 32.2. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 68.8 to - 69.4 (m, 6F). HRMS (ESI$^+$) calculated for $C_{19}H_{16}F_6N_2NaO_5S$ (M+Na$^+$) 521.0576; found 521.0569.

***cis*-2-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1-((4-methoxyphenyl)sulfonyl)-5-**

phenylpyrrolidine (2u). Condition A: Colourless viscous liquid, 92 mg, yield 95 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.59 (d, *J* = 9.2 Hz, 2H), 7.32 – 7.20 (m, 5H), 6.90 – 6.88 (d, *J* = 9.2 Hz, 2H), 5.69 – 5.68 (d, *J* = 5.6 Hz, 1H), 5.23 – 5.15 (m, 1 H), 4.44 – 4.40 (dd, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 2.28 – 2.09 (m, 3H), 1.65 – 1.56 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.5, 140.6, 130.0, 128.9, 128.4, 127.7, 127.0, 114.4, 93.2, 72.1 (m), 66.6, 55.8, 34.6, 32.7. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$): - 68.8 to - 69.2 (m, 6F). HRMS (ESI$^+$) calculated for $C_{20}H_{19}F_6NKO_4S$ (M+K$^+$) 522.0571; found 522.0565.

2-(4-methoxyphenyl)-5-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole (3v). Condition A: Yellowish solid, 36 mg, yield 89 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63–7.59 (m, 4H), 7.39–7.28 (m, 5H), 7.30 – 7.28 (d, J = 8.8 Hz, 2H), 6.89 – 6.87 (d, J = 8.8 Hz, 2H), 5.43 – 5.42 (q, J = 2.0, 3.2 Hz, 1H), 5.31 – 5.29 (d, J = 7.6 Hz, 1H), 3.80 (s, 3H), 2.44 (s, 3H), 2.41–2.27 (m, 2H).[22]

5-((2-methyl-1-tosylpyrrolidin-2-yl)methyl)-1-tosyl-2,3-dihydro-1H-pyrrole (4w). Condition B: Yellow liquid, 24 mg, yield 95 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.74 (d, *J* = 8.0 Hz, 2H), 7.67 – 7.64 (d, J = 8.4 Hz, 2H), 7.31 – 7.27 (t, *J* = 7.2 Hz, 4H), 5.41 (s, 1H), 3.86 –3.72 (m, 2H), 3.53–3.48 (m, 1H), 3.28–3.23 (m, 3H), 2.61–2.55 (m, 1H), 2.43 (d, 3H), 2.42 (s, 3H), 1.96–1.92 (m, 3H), 1.75–1.59 (m, 2H), 1.42 (s, 3H).[23]

4-benzyl-6-methylene-2-phenyl-5,6-dihydro-4*H*-1,3-oxazine (5y). Condition A: yellow viscous liquid, 21 mg, yield 80 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 – 8.01 (d, *J* = 7.6 Hz, 2H), 7.48– 7.39 (m, 3H), 7.34 – 7.22 (m, 5H), 4.75 (s, 1H), 4.23 (s, 1H), 3.89 – 3.83 (m, 1H), 3.22 – 3.17 (dd, *J* = 4.8 Hz, 1H), 2.71– 2.65 (dd, *J* = 9.6 Hz, 1H), 2.48 – 2.43 (dd, *J* = 4.4 Hz, 1H),. 2.23 – 2.17 (dd, *J* = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 138.8, 131.0, 129.7, 128.6, 128.3, 127.5, 126.6, 92.2, 54.2, 42.5, 29.7. HRMS (ESI$^+$) calculated for $C_{18}H_{18}NO$ (M+H$^+$) 264.1383; found 264.1387.

[6] Synthesis and characterization of 4 and 6

To a stirred solution of $BF_3{\cdot}Et_2O$ (0.05 mmol, 7.1 mg) in CH_2C1_2 (0.6 mL) was added **2a** (0.05 mmol, 23.4 mg) under air at room temperature. The resulting reaction mixture was stirred for 15 min and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel

(petroleum ether-ethyl acetate, 5:1) to give **4a** (90% yield).[4c]

To a stirred solution of **2a/2a'** (0.1 mmol, 46.7 mg) in CH_2Cl_2 (1.0 mL) was added **TMS-Nu** (0.2 mmol) and KF (0.2 mmol, 11.6 mg) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a/2a'** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to give desired product **6a/6a', 6b, 6n/6n'.**

***cis*-2-allyl-5-phenyl-1-tosylpyrrolidine(6a/6a').** Colorless liquid, 31 mg, yield 90 %, $[\alpha]_D^{20} = -41.1°$ (c = 0.50, $CHCl_3$), 97.6% ee, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.33 (d, *J* = 8.0 Hz, 2H), 7.14 – 6.98 (m, 7H), 5.81 – 5.71 (m, 1H), 5.12 – 4.97 (m, 3H), 4.20 – 4.15 (m, 1 H), 2.91 – 2.87 (q, *J* = 4.4 Hz, 1H), 2.46 – 2.27 (m, 5H), 2.21 – 2.11 (m, 1H), 1.86 – 1.81 (dd, *J* = 6.8, 7.2 Hz, 1H), 1.72 – 1.67 (dd, *J* = 6.8 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.5, 142.5, 138.9, 135.0, 129.1, 128.2, 127.1, 127.0, 126.7, 117.9, 64.3, 61.0, 39.4, 33.2, 27.8, 21.5.[6] HRMS (ESI$^+$) calculated for $C_{20}H_{24}NO_2S$ (M+H$^+$) 342.1522; found 342.1528. (Chiralpak IC column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 25.35 min (minor) and 38.52 min (major).

5-phenyl-1-tosylpyrrolidine-2-carbonitrile (6b). Colorless liquid, 32 mg, yield 98 %, $[\alpha]_D^{20} = -65.7°$ (c = 0.50, $CHCl_3$), *dr* = 1.2/1, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.64 (d, *J* = 8.4 Hz, 2H), 7.45 – 7.43 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.13 (m, 14H), 4.96 – 4.83 (m, 4H), 2.62 – 2.52 (m, 1H), 2.47 – 2.36 (m, 8 H), 2.30 – 2.08 (m, 4H), 1.97 – 1.92 (dd, *J* = 6.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.3, 144.1, 141.6, 139.6, 135.8, 135.2, 129.6, 128.6, 128.6, 128.1, 127.8, 127.7, 127.4, 127.0, 126.2, 118.9, 117.7, 65.1, 62.6, 50.3, 50.2, 36.2, 35.0, 31.1, 29.5, 21.7, 21.6. HRMS (ESI$^+$) calculated for $C_{18}H_{19}N_2O_2S$ (M+H$^+$) 327.1162; found 327.1166.

***cis*-2-azido-5-phenyl-1-tosylpyrrolidine (6n/6n').** Colourless liquid, 34 mg, yield 99 %, $[\alpha]_D^{20} = -151.0°$ (c = 0.50, $CHCl_3$), 99.7% ee, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.53 – 7.51 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.16 (m, 7H), 5.79 – 5.78 (d, *J* = 6.0 Hz, 1H), 4.64 – 4.60 (q, *J* = 7.2 Hz, 1H), 2.38 (s, 3H), 2.30 – 2.23 (m, 1H), 2.09 – 1.99 (m, 1H), 1.90 – 1.84 (q, *J* = 6.0 Hz, 1H), 1.79 – 1.70 (m, 1H) ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.9, 140.9,

135.8, 129.6, 128.5, 127.7, 127.6, 127.0, 77.8, 65.5, 35.1, 32.5, 21.6. HRMS (ESI^+) calculated for $C_{17}H_{18}N_4NaO_2S$ ($M+Na^+$) 365.1043; found 365.1033. (Chiralpak OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 5.23 min (minor) and 6.02 min (major).

To a stirred solution of phenylacetylene (0.2 mmol, 20.4 mg) in CH_2C1_2 (1 mL) was added CuI (0.2 mmol, 38 mg) and KF (0.2 mmol, 11.6 mg) under air at room temperature. The reaction mixture stired for 1 h. Then **2a/2a'** (0.1 mmol, 46.7 mg) and $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) were added the reaction system successively. The resulting reaction mixture was stirred overnight and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 15:1) to give **6c/6c'** (60% yield)

***cis*-2-phenyl-5-(phenylethynyl)-1-tosylpyrrolidine (6c/6c').** Colourless liquid, 24 mg, yield 60 %, $[\alpha]_D^{20} = -80.0°$ (c = 0.50, $CHCl_3$), 97.9% ee, ^1H NMR (400 MHz, Chloroform-*d*) δ 7.75 – 7.73 (d, *J* = 8.0 Hz, 2H), 7.56 – 7.45 (m, 1H), 7.31 – 7.18 (m, 7H), 7.16 (d, *J* = 1.6 Hz, 2H), 7.08 – 7.06 (d, *J* = 8.0 Hz, 2H), 5.15 – 5.13 (d, *J* = 7.2 Hz, 1H), 4.88 – 4.86 (d, *J* = 8.8 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.42 – 2.27 (m, 4 H), 2.03 – 1.99 (dd, *J* = 6.4 Hz, 1H), 1.89 – 1.85 (dd, *J* = 6.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ143.6, 143.1, 136.9, 131.8, 129.1, 128.4, 128.2, 127.2, 126.2, 122.7, 87.4, 85.2, 62.7, 52.7, 35.4, 31.6, 21.5. HRMS (ESI^+) calculated for $C_{25}H_{24}NO_2S$ ($M+H^+$) 402.1522; found 402.1526. (Chiralpak OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 8.06 min (major) and 9.18 min (minor).

To a stirred solution of **2a/2a'** (0.1 mmol, 46.7 mg) in CH_2C1_2 (1.0 mL) was added **NuH** (0.2 mmol) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a/2a'** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2C1_2 (3 × 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1- 5:1) to give desired product **6e/6e', 6k, 6l.**

***cis*-2-(but-3-yn-1-yloxy)-5-phenyl-1-tosylpyrrolidine (6e/6e').** Colourless liquid, 30 mg, yield 81 %, $[\alpha]_D^{20}$ = −120.0° (c = 0.50, $CHCl_3$), 98.7% ee, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.57 (d, *J* = 8.0 Hz, 2H), 7.32 – 7.19 (m, 7H), 5.42 – 5.41 (d, *J* = 4.8 Hz, 1H), 4.50 – 4.46 (t, *J* = 8.0 Hz, 1H), 4.08 – 4.02 (m, 1H), 3.78 – 3.72 (m, 1H), 2.58 – 2.55 (t, *J* = 6.4 Hz, 2H), 2.39 (s, 3H), 2.27 – 1.95 (m, 4H), 1.45 – 1.35 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.7, 142.6, 135.7, 129.6, 128.4, 127.6, 127.3, 127.1, 91.4, 81.7, 69.4, 65.5, 65.2, 35.0, 33.0, 21.6, 19.8. HRMS (ESI$^+$) calculated for $C_{21}H_{23}NNaO_3S$ (M+Na$^+$) 392.1291; found 392.1290. (Chiralpak OD column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 254 nm): t_R = 6.20 min (major) and 7.06 min (minor).

***cis*-2-(benzylthio)-5-phenyl-1-tosylpyrrolidine (6k).** Colorless liquid, 40 mg, yield 95 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.20 (m, 14H), 5.33 – 5.31 (d, *J* = 6.4 Hz, 1H), 4.65 – 4.61 (t, *J* = 8.0 Hz, 1H), 4.15 – 4.00 (q, *J* = 13.2 Hz, 2H), 2.39 (s, 3H), 2.26 – 2.09 (m, 2H), 1.83 – 1.64 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.7, 141.9, 138.3, 135.4, 129.7, 129.2, 128.7, 128.4, 127.8, 127.4, 127.2, 127.1, 67.2, 66.0, 35.9, 35.8, 33.5, 21.7. HRMS (ESI$^+$) calculated for $C_{24}H_{26}NO_2S_2$ (M+H$^+$) 424.1399; found 424.1394.

2-((*cis*-5-phenyl-1-tosylpyrrolidin-2-yl)thio)thiazole (6l). Yellow liquid, 21 mg, yield 51 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.86 – 7.84 (d, *J* = 8.0 Hz, 2H), 7.55 – 7.54 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.34 (m, 5H), 7.24 – 7.23 (d, *J* = 4.4 Hz, 1H), 6.64 – 6.61 (q, *J* = 6.0 Hz, 1H), 6.55 – 6.54 (d, *J* = 4.8 Hz, 1H), 4.90 – 4.87 (t, *J* = 5.6 Hz, 1H), 2.47 – 2.34 (m, 4H), 2.23 – 2.16 (m, 1H), 1.99 – 1.89 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ187.1, 144.9, 140.2, 133.2, 130.3, 129.1, 128.6, 128.2, 126.9, 111.3, 100.1, 75.3, 65.0, 31.8, 31.1, 21.8. HRMS (ESI$^+$) calculated for $C_{20}H_{20}N_2NaO_2S_3$ (M+Na$^+$) 439.0579; found 439.0575.

To a stirred solution of **2a** (0.1 mmol, 46.7 mg) in CH_2Cl_2/CH_3CN = 1/1 (1.0 mL) was added **$AgSCF_3$** (0.4 mmol, 83.6 mg) and LiCl (0.4 mmol, 17.0 mg) under air at room temperature. The reaction tube need to keep in dark place. Then $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a** disappeared and then the insoluble substance was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to give desired product **6m**. Particularly necessary to point out that the compound **6m** was highly unstable. We could only get imide positive ions by high resolution mass spectrometry.

***cis*-2-phenyl-1-tosyl-5-((trifluoromethyl)thio)pyrrolidine (6m).** Colourless liquid, 22 mg, yield 57 %, **highly unstable.** ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.38 – 7.36 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.09 (m, 7H), 5.96 (s, 1H), 4.82 – 4.78 (q, *J* = 7.6 Hz, 1H), 2.45 – 2.13 (m, 7H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.8, 139.9, 136.2, 129.4, 128.6, 127.9, 127.7, 127.3, 66.8 (d, *J* = 2.3 Hz), 65.6, 35.4, 35.1, 21.7. ^{19}F NMR (376 MHz, $CDCl_3$): -39.1 (s, 3F).

To a stirred solution of **2a** (0.1 mmol, 46.7 mg) in CH_2C1_2 (1.0 mL) was added **ROH** (0.4 mmol) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) was added into the reaction mixture, which was stirred until **2a** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2C1_2 (3 x 5 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1- 5:1) to give desired product **6f, 6g, 6i, 6r.**

***cis*-2-methoxy-5-phenyl-1-tosylpyrrolidine (6f).** Colourless liquid, 30 mg, yield 91 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.57 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.21 (m, 7H), 5.29 – 5.28 (d, *J* = 4.8 Hz, 1H), 4.53 – 4.49 (q, *J* = 7.6 Hz, 1H), 3.55 (s, 3H), 2.40 (s, 3H), 2.28 – 2.21 (m, 1H), 2.13 – 2.02 (m, 1H), 1.96 – 1.91 (m, 1H), 1.45 – 1.35 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.6, 142.7, 136.0, 129.6, 128.5, 127.7, 127.3, 127.0, 92.9, 65.2, 55.5, 35.0, 33.0, 21.6. HRMS (ESI^+) calculated for $C_{18}H_{21}NO_3SNa$ ($M+Na^+$) 354.1134; found 354.1140.

***cis*-2-enthoxy-5-phenyl-1-tosylpyrrolidine (6g).** Colourless liquid, 31 mg, yield 90 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.57 (d, *J* = 8.4 Hz, 2H), 7.28 – 7.21 (m, 7H), 5.39 – 5.38 (d, *J* = 4.8 Hz, 1H), 4.51 – 4.47 (q, *J* = 7.6 Hz, 1H), 4.01 – 3.97 (m, 1H), 3.66 – 3.63 (m, 1H), 2.40 (s, 3H), 2.27 – 2.20 (m, 1H), 2.14 – 2.05 (m, 1H), 1.95 – 1.90 (q, 1H), 1.43 – 1.34 (m, 1H), 1.31 – 1.28 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.5, 142.9, 135.9, 129.6, 128.4, 127.6, 127.3, 127.0, 91.2, 65.0, 63.0, 35.1, 33.1, 21.6, 15.1. HRMS (ESI^+) calculated for $C_{19}H_{23}NO_3SNa$ ($M+Na^+$) 368.1291; found 368.1295.

***cis*-2-phenyl-1-tosyl-5-(2,2,2-trifluoroethoxy)pyrrolidine (6i).** Colourless liquid, 34 mg, yield 85 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.59 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.25 (m, 7H), 5.45 – 5.44 (d, *J* = 5.2 Hz, 1H), 4.48 – 4.44 (q, *J* = 7.6 Hz, 1H), 4.32 – 4.11

(m, 2H), 2.42 (s, 3H), 2.28 – 2.01 (m, 3H), 1.47 – 1.37 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.2, 142.0, 135.1, 129.9, 128.6, 127.6, 127.6, 127.0, 92.2, 65.6, 64.8 (q, J_{C-F} = 4.2 Hz), 34.7, 32.9, 21.7. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$): -69.6 (t, 3F).HRMS (ESI^+) calculated for $C_{19}H_{21}F_3NO_3S$ ($M+H^+$) 400.1189; found 400.1182.

To a stirred solution of **2a** (0.1 mmol, 46.7 mg) in CH_2Cl_2/CH_3CN = 2/1 (1.0 mL) was added H_2O (0.2 mmol, 3.6 mg) under air at 60 °C on a heating block. Then $BF_3{\cdot}Et_2O$ (0.1 mmol) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2C1_2 (3 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 5:1) to give desired product **6j.**

***cis*-5-phenyl-1-tosylpyrrolidin-2-ol (6j) (cis/trans = 6/1).** Colourless liquid, 13 mg, yield 40 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.61 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.36 (d, *J* = 6.8 Hz, 2H), 7.29 – 7.23 (m, 5H), 5.68 (s,1H), 4.59 – 4.55 (t, *J* = 6.8 Hz, 1H), 3.30 (s, 1H), 2.40 (s, 3H), 2.14 –1.91 (m, 3H), 1.83 – 1.74 (m, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 143.7, 141.9, 135.9, 129.8, 128.4, 127.4, 126.9, 85.7, 64.7, 34.4, 32.3, 21.6. HRMS (ESI^+) calculated for $C_{17}H_{19}NNaO_3S$ ($M+Na^+$) 340.0978; found 340.0979.

To a stirred solution of **2n** or **2q** (0.1 mmol) in CH_2C1_2 (1.0 mL) was added **TMS-CN** (0.2 mmol) and KF (0.2 mmol, 11.6 mg) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (0.1 mmol, 14.2 mg) was added into the reaction mixture. The resulting reaction mixture was stirred until **2n** or **2q** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2C1_2 (3 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) to give desired product **6o, 6p.**

1-tosylpyrrolidine-2-carbonitrile (6o). Yellow liquid, 24 mg, yield 96 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.78 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.35 (d, *J* = 8.0 Hz, 2H), 4.60 – 4.57 (q, *J* = 2.4, 7.2 Hz, 1H), 3.40 – 3.36 (q, *J* = 6.0, 7.6 Hz, 2H), 2.44 (s, 3H), 2.26 – 1.94 (m, 4H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 144.5, 134.2, 130.0, 127.6, 118.1, 48.6, 47.5, 31.9, 24.7, 21.6.[24]

***cis*-1-tosyloctahydro-1*H*-indole-2-carbonitrile (6p).** Colourless liquid, 30 mg, yield 99 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.80 – 7.78 (d, *J* = 8.0 Hz, 2H), 7.37 – 7.35 (d, *J* = 8.0 Hz, 2H), 4.60 – 4.57 (q, *J* = 2.4, 7.2 Hz, 1H), 3.40 – 3.36 (q, *J* = 6.0, 7.6 Hz, 1H), 2.44 (s, 3H), 2.26 – 1.94 (m, 4H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.5, 134.2, 130.0, 127.6, 118.1, 48.6, 47.5, 31.9, 24.7, 21.6.[13]

To a stirred solution of **2a** (23.5 mg, 0.05 mmol) in HFIP (1.0 mL) was added $NaBH_4$ (15.2 mg, 0.4 mmol) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (7.1 mg, 0.05 mmol) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a** disappeared and then poured into saturated brine (5 mL). The organic portion was extracted with CH_2C1_2 (3 x 5 mL). The combined organic layer was dried over anhydrous magnesium sulfate. After the drying agent was removed by filtration, the solvent was evaporated and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 8:1) to give desired product **6q.**

2-phenyl-1-tosylpyrrolidine (6q). Colorless liquid, 10 mg, yield 66 %, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.66 (d, *J* = 8.0 Hz, 2H), 7.31 – 7.20(m, 7H), 4.80 – 4.77 (dd, *J* = 3.6 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.45 – 3.39 (m, 1H), 2.43 (s, 3H), 2.01 – 1.94 (m, 1H), 1.91 – 1.78 (m, 2H), 1.70 – 1.62 (m, 1H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.3, 143.0, 135.1, 129.6, 128.3, 127.5, 127.0, 126.1, 63.3, 49.4, 35.8, 24.0, 21.5.[4e]

To a stirred solution of **2a** (0.15 mmol, 70 mg) in HFIP (1.0 mL) was added Ovocylin Dihydroxyestrin (0.18 mmol, 49 mg) under air at room temperature. Then $BF_3{\cdot}Et_2O$ (0.15 mmol, 21 mg) was added into the reaction mixture. The resulting reaction mixture was stirred until **2a** disappeared and the residue was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 5:1 ~ 2:1) to give desired product **6s.**

(8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-2-((*S*)-5-phenyl-1-tosylpyrrolidin-2-yl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (6s). Colourless visous liquid, 72 mg, yield 85 %, *trans*:*cis* = 4:5, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.43 (m, 4H), 7.33 – 7.17 (m, 6H), 6.55 – 6.46 (s, 1H), 6.33 – 6.12 (s, 1H), 5.23 – 5.20 (t, *J* = 6.4 Hz, 1H), 4.99 – 4.90 (t, J = 5.6 Hz, 1H), 3.76 – 3.70 (m, 1H), 2.80 – 2.73 (m, 2H), 2.40 – 2.39 (s, 3H), 2.14 – 1.83 (m, 20H), 0.80 – 0.76 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.5, 151.0, 143.6, 143.5, 141.9, 141.8, 137.4, 136.9, 135.0, 132.8, 132.3, 129.5, 129.5, 128.5, 128.0, 127.5, 127.5, 127.3, 127.2, 125.7, 125.4. 125.2,

125.1, 117.1, 116.3, 82.1, 65.0, 64.7, 60.9, 60.4, 50.1, 44.1, 44.1, 43.3, 38.9, 36.9, 36.8, 33.7, 33.4, 33.2, 33.0, 30.7, 29.3, 29.2, 27.4, 26.5, 23.3, 21.7, 11.3, 11.2. HRMS (ESI^+) calculated for $C_{19}H_{21}F_3NO_3S$ ($M+H^+$) 572.2829; found 572.2821.

ASSOCIATED CONTENT

Supporting Information.

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

Mass spectra, ^1H and ^{13}C NMR spectra, and structures (PDF)

X-ray structure of **2e** (CIF)

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The authors declare no competing financial interest.

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[13] Crystal data for the compound **2e**: Crystal data for the compound **2e**: $C_{20}H_{18}F_7NO_3S$, MW) 485.0896, Monoclinic, P2(1)/n, Final R indices [I> 2ó(I)], R1 = 0.0650, wR2 = 0.1946, R indices (all data) R1 = 0.0895, wR2 = 0.1699, a = 15.825(3) Å, b = 7.3310 (15) Å, c = 18.791 (4) Å, V) 2124.6 (8) A^3, T) 113 K, Z) 4.

Reflections collected / unique: 3745/ 2796 [R(int) = 0.077], number of observations [>2ó(I)] 3745, parameters) 291, Goodness-of-fit on F^2) 1.07. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1898568.

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