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# A Systematic Investigation of the Scope of Transannular C-H Heteroarylation of Cyclic Secondary Amines for Synthetic Application in Medicinal Chemistry

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***ABSTRACT***

Transannular C-H heteroarylation of amines provides rapid access to complex scaffolds that are otherwise difficult to synthesize. Wide adaptation of this emerging reaction for medicinal chemistry requires a broad understanding of substrate scope and more robust experimental conditions. In this article, we report a new ligand to promote the transannular reaction of a range of fused- and bridged-bicyclic secondary amines with a broad set of heteroarenes. The method was also successfully applied to the arylation of one spiro-bicyclic amine, a class of substrates that has not been studied in the context of transannular C-H activation reactions. The broad application of this transannular C-H heteroarylation methodology is currently hampered by the difficulty of removing the directing group. The development of a new directing group that is easier to remove will expand the utility of this reaction.

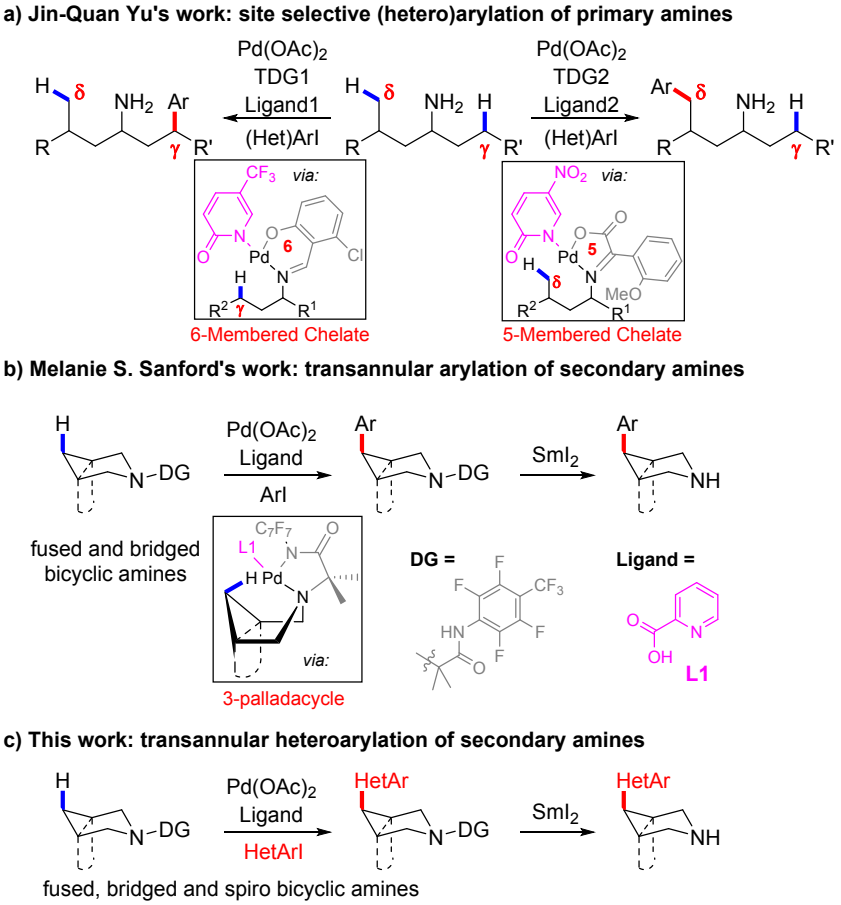
***INTRODUCTION***

A very small number of synthetic organic transformations including amide bond formation, cross coupling, aromatic nucleophilic substitution and reductive amination continues to dominate the

landscape of chemical reactions used by medicinal chemists to invent small molecule drugs.[1] Many modern advances in synthetic organic chemistry can better impact medicinal chemistry if scopes and limitations of the reactions were better studied.

Recently, the development of palladium catalyzed $sp^3$ C-H activation of amines to functionalize inert aliphatic C-H bonds has enabled rapid synthesis of complex scaffolds.[2,3,4] In 2018, the Yu group reported direct site-selective arylation and heteroarylation of aliphatic primary amines using different transient directing groups (TDGs) and ligands (Scheme 1a).[5] Sanford and co-workers developed the transannular C-H arylation of secondary amines using a pre-installed directing group (Scheme 1b).[6] Presumably, this reaction involves a boat-like palladacycle intermediate for functionalizing the transannular C-H bond.[7,8,9] The arylation of various fused- and bridged-bicyclic secondary amines were demonstrated successfully under the reaction conditions. However, only two examples of heteroarylation were presented involving Boc-protected indole and pyridine substrates.[10] In this article, we report a broad investigation into the scope of this relatively new transannular C-H arylation reaction using a panel of heteroaryl iodides, the identification of an optimal ligand, as well as the evaluation of diverse fused- / bridged-bicyclic amines and a new class of spiro-bicyclic amine substrate.

**Scheme 1. Development of palladium catalyzed $sp^3$ C-H functionalization of amines**



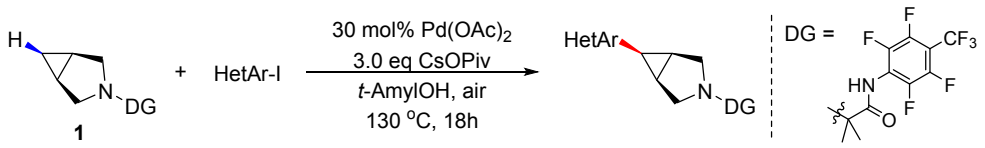

## *RESULTS AND DISCUSSION*

Sanford and co-workers have identified 3-azabicyclo[3.1.0]hexane derivative **1** as the preferred substrate for this transannular C-H activation reaction. Hence, we started our investigation with **1** and five common heteroaryl iodides using the first-generation conditions reported by Sanford (Table 1). Unfortunately, most reactions failed to afford the desired heteroarylated amines except the one with 3-iodopyrazole. The pyrazole-coupled amine **4** was detected with 80% uncalibrated yield in the crude reaction mixture. We postulate that the failure of reactions using the current conditions results from the large excess amount of heteroaryl iodide (30 equivalent) which may strongly coordinate to the palladium and hence prohibit the successful completion of the catalytic cycle. In 2018, the Sanford group reported their second-generation conditions for the transannular

C-H arylation of amines using picolinic acid (**L1**) as the ligand to rescue the palladium catalyst from forming off-cycle inactive species.[11] Using this second generation conditions, we also observed improved yields of products across all cases using only 3 equivalents of the heteroaryl iodides. For example, quinazoline- and pyrazine-coupled amines (**5** & **6**) proceeded with more than 85% uncalibrated yield, although thiazole- and pyridazine-coupled amine (**3** & **7**) were only detected with 31% and 3% uncalibrated yields.

Recently, it was demonstrated that the ligand could play a critical role to promote palladium catalyzed C-H functionalization reactions by accelerating C-H bond cleavage or stabilizing the active palladium catalyst.[12] Numerous examples have been reported with different types of ligands. Therefore, we conducted a screen to find a better ligand than picolinic acid (**L1**) to improve the yield of heteroarylated amine product. We utilized the on-site automation capabilities for the development of a rapid medium-throughput ligand screening protocol. A collection of 112 ligands was screened at a 0.01 mmol reaction scale and the high-performance liquid chromatography (HPLC) yield of product was assessed based on the biphenyl internal standard (see the Supporting Information for the representative ligands). In general, the employment of a ligand improved the yields. Compared to other types of mono- and bi-dentate ligands, the derivatives of pyridine-2-carboxylic acid were found to be superior to promote the reaction (Table 2). Compared to picolinic acid, 6-methylpicolinic acid increased the yield of product **3** from 27% to 43%. More hindered substituents on the 6-position of the pyridine ligand appeared to be detrimental. 6-Cl substituent on the ligand did not provide an improved yield of desired product **3**. 6-methoxy picolinic acid facilitated the formation of product **3**, although still not as effectively as 6-methyl picolinic acid. The bidentate chelation was shown to be necessary and the removal of either the carboxylic acid or the pyridine functionality resulted in lower yields of **3**.

**Table 1. Initial investigation of transannular C-H heteroarylation reactions**[a,b,c]

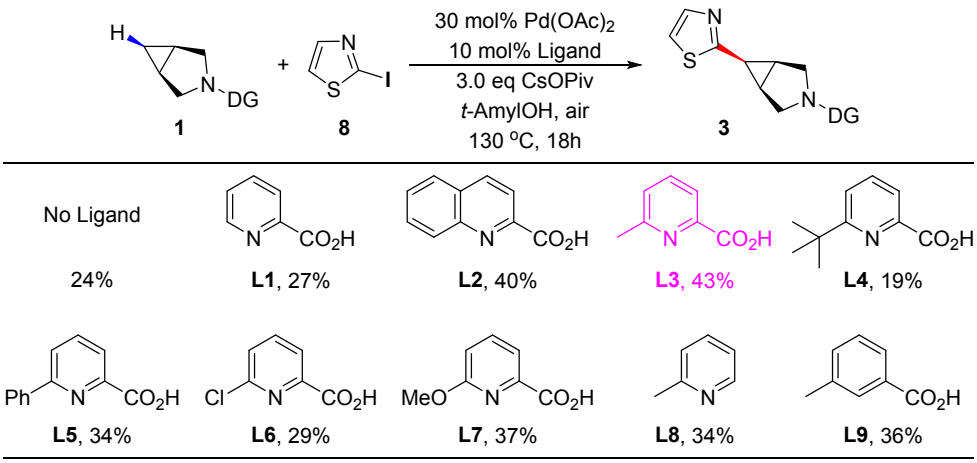



| | 2 | 3 | 4 |
|---|---|---|---|
| No ligand, **HetAr-I** (30 eq): (Sanford's 1st gen conditions) | 94% | 0% | 80% |
| 5 mol% **L1**, **HetAr-I** (3.0 eq): (Sanford's 2nd gen conditions) | 94% | 31% | 77% |

| | 5 | 6 | 7 |
|---|---|---|---|
| No ligand, **HetAr-I** (30 eq): (Sanford's 1st gen conditions) | 0% | 18% | 0% |
| 5 mol% **L1**, **HetAr-I** (3.0 eq): (Sanford's 2nd gen conditions) | 87% | 86% | 3% |

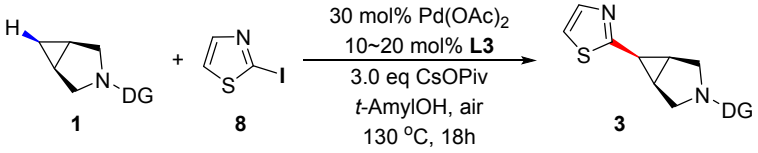
[a]Sanford's 1st-gen conditions: **1** (0.01 mmol, 1 eq), HetArI (30 eq), $Pd(OAc)_2$ (30 mol%), CsOPiv (3 eq), *t*-AmylOH (100 μL), 130 °C, 18h. [b]Sanford's 2nd-gen conditions: **1** (0.01 mmol, 1 eq), HetArI (3 eq), **L1** (5 mol%), $Pd(OAc)_2$ (30 mol%), CsOPiv (3 eq), *t*-AmylOH (100 μL), 130 °C, 18h. [c]High performance liquid chromatography (HPLC) yield was measured without calibration, see the Supporting Information for details.

**Table 2. Ligand evaluation[a,b]**




[a]Conditions: **1** (0.01 mmol, 1 eq), **8** (3 eq), ligand (10 mol%), $Pd(OAc)_2$ (30 mol%), CsOPiv (3 eq), *t*-AmylOH (100 μL), 130 °C, 18h. [b]Calibrated HPLC yield using internal standard. See the Supporting Information for the detailed procedure of ligand screening.

**Table 3. Conditions optimization[a]**



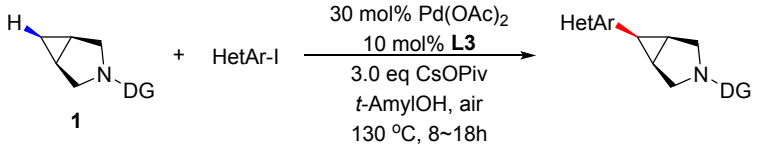

| Entry | $Pd(OAc)_2$ (mol%) | **L3** (mol%) | **8** (eq) | T (°C) | HPLC yield (%)[b] | Isolated yield (%) |
|---|---|---|---|---|---|---|
| 1 | 30 | 10 | 1.3 | 130 | 41 | - |
| 2 | 30 | 10 | 2.0 | 130 | 48 | - |
| 3 | 30 | 10 | 3.0 | 130 | 43 | - |
| 4 | 50 | 10 | 3.0 | 130 | 53 | 40[c]/ 32[d] |
| 5 | 100 | 10 | 3.0 | 130 | 20 | - |
| 6 | 50 | 20 | 3.0 | 130 | 50 | - |
| 7 | 50 | 10 | 3.0 | 150 | 52 | - |
| 8 | 50 | 10 | 2.0 | 150 | 38 | - |

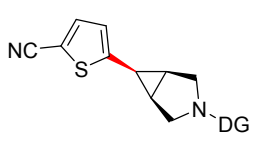
[a]Conditions: **1** (0.01 mmol, 1 eq), **8** (x eq), **L3** (y mol%), $Pd(OAc)_2$ (z mol%), CsOPiv (3 eq), *t*-AmylOH (100 μL), 130 or 150 °C, 18h. [b]Calibrated HPLC yield using internal standard. See the Supporting Information for the detailed procedure of conditions optimization. [c]0.2 mmol scale reaction. Flash silica gel chromatography purification. [d]0.2 mmol scale reaction. HPLC purification.

With the best ligand in hand, we optimized the conditions to improve the HPLC yield of product up to 53% (Table 3). No attempt was made to decrease the loading of $Pd(OAc)_2$, since this is not a limiting factor at the discovery stages of a drug development program. Direct preparative HPLC purification only afforded 18% isolated yield. Following Sanford's procedure, treating the reaction mixture with excess amount of aqueous hydrazine could rescue the product **3** from the coordination to the palladium catalyst and an improved yield (32%) was obtained after preparative HPLC purification. The yield could be further improved to 40% by switching the preparative HPLC purification to silica gel chromatography purification.

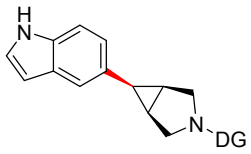
With the optimized conditions in hand, we next explored the scope of the heteroaryl iodides using the 3-azabicyclo[3.1.0]hexane scaffold **1** as the substrate (Table 4). For efficiency of analysis and separation, the heteroarylated products were isolated using our on-site automatic preparative HPLC purification service. Heteroarylation with various iodoarenes containing one hetero atom, such as thiophene, indole and pyridines, proceeded smoothly with around 50% yield of heteroarylated amines (**9-13**). A broad collection of heteroarenes with two hetero atoms were all successfully coupled with the amine substrate **1**. The strongly coordinating thiazoles (**3** & **14**) and benzothiazole groups (**15**) were compatible with the reaction conditions, as well as pyrazole (**4**) and indazoles (**16** & **17**). Pyrimidines and pyrazines were also competent coupling partners and functionalities such as bromo and ester groups were tolerated (**5**, **6**, **18-21**), allowing for further derivatizations. Notably, reactions with protected azaindole (**22**) proceeded smoothly while those with unsubstituted azaindole and indazole iodides failed to provide any product, probably due to poisoned palladium catalyst by these strong coordinating heteroarenes. More importantly, various heteroarenes containing three heteroatoms, such as aza-indazoles (**23-24**), imidazopyridine (**25**) and imidazopyridazine (**26**), were also identified with more than 20% yield, which makes this methodology attractive and synthetically useful for medicinal chemists.

**Table 4. Scope of heteroaryl iodide coupling partners**[a,b]

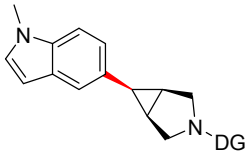


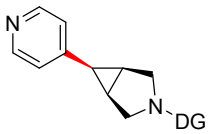

**9**, 36%



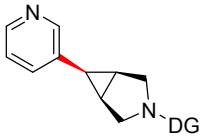

**10**, 54%[b]



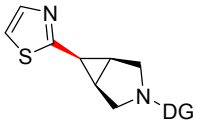

**11**, 59%[b]



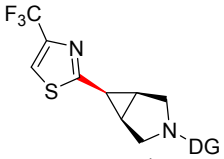

**12**, 61%[b]



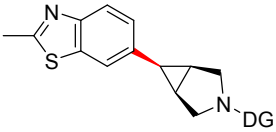

**13**, 60%[b]



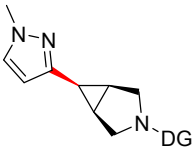

**3**, 40%



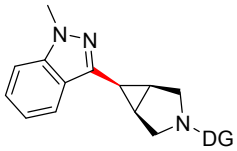

**14**, 41%[b]



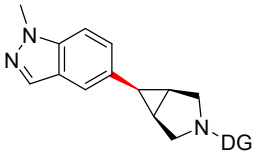

**15**, 78%[b]



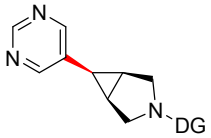

**4**, 56%[b]



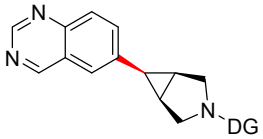

**16**, 44%



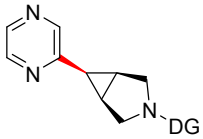

**17**, 31%



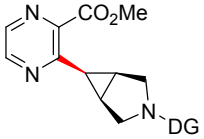

**18**, 59%



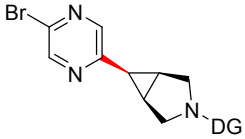

**5**, 56%[b]



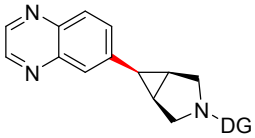

**6**, 60%[b]



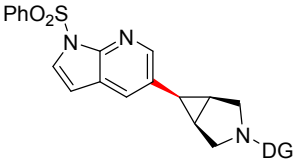

**19**, 24%



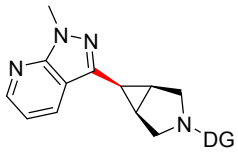

**20**, 41%



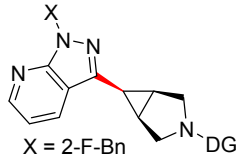

**21**, 54%




**22**, 45%

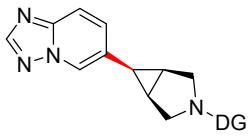



**23**, 35%

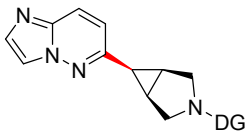



X = 2-F-Bn

**24**, 29%




**25**, 28%



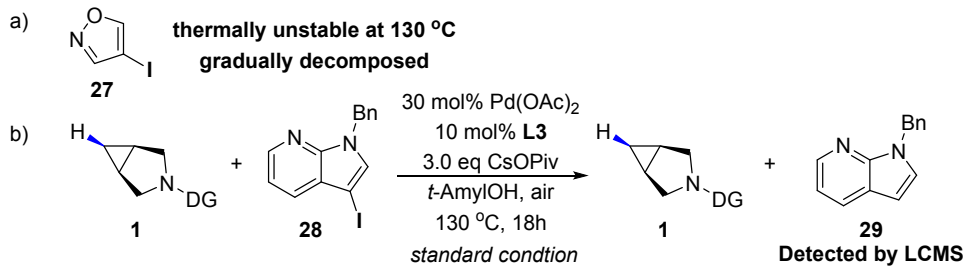

**26**, 18%

[a]Conditions: **1** (0.2 mmol, 1 eq), HetAr-I (2~3 eq), **L3** (10 mol%), $Pd(OAc)_2$ (30 mol%), CsOPiv (3 eq), *t*-AmylOH (2.0 mL), 130 °C, 8~18h. Unless noted, products were purified by HPLC. [b]Isolated yield by flash chromatography purification.

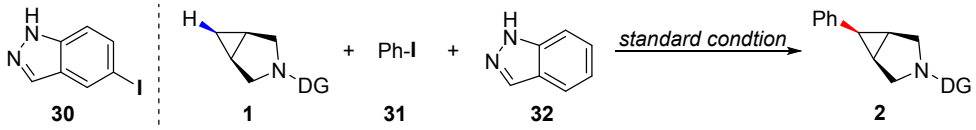
While our protocol demonstrated extraordinary compatibility of a broad collection of heteroarenes, numerous unsuccessful examples were also identified (see the supporting information for details). We propose three possible reasons for the failure of reactions with these heteroaryl iodides. First, the heteroaryl iodide is unstable under the reaction conditions. For instance, the iodo isoxazole (**27**) underwent gradual decomposition at 130 °C (Scheme 2.1a). Dehalogenation of heteroaryl iodide in the presence of palladium catalyst, such as **28**, was also detected as the major competing reaction pathway to form the dehalogenated side product (**29**) dominantly. Second, the heteroaryl iodide poisons the palladium catalyst. As mentioned above, the unsubstituted iodo indazole **30** was inactive as a coupling partner in the reaction with **1**, probably resulting from the palladium catalyst poisoning. This postulation was supported by adding the corresponding indazole (**32**) into the reaction of amine **1** with iodobenzene (**31**). The indazole **32** completely inhibited the formation of arylated product **2** (Scheme 2.2). The third reason was the low reactivity of heteroaryl iodide towards oxidative addition to palladium catalyst. For example, the success of 5-iodopyrimidine **33** as the coupling partner suggested pyrimidine would not poison the catalyst under the standard conditions. The decomposition of 2-iodopyrimidine **34** was also excluded indicated by the LCMS analysis of the reaction mixture and hence the low activity of **34** in the Pd(II)/Pd(IV) catalytic cycle was likely the reason for the low yield of heteroarylated product **35**.

**Scheme 2. Rationale for unsuccessful heteroaryl iodides coupling partners**

**1). The heteroaryl iodide was unstable under the reaction condition.**

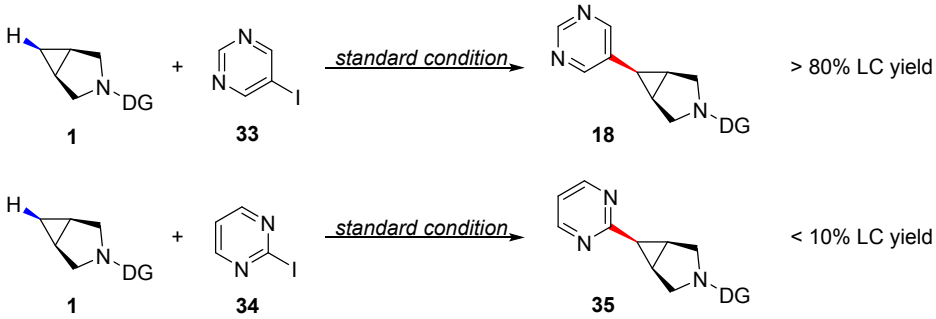



**2). Palladium catalyst was poisoned from the strong coordination of heteroarenes.**



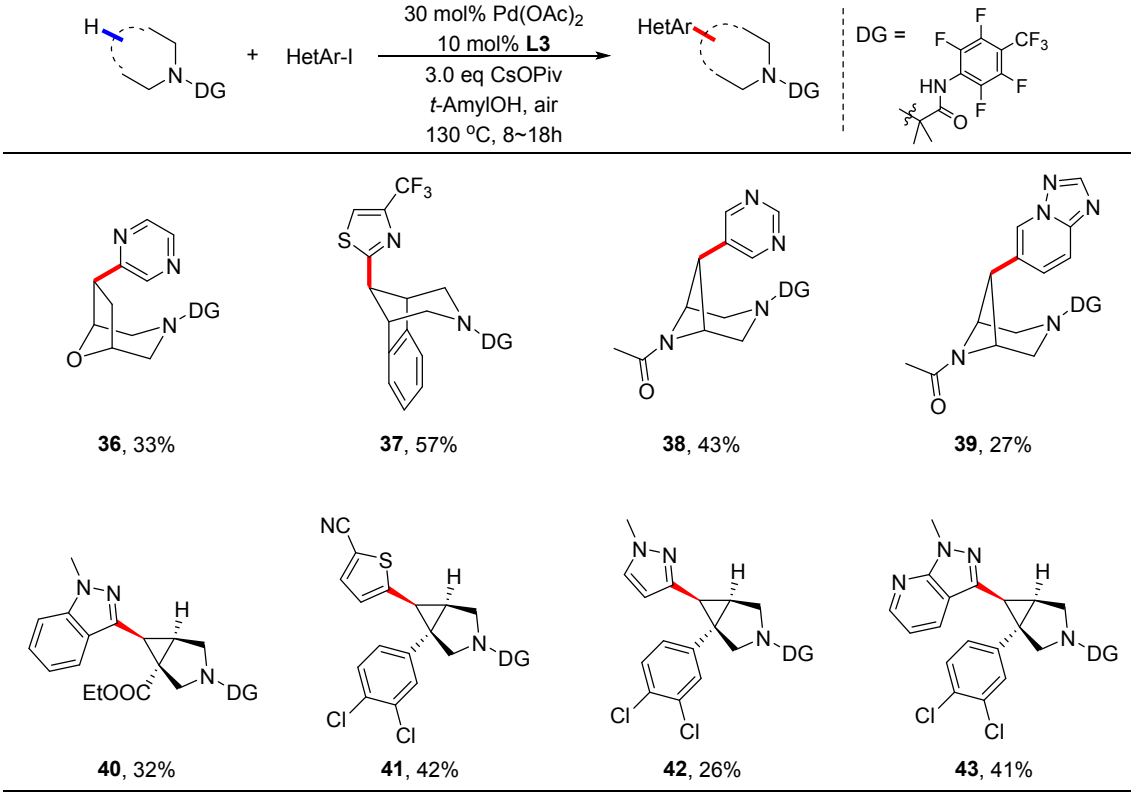

| | | | | |
|---|---|---|---|---|
| **Condition 1:** | 1.0 eq | 3.0 eq | None | > 90% LC yield |
| **Condition 2:** | 1.0 eq | 3.0 eq | 3.0 eq | < 5% LC yield |

**3). Poor reactivity of heteroaryl iodide towards oxidative addition of palladium catalyst.**



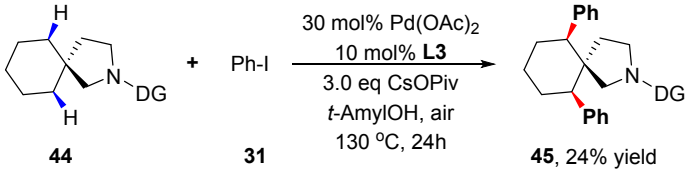

Next, we also examined the scope of amines (Table 5). Transannular C-H bonds of various bridged- (**36-39**) and fused-bicyclic amines (**40-43**) were functionalized smoothly with different identified heteroarenes in good yields. This appealing reaction provides medicinal chemists a useful tool for the rapid synthesis of these three-dimensional drug-like scaffolds. More importantly, an unprecedented transannular arylation of spirocyclic amine was identified (Scheme 3). The diarylated product **45** could be isolated with moderate yield, although large excess amount of iodobenzene (**31**) was required. To our best knowledge, the functionalization of these two transannular C-H bonds next to the quaternary center were not reported before using other methods, which indicated the superiority of this transannular C-H activation strategy.

**Table 5. Scope of alkyl amines for transannular C-H heteroarylation** [a]




[a]Conditions: Amine (0.2 mmol, 1 eq), HetAr-I (2~3 eq), **L3** (10 mol%), $Pd(OAc)_2$ (30 mol%), CsOPiv (3 eq), *t*-AmylOH (2.0 mL), 130 °C, 8~18h. Products were purified by HPLC.

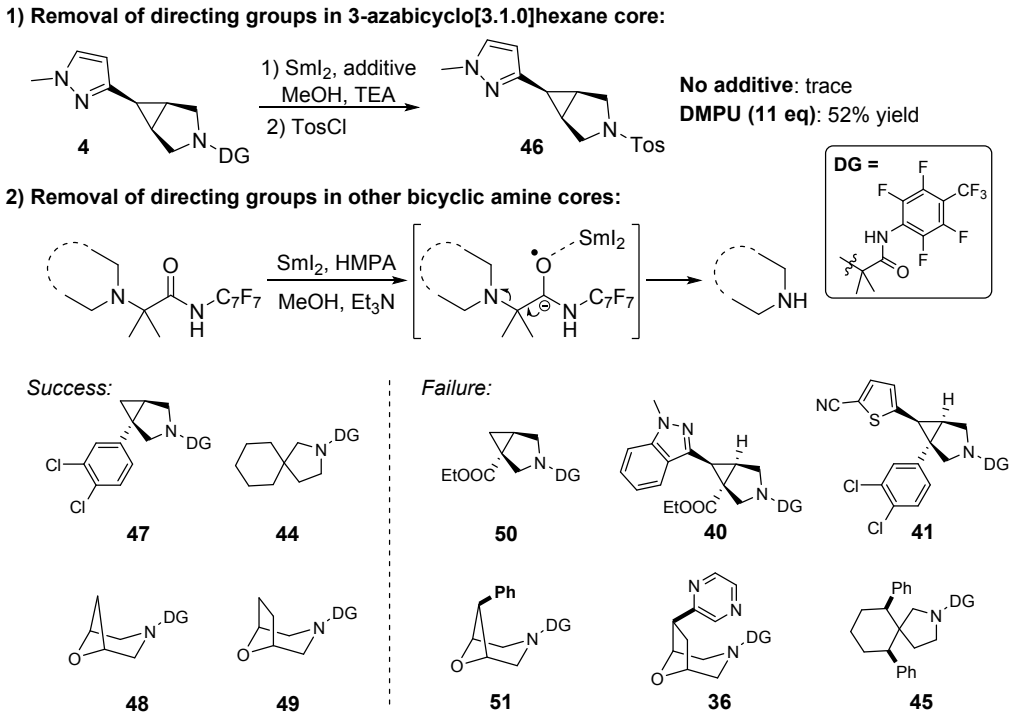
**Scheme 3. Arylation of spirocyclic amine**




With broad scopes of both amines and heteroaryl iodides explored, we investigated the feasibility to remove the directing group of the heteroarylated amines (Scheme 4). Sanford's group reported the directing group (DG) could be successfully cleaved in the transannular arylated 3-azabicyclo[3.1.0]hexane and piperidine cores using samarium diiodide ($SmI_2$).[6,13] However,

whether $SmI_2$-mediated deprotections are compatible with sensitive heterocycles was not clear. We chose **4** containing a pyrazole group as the model substrate owing to its relative low aromaticity and the presence of a reductively sensitive N-N bond. Reaction of **4** with $SmI_2$ and subsequent trapping of the secondary amines with TsCl only provided trace amount of **46**. However, addition of DMPU significantly improved the yield of **46** to 52% (Scheme 4.1). The major competing reaction pathways in the reaction were the rapid mono-, di- and tri-defluorinations on the electron-deficient phenyl ring in the directing group. For those vulnerable heterocycles under $SmI_2$ condition, such as pyridines, a new method was developed earlier this year by Sanford and Abbvie to afford acyl amides, although in low yields.[14]

**Scheme 4. Challenges to remove the directing auxiliary**




When we attempted to remove the directing group from other bicyclic amine cores, we encountered significant difficulties (Scheme 4.2). After screening a collection of both amine substrates and heteroarylated amine products, we found that the reactivity of desired C-N

cleavage dramatically decreased as the steric hinderance around the amide carbonyl increased, probably due to the weaker coordination of samarium to the carbonyl. To our surprise, even the simple arylated bridged-bicyclic amine **51** turned out to be a difficult substrate for directing group removal.[15] These results suggested that the development of a new strategy to remove the DG in sterically hindered bicyclic amine cores is necessary.

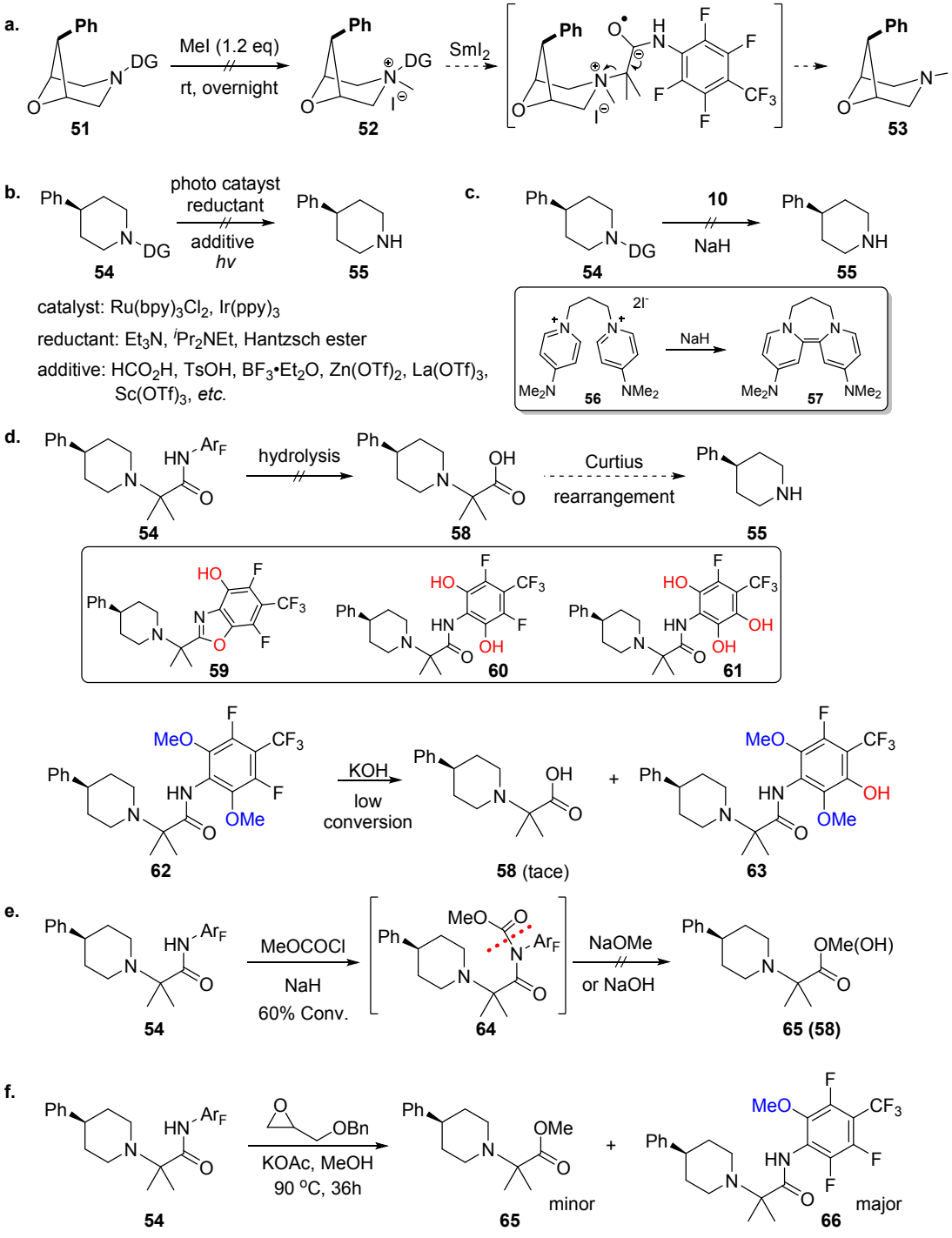
In consideration of the neutral amine as an inert leaving group, we attempted to convert it to the labile cationic ammonium. Surprisingly, the amine **51** could not be smoothly methylated probably due to the steric hinderance from the gem-dimethyl group (Scheme 5a). Next, we examined different single-electron reduction methods other than $SmI_2$ and the more readily available compound **54**, in which the directing group could be smoothly removed by $SmI_2$, was chosen as the model substrate. Photoredox catalyzed reduction of $\alpha$-functionalized carbonyl compounds has been reported involving a single-electron process.[16] Unfortunately, no desired free amine **55** was formed using a variety of photo catalysts, reductants and additives, while the dominant reaction pathway was still the defluorination reaction of the electron-deficient phenyl ring (Scheme 5b). Various organic single electron donors (SED) have been developed to reduce the $\alpha$-functionalized carbonyl compounds.[17] One of the most reductive SED (**57**) was tested and only led to the decomposition of **54** (Scheme 5c).[18] Because of the difficulty to remove the directing group via a single-electron pathway, we designed a multi-step strategy involving the hydrolysis of amide[19] and the subsequent Curtius rearrangement[20] to deliver the desired free amine product (Scheme 5d). However, **54** was completely inert under acidic conditions (TFA, HCl, $BF_3$*$Et_2O$) and suffered from the dominant $S_NAr$ side reaction under basic conditions (Scheme 5d). Hydrolysis of the amide adjacent to a quaternary carbon center remained extremely difficult in compound **62** with a less electron deficient phenyl ring and only side products from $S_NAr$ reaction were detected. In addition, a two-step procedure, reported by the Jin-Quan Yu group to hydrolyze the same amide bond next to a tertiary carbon center, was also examined (Scheme 5e).[21] The acylation of aniline

using NaH as the base performed smoothly to afford compound **64**. However, NaOMe hydrolyzed the carbamate in compound **64** to form amide **54** rather than the amide to form ester **65**. At last, an epoxide-mediated deprotection strategy was also investigated.[22] Unfortunately, the reaction still favored $S_NAr$ pathway on the electron-deficient phenyl ring over the desired amide hydrolysis pathway (Scheme 5f). Unfortunately, removal of this directing group remains an open problem.

***Summary***

A novel transannular C-H heteroarylation of fused- and bridged-bicyclic amines was developed. This methodology allows medicinal chemists to rapidly synthesize transannular heteroarylated 3-azabicyclo[3.1.0]hexane core. A new ligand was identified to improve the yield of heteroarylation reactions. The first transannular arylation reaction of spiro-bicyclic amine was also reported for the rapid functionalization of the spiro-bicyclic scaffold. At the outset, we expected the $SmI_2$-mediated deprotection may not be compatible to sensitive heterocycles. However, to our surprise, the $SmI_2$ reaction turned out to be more sensitive to the nature of the amine scaffold. Design of new directing groups that are easier to remove will advance this transannular C-H activation reaction.

**Scheme 5. Efforts to develop new directing group removal strategy** [a]




[a]Unless noted, all reactions were monitored through LC-MS analysis of crude reaction mixture and the possible products in each reaction were not isolated.

***Experimental Section***

Unless otherwise noted, all reactions were carried out with anhydrous solvents (dichloromethane, toluene, tetrahydrofuran, 1,4-dioxane, acetonitrile) purchased from Fisher Scientific. All reagents, including heteroaryl iodides and amines, were purchased from Sigma-Aldrich, Acros, Enamine, Combi-Blocks, WUXI Tech, Alfa, SpiroChem or TCI and used as received, unless noted otherwise. Unless indicated, reactions were performed under ambient conditions. Reactions conducted at elevated temperatures were heated on a hot plate with temperature control (*Chemglass*) using an aluminum PIE-Block system (*Chemglass*). The final compounds were analyzed or purified according to one of the analytical or purification methods referred to below unless otherwise described and characterized by $^{1}H$, $^{19}F$, $^{13}C\{^{1}H\}$ NMR, and high-resolution mass spectrometry. For LC/MS analysis, a sample is dissolved in a suitable solvent such as acetonitrile (MeCN), dimethyl sulfoxide (DMSO), or methanol (MeOH) and is injected directly into the column using an automated sample handler. All the compounds in this paper were racemic. The stereocenters were defined in the structure to indicate the relative configurations and the absolute configuration was arbitrarily assigned.

The analysis used the following acidic method (3.5 min run): conducted on a Waters Acquity UPLC BEH. (MS ionization: ESI) instrument equipped with a C18 column (2.1 mm × 50 mm, C18, 1.7 μm), eluting with 0.1% v/v of trifluoroacetic acid (TFA) in water (solvent A) and 0.1% v/v of TFA in acetonitrile (solvent B). Silica gel column chromatography was performed using 20−40 μm (particle size) mesh silica gel using a Grace Reveleris X2 with ELSD purification system. Preparative HPLC purifications were performed on a Waters Acquity UPLC BEH used the following acidic method (7.0 min run). (MS ionization: ESI) instrument equipped with a SunFire

Prep C18 OBD column (19 mm × 100 mm, C18, 5 μm), eluting with 0.1% v/v of trifluoroacetic acid (TFA) in water (solvent A) and 0.1% v/v of TFA in acetonitrile (solvent B).

The $^{1}H$, $^{19}F$, $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Ultrashield Plus 500 MHz. Chemical shifts are expressed in parts per million (ppm) units and referenced to the residual solvent resonance as noted in the spectra (i.e., $CDCl_3$; 7.27 ppm for $^{1}H$ & 77.0 ppm for $^{13}C\{^{1}H\}$). Coupling constants (J) are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as: s (singlet), d (doublet), t (triplet), dd (doubled doublet), dt (doubled triplet), dq (doubled quartet), m (multiplet), or br (broad). The carbon resonances corresponding to the perfluoroarene ($C_7F_7$), trifluoromethyl ($CF_3$) and fluoro-substituted phenyl ring (F-Ar) in this compound appear as a complex series of multiplets between 105 ppm to 155 ppm as a result of $^{13}C/^{19}F$ coupling. Due to the complexities of the system, the peaks are not listed. $^{19}F$ NMR and HRMS were used to confirm the presence of these ring systems.

High-resolution mass spectrometry data were recorded using Sciex Triple TOF 5600 mass spectrometer (column: Waters UPLC Acquity HSS T3 C18 1.8 μm, 2.1 mm × 50 mm; mobile phase: A = 0.1% formic acid in $H_2O$; B = 0.1% formic acid in acetonitrile; method: 7 min, A to B gradient 5−>65%, positive ionization mode). All masses were reported as the exact masses in the format of $[M + H]^+$ , unless noted otherwise.

Substrates **1**, **44**, **47**, **48**, **49**, **50**, **54**, **S-1, S-2** (see the Supporting Information for the structures of **S-1** and **S-2**) were prepared from the corresponding free amine or amine salts following the literature procedure.[6] Known compounds **1**, **47**, **48**, **54, S-1** were characterized by NMR analysis and the data matched with the literature. New compounds **44**, **49**, **50**, **S-2** were characterized and the data were shown as follow:

*2-methyl-2-(2-azaspiro[4.5]decan-2-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**44**, 1.84 g, white solid, Yield: 82%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-15%). $^{1}$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.34 (s, 6 H), 1.38 - 1.51 (m, 10 H), 1.63 (t, *J*=6.7 Hz, 2 H), 2.47 (s, 2 H), 2.71 (t, *J*=7.0 Hz, 2 H). $^{19}$F NMR (471 MHz, $CDCl_3$) δ ppm <-144.04> - <-143.90> (m, 2 F), <-141.35> - <-141.07> (m, 2 F), -55.99 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 175.4, 61.8, 46.0, 41.0, 38.2, 26.0, 23.5, 20.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}F_7N_2O$ 441.1772; Found 441.1765.

*2-((1R,5S)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**49**, 1.83 g, white solid, Yield: 74%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-30%). $^{1}$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.32 (s, 6 H), 1.92 - 2.04 (m, 4 H), 2.54 (d, *J*=11.0 Hz, 2 H), 2.71 (dd, *J*=11.0, 1.8 Hz, 2 H), 4.39 - 4.43 (m, 2 H), 9.01 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.81> - <-143.62> (m, 2 F), <-140.97> - <-140.70> (m, 2 F), -56.03 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 174.9, 74.4, 64.1, 51.9, 28.1, 20.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}F_7N_2O_2$ 415.1251; Found 415.1245.

*Ethyl (1R,5R)-3-(2-methyl-1-oxo-1-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)propan-2-yl)-3-azabicyclo[3.1.0]hexane-1-carboxylate (**50**, 354.3 mg, white solid, Yield: 78%)*. The crude material was purified by silica gel column chromatography (DCM in Heptanes from 0%-100%). $^{1}$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.27 (t, *J*=7.3 Hz, 3 H), 1.31 (t, *J*=4.6 Hz, 1 H), 1.34 (s, 3 H), 1.39 (s, 3 H), 1.47 (dd, *J*=8.6, 4.3 Hz, 1 H), 2.00 - 2.06 (m, 1 H), 2.81 (dd, *J*=9.2, 3.7 Hz, 1 H), 2.91 (d, *J*=9.2 Hz, 1 H), 3.04 (d, *J*=9.2 Hz, 1 H), 3.10 (d, *J*=9.2 Hz, 1 H), 4.17 (q, *J*=7.1 Hz, 2 H), 8.82 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-144.25> - <-143.97> (m, 2 F), <-141.05> - <-140.72> (m, 2 F), -56.00 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 174.5, 172.7, 61.4,

60.8, 47.3, 47.2, 28.6, 26.3, 21.8, 20.3, 16.0, 14.3. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}F_7N_2O_3$ 457.1357; Found 457.1355.

*2-((1R,5S)-6-acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-1-(2,3,5,6-tetrafluoro-4-(trifleoromethyl)phenyl)propan-1-one (**S-2**, 386.0 mg, white solid, Yield: 50%)*. The crude material was purified by silica gel column chromatography (EtOAc/EtOH=3/1 <v/v> in Heptanes from 0%-30%). $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.38 (s, 3 H), 1.45 (s, 3 H), 1.55 (d, *J*=8.6 Hz, 1 H), 1.98 (s, 3 H), 2.62 - 2.70 (m, 1 H), 2.79 (d, *J*=11.0 Hz, 1 H), 2.87 (d, *J*=11.0 Hz, 1 H), 3.30 (br d, *J*=9.8 Hz, 1 H), 3.42 (br d, *J*=9.8 Hz, 1 H), 4.35 (br d, *J*=3.7 Hz, 2 H), 8.64 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) δ ppm -143.42 (td, *J*=16.8, 6.4 Hz, 2 F), <-141.26> - <-140.93> (m, 2 F), -56.09 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 175.1, 174.7, 63.3, 60.7, 58.2, 47.5, 46.3, 31.3, 24.7, 20.0, 18.2. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}F_7N_3O_2$ 442.1360; Found 442.1352.

**Experimental Procedure for Ligand Screening.** Each reaction was performed in a 1.0 mL vial for the 96-well parallel synthesis/optimization plate (see the supporting information). $Pd(OAc)_2$ was prepared as stock solution in DCM (0.05M). Each ligand was prepared as stock solution in DCM (or MeOH, 0.02M). Amine **1** (1.0 eq) and CsOPiv (3.0 eq) were prepared as stock solution in t-amylOH (0.1M for **1**, volatile ligands were also included in this stock solution if necessary). 4-CN-4'-Me-biphenyl was employed as internal standard and prepared as stock solution in MeCN (0.1M). To each vial was added $Pd(OAc)_2$ stock solution (60 uL, 30 mol%) and the corresponding ligand stock solution (50 uL, 10 mol%). The solution in each vial was stirred and heated to 50~60 $^o$C for 15 min to remove the solvent. After cooling down to room temperature, 2-iodothiazole **8** (3.0 eq) was weighed out and transferred into each vial. Then the stock solution of amine **1** and CsOPiv (100 uL) was transferred into each vial. The reaction block was sealed, stirred and heated to 130 $^o$C for 18h. After cooling down to room temperature, to each vial was added the stock

solution of internal standard (100 uL) and DMSO (200 uL). Then the mixture in each vial was transferred into a 2-dr vial and the original reaction vial was rinsed with DMSO (300 uL * 2). The combined solution of each sample in 2-dr vial was transferred to 96-well plate automatically by TECAN and subjected to LC/MS analysis. The integrations of UV peaks of each compound and internal standard were measured at 232 nm and the according calibrated yield was calculated.

**Representative Experimental Procedure for Transannular C-H Heteroarylation of Amines.** A 5 mL microwave vial was charged with amine **1** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.06 mmol, 30 mol %), CsOPiv (0.6 mmol, 3 equiv), **L3** (0.02 mmol, 10 mol %), heteroaryl iodide (0.4 mmol, 2 equiv) and t-amylOH (2.0 mL, 0.1 M). The vial was equipped with a magnetic stir bar, sealed and heated to an external temperature of 130 ºC in an aluminum heating block. After 12 h, the reaction was cooled to room temperature. Hydrazine hydrate (0.25 mL) was added to the solution and the mixture was allowed to stir for 30 min at 60 °C to sequester Pd from the product. The mixture was diluted with EtOAc (3.0 mL), filtered through Celite and rinsed with EtOAc (10 mL). The volatiles were removed under vacuum, and the residue was purified via reversed-phase preparative HPLC to afford the desired product. If the compound was very non-polar or inseparable from byproducts on preparative HPLC, silica gel flash chromatography was employed.

*2-((1R,5S,6s)-6-(5-cyanothiophen-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetra-fluoro-4-(trifluoromethyl)phenyl)propenamide (**9**, 35.1 mg, white solid, Yield: 36%).* $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.19 (s, 6 H), 2.00 - 2.08 (m, 3 H), 2.90 - 2.98 (m, 2 H), 3.02 (d, *J*=9.78 Hz, 2 H), 6.74 (s, 1 H), 6.93 (d, *J*=3.7 Hz, 1 H), 7.31 (d, *J*=3.7 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm -143.00 (td, *J*=16.5, 5.7 Hz, 2 F), <-140.63> - <-140.33> (m, 2 F), -56.15 (t, *J*=21.5 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.0, 150.0, 137.0, 125.2, 113.6, 107.3, 61.5, 45.3, 22.4, 21.0, 17.8. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{16}F_7N_3OS$ 492.0975; Found 492.0979.

*2-((1R,5S,6r)-6-(1H-indol-5-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**10**, 54.0 mg, white solid, Yield: 54%).* The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ ppm 1.02 (s, 6 H), 1.83 - 1.89 (m, 2 H), 2.12 (t, *J*=7.9 Hz, 1 H), 2.85 (br d, *J*=8.6 Hz, 2 H), 2.95 (d, *J*=8.6 Hz, 2 H), 3.33 (s, 1 H), 5.95 - 6.00 (m, 1 H), 6.13 (s, 1 H), 6.84 - 6.88 (m, 1 H), 7.11 (d, *J*=7.9 Hz, 1 H), 7.25 (d, *J*=7.9 Hz, 1 H), 7.36 (s, 1 H), 10.87 (br s, 1 H). $^{19}$F NMR (471 MHz, DMSO-$d_6$) $\delta$ ppm <-144.19> - <-143.80> (m, 2 F), <-143.16> - <-142.81> (m, 2 F), -55.39 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, DMSO-$d_6$) $\delta$ ppm 175.6 (175.5), 134.1 (134.0), 127.6, 127.3 (127.2), 124.7 (124.5), 121.5, 118.7, 111.2 (111.1), 99.7 (99.6), 60.1, 44.7, 22.4, 20.8, 19.7. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}F_7N_3O$ 500.1568; Found 500.1572.

*2-methyl-2-((1R,5S,6r)-6-(1-methyl-1H-indol-5-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**11**, 60.4 mg, white solid, Yield: 59%).* The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.04 (s, 6 H), 1.77 - 1.80 (m, 2 H), 2.10 (t, *J*=7.9 Hz, 1 H), 2.80 - 2.84 (m, 2 H), 2.96 (d, *J*=9.2 Hz, 2 H), 3.58 (s, 3 H), 5.90 (d, *J*=3.1 Hz, 1 H), 6.04 (br s, 1 H), 6.54 (d, *J*=3.1 Hz, 1 H), 7.13 - 7.15 (m, 2 H), 7.36 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm -144.08 (br s, 2 F), <-143.09> - <-142.79> (m, 2 F), -56.22 (t, *J*=22.2 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 176.5, 135.0, 128.6 (two peaks), 128.3, 122.1, 119.8, 109.3, 99.9, 60.8, 45.2, 32.5, 23.0, 20.3. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{25}H_{22}F_7N_3O$ 514.1724; Found 514.1719.

*2-methyl-2-((1R,5S,6r)-6-(pyridin-4-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**12**, 56.2 mg, white solid, Yield: 61%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.14 (s, 6 H), 1.94 - 2.01 (m, 2 H), 2.05 - 2.12 (m, 1 H), 2.87 - 3.00 (m,

4 H), 6.37 (br s, 1 H), 7.35 (d, *J*=4.9 Hz, 2 H), 8.39 (d, *J*=5.5 Hz, 2 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.07> - <-142.81> (m, 2 F), <-140.91> - <-140.58> (m, 2 F), -56.12 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 175.4, 149.5, 147.6, 123.8, 61.3, 45.2, 27.3, 22.3, 21.0, 20.1. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}F_7N_3O$ 462.1411; Found 462.1412.

*2-methyl-2-((1R,5S,6r)-6-(pyridin-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide* (***13**, 55.2 mg, white solid, Yield: 60%*). $^1$H NMR (500 MHz, MeOD-$d_4$) *δ* ppm 1.10 (s, 6 H), 1.98 - 2.01 (m, 2 H), 2.07 - 2.13 (m, 1 H), 2.92 - 3.01 (m, 4 H), 4.86 (s, 1 H), 7.32 (dd, *J*=7.9, 4.9 Hz, 1 H), 7.84 - 7.89 (m, 1 H), 8.21 (d, *J*=4.9 Hz, 1 H), 8.51 (d, *J*=1.2 Hz, 1 H). $^{19}$F NMR (471 MHz, MeOD-$d_4$) *δ* ppm <-145.02> - <-144.83> (m, 2 F), <-143.81> - <-143.54> (m, 2 F), -57.67 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 177.1, 149.9, 147.9, 138.2, 136.2, 125.1, 62.3, 46.1, 21.4, 21.3, 21.0. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{18}F_7N_3O$ 462.1411; Found 462.1400.

*2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-((1R,5S,6s)-6-(thiazol-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)propenamide (**3**, 37.6 mg, light yellow solid, Yield: 40%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-20%). $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.17 (s, 6 H), 2.03 - 2.09 (m, 2 H), 2.20 (t, *J*=7.3 Hz, 1 H), 2.86 - 2.95 (m, 2 H), 3.17 (d, *J*=9.8 Hz, 2 H), 7.17 (d, *J*=3.1 Hz, 1 H), 7.39 (d, *J*=3.1 Hz, 1 H), 7.55 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-142.36> - <-142.21> (m, 2 F), <-141.36> - <-141.05> (m, 2 F), -56.08 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) *δ* ppm 175.5, 168.0, 141.7, 119.1, 61.5, 45.4, 22.6, 21.0, 20.7. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{19}H_{16}F_7N_3OS$ 468.0975; Found 468.0969.

*2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-((1R,5S,6s)-6-(4-(trifluoromethyl)-thiazol-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)propenamide (**14**, 43.7 mg, yellow solid, Yield: 41%)*.

The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.20 (s, 6 H), 2.09 - 2.16 (m, 2 H), 2.22 (t, *J*=7.9 Hz, 1 H), 2.92 - 2.98 (m, 2 H), 3.19 (d, *J*=9.2 Hz, 2 H), 7.10 (br s, 1 H), 7.60 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.34> - <-143.21> (m, 2 F), <-141.58> - <-141.33> (m, 2 F), -64.36 (s, 3 F), -56.14 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 174.6, 170.1, 61.6, 45.4, 22.9, 20.9, 20.8. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{15}F_{10}N_3OS$ 536.0849; Found 536.0851.

*2-methyl-2-((1R,5S,6r)-6-(2-methylbenzo[d]thiazol-6-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**15**, 82.8 mg, white solid, Yield: 78%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-20%). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.12 (s, 6 H), 1.89 - 1.95 (m, 2 H), 2.18 (t, *J*=7.9 Hz, 1 H), 2.65 (s, 3 H), 2.91 (br d, *J*=9.2 Hz, 2 H), 3.00 (d, *J*=9.2 Hz, 2 H), 6.18 (br s, 1 H), 7.43 (d, *J*=8.6 Hz, 1 H), 7.71 (s, 1 H), 7.75 (d, *J*=8.6 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.03> - <-142.88> (m, 2 F), <-141.65> - <-141.38> (m, 2 F), -55.89 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.9, 166.6, 151.8, 135.9, 135.0, 126.5, 122.3, 120.5, 61.0, 45.2, 22.9, 21.1, 20.4, 19.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{20}F_7N_3OS$ 532.1288; Found 532.1284.

*2-methyl-2-((1R,5S,6s)-6-(1-methyl-1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**4**, 52.0 mg, light yellow solid, Yield: 56%)*. The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-30%). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.17 (s, 6 H), 1.82 - 1.89 (m, 3 H), 2.82 - 2.89 (m, 2 H), 3.08 (d, *J*=8.6 Hz, 2 H), 3.64 (s, 3 H), 6.11 (d, *J*=1.8 Hz, 1 H), 7.08 (d, *J*=1.8 Hz, 1 H), 7.59 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-142.88> - <-142.66> (m, 2 F), <-141.35> - <-141.05> (m, 2 F), -56.07 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 176.1, 149.5, 130.1, 105.0, 61.3, 45.6, 38.6, 21.0, 20.4, 16.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}F_7N_4O$ 465.1520; Found 465.1524.

*2-methyl-2-((1R,5S,6s)-6-(1-methyl-1H-indazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**16**, 45.5 mg, white solid, Yield: 44%)*. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.11 (s, 6 H), 2.06 (s, 3 H), 2.89 (br d, *J*=9.2 Hz, 2 H), 3.15 (d, *J*=8.6 Hz, 2 H), 3.97 (s, 3 H), 6.45 (br s, 1 H), 6.82 - 6.89 (m, 2 H), 7.05 (d, *J*=7.3 Hz, 1 H), 7.70 (d, *J*=7.3 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.77> - <-143.58> (m, 2 F), <-142.42> - <-142.10> (m, 2 F), -56.10 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.7, 141.9, 140.2, 125.6, 123.2, 120.9, 119.9, 108.5, 61.0, 45.7, 35.3, 20.9, 20.0, 15.2. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}F_7N_4O$ 515.1677; Found: 515.1676.

*2-methyl-2-((1R,5S,6r)-6-(1-methyl-1H-indazol-5-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**17**, 32.1 mg, white solid, Yield: 31%)*. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.10 (s, 6 H), 1.86 - 1.93 (m, 2 H), 2.17 (t, *J*=7.9 Hz, 1 H), 2.90 (br d, *J*=9.2 Hz, 2 H), 2.99 (d, *J*=9.2 Hz, 2 H), 3.91 (s, 3 H), 6.08 (br s, 1 H), 7.28 (d, *J*=8.6 Hz, 1 H), 7.40 (d, *J*=8.6 Hz, 1 H), 7.46 (s, 1 H), 7.54 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-144.63> - <-144.29> (m, 2 F), <-142.07> - <-141.78> (m, 2 F), -56.17 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 176.0, 138.3, 131.5, 130.1, 127.3, 123.9, 119.3, 109.0, 61.0, 45.2, 35.3, 22.8, 21.1, 20.3. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}F_7N_4O$ 515.1677; Found 515.1676.

*2-methyl-2-((1R,5S,6r)-6-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**22**, 57.7 mg, white solid, Yield: 45%)*. $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.08 (s, 6 H), 1.89 - 1.99 (m, 2 H), 2.05 (t, *J*=7.3 Hz, 1 H), 2.87 - 3.00 (m, 4 H), 6.25 (br s, 1 H), 6.31 (d, *J*=3.7 Hz, 1 H), 7.38 - 7.46 (m, 2 H), 7.48 (d, *J*=3.7 Hz, 1 H), 7.53 (t, *J*=7.3 Hz, 1 H), 7.77 (s, 1 H), 8.05 - 8.11 (m, 2 H), 8.43 (d, *J*=1.8 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.39> - <-143.18> (m, 2 F), <-141.32> - <-141.00> (m, 2 F), -56.19 (t, *J*=22.2 Hz, 3 F). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.4, 145.9, 145.2, 138.3,

134.2, 129.0, 128.8, 128.6, 127.8, 126.7, 122.4, 104.6, 61.2, 45.3, 21.0, 20.5, 20.2. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{29}H_{23}F_7N_4O_3S$ 641.1452; Found 641.1450.

*2-methyl-2-((1R,5S,6r)-6-(pyrimidin-5-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide* (***18**, 54.4 mg, white solid, Yield: 59%*). $^1$H NMR (500 MHz, MeOD-$d_4$) $\delta$ ppm 1.09 (s, 6 H), 2.00 - 2.10 (m, 3 H), 2.96 - 3.02 (m, 4 H), 8.79 (s, 2 H), 8.91 (s, 1 H). $^{19}$F NMR (471 MHz, MeOD-$d_4$) $\delta$ ppm -144.88 (dq, *J*=16.8, 6.8 Hz, 2 F), <-143.99> - <-143.67> (m, 2 F), -57.69 (t, *J*=22.2 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, MeOD-$d_4$) $\delta$ ppm 175.9, 157.7, 157.0, 134.1, 62.1, 46.1, 22.1, 20.9, 18.8. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{17}F_7N_4O$ 463.1364; Found 463.1363.

*2-methyl-2-((1R,5S,6r)-6-(quinazolin-6-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide* (***5**, 56.9 mg, white solid, Yield: 56%*). The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^1$H NMR (500 MHz, $CDCl_3$) δ ppm 1.09 (s, 6 H), 2.01 (br d, *J*=7.3 Hz, 2 H), 2.26 (t, *J*=7.9 Hz, 1 H), 2.90 - 3.04 (m, 4 H), 7.81 (s, 1 H), 7.86 (d, *J*=8.6 Hz, 1 H), 7.92 (d, *J*=8.6 Hz, 1 H), 9.09 (s, 1 H), 9.15 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) δ ppm <-143.76> - <-143.48> (m, 2 F), <-140.95> - <-140.60> (m, 2 F), -56.23 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) δ ppm 175.3, 159.3, 155.0, 148.5, 138.5, 135.6, 128.4, 125.1, 124.8, 61.2, 45.3, 22.9, 21.0, 20.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}F_7N_4O$ 513.1520; Found: 513.1521.

*2-methyl-2-((1R,5S,6s)-6-(pyrazin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide* (***6**, 55.3 mg, white solid, Yield: 60%*). The crude material was purified by silica gel column chromatography (EtOAc in Heptanes from 0%-50%). $^1$H NMR (500 MHz, MeOD-$d_4$) $\delta$ ppm 1.08 (s, 6 H), 2.05 - 2.10 (m, 2 H), 2.23 (t, *J*=7.9 Hz, 1 H), 2.95 - 3.00 (m, 2 H), 3.10 (d, *J*=9.2 Hz, 2 H), 4.88 (s, 1 H), 8.38 (d, *J*=3.7 Hz, 1 H), 8.46 (dd, *J*=2.8, 1.5 Hz, 1 H),

8.67 (s, 1 H). $^{19}$F NMR (471 MHz, MeOD-$d_4$) $\delta$ ppm -144.89 (dq, $J$=17.5, 7.0 Hz, 2 F), <-144.02> - <-143.73> (m, 2 F), -57.65 (t, $J$=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, MeOD-$d_4$) $\delta$ ppm 175.9, 156.0, 146.5, 144.8, 143.1, 62.1, 46.3, 22.7, 22.3, 21.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{17}F_7N_4O$ 463.1364; Found 463.1364.

*Methyl 3-((1R,5S,6s)-3-(2-methyl-1-oxo-1-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)-propan-2-yl)-3-azabicyclo[3.1.0]hexan-6-yl)pyrazine-2-carboxylate* (***19**, 25.0 mg, colorless oil, Yield: 24%*). $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.07 (s, 6 H), 2.06 - 2.12 (m, 2 H), 2.46 (t, $J$=7.9 Hz, 1 H), 2.75 - 2.82 (m, 2 H), 2.92 (d, $J$=9.8 Hz, 2 H), 3.91 (s, 3 H), 6.25 (br s, 1 H), 8.45 (d, $J$=2.4 Hz, 1 H), 8.63 (d, $J$=2.4 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.39> - <-143.22> (m, 2 F), <-141.32> - <-141.03> (m, 2 F), -56.06 (t, $J$=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 174.6, 165.5, 154.6, 145.8, 144.4, 141.5, 61.5, 53.1, 45.5, 23.2, 21.9, 20.7. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}F_7N_4O_3$ 521.1418; Found 521.1423.

*2-((1R,5S,6s)-6-(5-bromopyrazin-2-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide* (***20**, 44.8 mg, light yellow solid, Yield: 41%*). $^1$H NMR (500 MHz, MeOD-$d_4$) $\delta$ ppm 1.09 (s, 6 H), 2.02 - 2.06 (m, 2 H), 2.13 (t, $J$=7.9 Hz, 1 H), 2.93 - 2.98 (m, 2 H), 3.06 (d, $J$=9.8 Hz, 2 H), 4.86 (br s, 1 H), 8.44 (s, 1 H), 8.58 (d, $J$=1.2 Hz, 1 H). $^{19}$F NMR (471 MHz, MeOD-$d_4$) $\delta$ ppm <-144.72> - <-144.55> (m, 2 F), <-143.73> - <-143.48> (m, 2 F), -57.63 (t, $J$=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, MeOD-$d_4$) $\delta$ ppm 176.0, 154.5, 147.3, 146.4, 138.8, 62.1, 46.2, 22.4, 22.0, 21.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{20}H_{16}BrF_7N_4O$ 541.0469; Found: 541.0464.

*2-methyl-2-((1R,5S,6r)-6-(quinoxalin-6-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**21**, 55.1 mg, light yellow solid, Yield: 54%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.08 (s, 6 H), 1.97 - 2.06 (m, 2 H), 2.27 (t, $J$=7.9 Hz, 1 H), 2.87 - 2.97 (m, 2

H), 3.05 (d, *J*=9.2 Hz, 2 H), 7.77 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.92 (d, *J*=8.6 Hz, 1 H), 7.96 (s, 1 H), 8.52 (d, *J*=1.8 Hz, 1 H), 8.63 (d, *J*=1.8 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.26> - <-143.06> (m, 2 F), <-141.41> - <-141.08> (m, 2 F), -56.19 (t, *J*=22.2 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 175.4, 145.0, 144.5, 142.7, 141.6, 140.9, 131.6, 129.4, 127.4, 61.1, 45.2, 23.1, 21.0, 20.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{19}F_7N_4O$ 513.1520; Found 513.1524.

*2-methyl-2-((1R,5S,6s)-6-(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**23**, 35.9 mg, white solid, Yield: 35%)*. $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.11 (s, 6 H), 2.05 - 2.11 (m, 3 H), 2.91 (br d, *J*=9.2 Hz, 2 H), 3.11 (d, *J*=9.2 Hz, 2 H), 3.98 (s, 3 H), 6.67 (br s, 1 H), 6.88 (dd, *J*=7.9, 4.3 Hz, 1 H), 8.04 (dd, *J*=7.9, 1.2 Hz, 1 H), 8.08 (dd, *J*=4.3, 1.8 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.67> - <-143.43> (m, 2 F), <-141.57> - <-141.27> (m, 2 F), -56.07 (t, *J*=21.5 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 175.6, 150.5, 148.5, 141.3, 129.8, 116.0 ,115.1, 61.1, 45.8, 33.6, 21.0, 20.2, 15.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}F_7N_5O$ 516.1629; Found 516.1637.

*2-((1R,5S,6s)-6-(1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**24**, 35.6 mg, color-less oil, Yield: 29%)*. $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.07 (s, 6 H), 2.06 - 2.17 (m, 3 H), 2.90 (br d, *J*=9.2 Hz, 2 H), 3.10 (d, *J*=9.2 Hz, 2 H), 5.60 (s, 2 H), 6.90 - 7.02 (m, 4 H), 7.16 - 7.23 (m, 1 H), 7.27 (br s, 1 H), 8.09 (dd, *J*=7.9, 1.2 Hz, 1 H), 8.21 (dd, *J*=4.6, 1.5 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.05> - <-142.73> (m, 2 F), <-141.66> - <-141.22> (m, 2 F), -118.49 (s, 1 F), -56.09 (t, *J*=22.2 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 175.6, 161.3, 159.4, 150.8, 148.9, 142.3, 129.8, 129.6, 129.5, 129.18, 129.15, 124.29, 124.26, 124.1, 123.9, 116.4, 115.5, 115.4, 61.3, 45.8, 44.1, 44.0, 20.8, 20.7, 16.2. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{29}H_{23}F_8N_5O$ 610.1848; Found 610.1841.

*2-((1R,5S,6r)-6-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**25**, 27.7 mg, white solid, Yield: 28%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.14 (s, 6 H), 1.98 - 2.03 (m, 2 H), 2.12 (t, *J*=8.6 Hz, 1 H), 2.93 - 3.04 (m, 4 H), 6.56 (br s, 1 H), 7.56 (dd, *J*=9.2, 1.2 Hz, 1 H), 7.62 (d, *J*=9.2 Hz, 1 H), 7.98 (s, 1 H), 8.51 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.76> - <-143.54> (m, 2 F), <-140.82> - <-140.50> (m, 2 F), -56.15 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.0, 153.8, 149.3, 131.6, 126.4, 124.6, 116.3, 61.4, 45.3, 21.1, 20.4, 20.0. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}F_7N_5O$ 502.1473; Found 502.1474.

*2-((1R,5S,6s)-6-(imidazo[1,2-b]pyridazin-6-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**26**, 18.3 mg, yellow solid, Yield: 18%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.16 (s, 6 H), 2.03 - 2.08 (m, 2 H), 2.17 (t, *J*=7.9 Hz, 1 H), 2.89 - 2.96 (m, 2 H), 3.12 (d, *J*=9.8 Hz, 2 H), 6.56 (br s, 1 H), 7.10 (d, *J*=9.2 Hz, 1 H), 7.37 (s, 1 H), 7.67 (s, 1 H), 7.83 (d, *J*=9.2 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.64> - <-143.45> (m, 2 F), <-141.03> - <-140.74> (m, 2 F), -56.15 (t, *J*=22.2 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 174.9, 152.3, 137.7, 133.4, 125.5, 118.8, 116.2, 61.5, 45.5, 22.1, 21.1, 20.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{18}F_7N_5O$ 502.1473; Found 502.1476.

*2-methyl-2-((1R,5S,6S)-6-(pyrazin-2-yl)-8-oxa-3-azabicyclo[3.2.1]octan-3-yl)-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**36**, 32.7 mg, white solid, Yield: 33%)*. $^1$H NMR (500 MHz, MeOD-$d_4$) $\delta$ ppm 0.88 (s, 3 H), 1.11 (s, 3 H), 2.28 (d, *J*=11.6 Hz, 1 H), 2.36 (td, *J*=11.9, 7.3 Hz, 1 H), 2.51 - 2.57 (m, 2 H), 2.85 (dd, *J*=11.3, 2.1 Hz, 1 H), 2.99 (dd, *J*=12.5, 5.8 Hz, 1 H), 3.93 (dt, *J*=12.2, 6.1 Hz, 1 H), 4.51 (br d, *J*=6.7 Hz, 1 H), 4.63 (br d, *J*=7.3 Hz, 1 H), 8.41 (dd, *J*=2.4, 1.2 Hz, 1 H), 8.47 (d, *J*=2.4 Hz, 1 H), 8.69 (d, *J*=1.2 Hz, 1 H). $^{19}$F NMR (471 MHz, MeOD-$d_4$) $\delta$ ppm <-145.16> - <-144.99> (m, 2 F), <-144.07> - <-143.79> (m, 2 F), -57.56 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, MeOD-$d_4$) $\delta$ ppm 178.3, 156.1, 148.3, 144.3, 144.1, 79.5, 76.6, 64.9,

54.2, 48.0, 46.8, 31.0, 25.9 ,14.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{21}H_{19}F_7N_4O_2$ 493.1469; Found 493.1466.

*2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-2-((1R,5S,10r)-10-(4-(trifluoromethyl)-thiazol-2-yl)-1,2,4,5-tetrahydro-3H-1,5-methanobenzo[d]azepin-3-yl)propenamide (**37**, 69.7 mg, white solid, Yield: 57%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.17 (s, 6 H), 2.68 (dd, *J*=11.6, 3.7 Hz, 2 H), 3.30 (d, *J*=11.6 Hz, 2 H), 3.68 (t, *J*=3.7 Hz, 2 H), 3.84 (t, *J*=4.3 Hz, 1 H), 7.17 (dd, *J*=5.5, 3.1 Hz, 2 H), 7.27 - 7.30 (m, 2 H), 7.49 (br s, 1 H), 7.79 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.17> - <-142.94> (m, 2 F), <-141.56> - <-141.29> (m, 2 F), -63.96 (s, 3 F), -56.06 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.9, 171.9, 144.8, 127.4, 122.0, 63.9, 51.2, 44.6, 44.5, 21.6. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{26}H_{19}F_{10}N_3OS$ 612.1162; Found 612.1152.

*2-((1R,5S,7s)-6-acetyl-7-(pyrimidin-5-yl)-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propan-1-one (**38**, 44.9 mg, white solid, Yield: 43%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.15 (s, 3 H), 1.19 (s, 3 H), 2.02 (s, 3 H), 3.00 (dd, *J*=11.6, 2.4 Hz, 1 H), 3.09 (dd, *J*=11.6, 2.4 Hz, 1 H), 3.20 (dd, *J*=11.6, 1.2 Hz, 1 H), 3.44 (dd, *J*=11.6, 1.2 Hz, 1 H), 4.06 (t, *J*=5.8 Hz, 1 H), 4.80 - 4.93 (m, 2 H), 6.59 (br s, 1 H), 8.57 (s, 2 H), 9.04 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.36> - <-143.17> (m, 2 F), <-140.78> - <-140.43> (m, 2 F), -56.12 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 173.4, 170.6, 157.5, 153.7, 131.1, 63.6, 63.2, 60.4, 44.6, 42.3, 37.4, 22.5, 20.5, 19.0. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}F_7N_5O_2$ 520.1578; Found 520.1575.

*2-((1R,5S,7s)-7-([1,2,4]triazolo[1,5-a]pyridin-6-yl)-6-acetyl-3,6-diazabicyclo[3.1.1]heptan-3-yl)-2-methyl-1-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propan-1-one (**39**, 30.6 mg, white solid, Yield: 27%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.17 (s, 3 H), 1.22 (s, 3 H), 2.05 (s, 3 H), 3.09 (dd, *J*=11.6, 2.4 Hz, 1 H), 3.15 (dd, *J*=11.6, 2.4 Hz, 1 H), 3.23 (dd, *J*=11.6, 1.2 Hz, 1 H), 3.46 (dd,

*J*=11.6, 1.2 Hz, 1 H), 4.12 (td, *J*=5.8, 1.2 Hz, 1 H), 4.77 - 4.94 (m, 2 H), 6.80 (s, 1 H), 7.36 (dd, *J*=9.2, 1.2 Hz, 1 H), 7.75 (d, *J*=9.2 Hz, 1 H), 8.11 (s, 1 H), 8.38 (s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.79> - <-143.60> (m, 2 F), <-140.54> - <-140.25> (m, 2 F), -56.13 (t, *J*=21.5 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 173.9, 170.7, 154.3, 149.2, 127.8, 124.2, 124.0, 117.4, 63.5, 63.2, 60.4, 44.6, 42.4, 38.9, 22.9, 20.5, 19.0. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{24}H_{21}F_7N_6O_2$ 559.1687; Found 559.1682.

*ethyl (1S,5R,6S)-3-(2-methyl-1-oxo-1-((2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amino)prop-an-2-yl)-6-(1-methyl-1H-indazol-3-yl)-3-azabicyclo[3.1.0]hexane-1-carboxylate (**40**, 37.3 mg, white solid, Yield: 32%)*. $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.13 (s, 6 H), 1.34 (t, *J*=7.3 Hz, 3 H), 2.55 (dd, *J*=8.6, 3.7 Hz, 1 H), 2.97 - 3.03 (m, 2 H), 3.19 (d, *J*=9.2 Hz, 1 H), 3.25 - 3.31 (m, 2 H), 3.97 (s, 3 H), 4.27 (q, *J*=7.3 Hz, 2 H), 6.38 (s, 1 H), 6.86 - 6.93 (m, 2 H), 7.05 - 7.09 (m, 1 H), 7.60 - 7.66 (m, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) δ ppm <-143.71> - <-143.50> (m, 2 F), <-142.20> - <-141.86> (m, 2 F), -56.10 (t, *J*=22.2 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 175.1, 172.3, 140.2, 139.9, 125.9, 122.8, 120.5, 150.3, 108.7, 61.4, 61.2, 45.7, 45.5, 35.4, 33.6, 30.6, 24.4, 21.5, 20.2, 14.4. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{27}H_{25}F_7N_4O_3$ 587.1888; Found 587.1876.

*2-((1R,5R,6S)-6-(5-cyanothiophen-2-yl)-1-(3,4-dichlorophenyl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**41**, 53.0 mg, white solid, Yield: 42%)*. $^1$H NMR (500 MHz, $CDCl_3$) *δ* ppm 1.24 (d, *J*=6.1 Hz, 6 H), 2.34 - 2.41 (m, 2 H), 3.10 (d, *J*=9.8 Hz, 1 H), 3.19 (br s, 2 H), 3.36 (d, *J*=9.8 Hz, 1 H), 6.67 (s, 1 H), 7.01 (d, *J*=3.7 Hz, 1 H), 7.12 (dd, *J*=8.2, 2.1 Hz, 1 H), 7.33 - 7.39 (m, 2 H), 7.45 (d, *J*=8.2 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) *δ* ppm <-143.03> - <-142.85> (m, 2 F), <-140.31> - <-140.04> (m, 2 F), -56.14 (t, *J*=21.5 Hz, 3 F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) *δ* ppm 174.4, 148.3, 140.3, 137.1, 133.1, 131.7, 131.0,

129.3, 126.6, 125.2, 113.3, 107.9, 61.8, 50.5, 45.9, 37.3, 29.6, 26.9, 21.1, 21.0. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{29}H_{22}Cl_2F_7N_5O$ 660.1163; Found 660.1155.

*2-((1R,5R,6S)-1-(3,4-dichlorophenyl)-6-(1-methyl-1H-pyrazol-3-yl)-3-azabicyclo[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**42**, 32.0 mg, white solid, Yield: 26%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.22 (d, *J*=1.2 Hz, 6 H), 2.17 - 2.26 (m, 2 H), 3.02 (d, *J*=8.6 Hz, 1 H), 3.09 (dd, *J*=9.2, 3.1 Hz, 1 H), 3.26 (d, *J*=9.2 Hz, 1 H), 3.42 (d, *J*=8.6 Hz, 1 H), 3.67 (s, 3 H), 6.17 (d, *J*=1.8 Hz, 1 H), 7.10 - 7.17 (m, 2 H), 7.36 - 7.42 (m, 2 H), 7.62 (br s, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-142.78> - <-142.62> (m, 2 F), <-141.06> - <-140.77> (m, 2 F), -56.04 (t, *J*=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.6, 148.4, 142.4, 132.7, 130.7, 130.6, 130.4, 129.3, 126.7, 105.1, 61.5, 50.4, 46.2, 38.7, 35.2, 28.4, 26.7, 21.5, 20.5. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{26}H_{21}Cl_2F_7N_4O$ 609.1054; Found 609.1055.

*2-((1R,5R,6S)-1-(3,4-dichlorophenyl)-6-(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)-3-azabicyclo-[3.1.0]hexan-3-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propenamide (**43**, 54.6 mg, light yellow solid, Yield: 41%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.17 (d, *J*=5.5 Hz, 6 H), 2.39 - 2.47 (m, 2 H), 3.09 (d, *J*=9.2 Hz, 1 H), 3.14 (dd, *J*=9.2, 4.3 Hz, 1 H), 3.30 (d, *J*=9.2 Hz, 1 H), 3.46 (d, *J*=9.2 Hz, 1 H), 4.01 (s, 3 H), 6.69 (s, 1 H), 6.92 (dd, *J*=7.9, 4.6 Hz, 1 H), 7.22 (dd, *J*=7.9, 1.8 Hz, 1 H), 7.44 - 7.48 (m, 2 H), 7.97 (dd, *J*=7.9, 1.2 Hz, 1 H), 8.13 (dd, *J*=4.6, 1.2 Hz, 1 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.57> - <-143.40> (m, 2 F), <-141.30> - <-140.99> (m, 2 F), -56.06 (t, *J*=22.2 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.1, 150.5, 148.7, 141.9, 140.2, 133.0, 131.1, 130.8, 129.5, 129.1, 126.5, 116.3, 115.0, 61.4, 50.5, 46.3, 35.2, 33.7, 28.5, 25.8, 21.2, 20.7. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{27}H_{18}Cl_2F_7N_3OS$ 636.0509; Found 636.0502.

**Experimental Procedure for Transannular C-H Diarylation of Spiro-cyclic Amine 44.** A 5 mL microwave vial was charged with amine **44** (0.2 mmol, 1 equiv), $Pd(OAc)_2$ (0.10 mmol, 50 mol %), CsOPiv (0.6 mmol, 3 equiv), **L3** (0.02 mmol, 10 mol %), iodobenzene **31** (6.0 mmol, 30 equiv) and t-amylOH (2.0 mL, 0.1 M). The vial was equipped with a magnetic stir bar, sealed and heated to an external temperature of 130 ºC in an aluminum heating block. After 18h, the reaction was cooled to room temperature. Hydrazine hydrate (0.25 mL) was added to the solution and the mixture was allowed to stir for 30 min at 60 ºC to sequester Pd from the product. The mixture was diluted with EtOAc (3.0 mL), filtered through Celite and rinsed with EtOAc (10 mL). The volatiles were removed under vacuum, and the residue was purified via reversed-phase preparative HPLC to afford the product *2-((5r,6R,10S)-6,10-diphenyl-2-azaspiro[4.5]decan-2-yl)-2-methyl-N-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)propanamide (**45**, 28.0 mg, white solid, Yield: 24%)*. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.07 (br s, 6 H), 1.48 (br d, J=8.55 Hz, 2 H), 1.58 - 1.71 (m, 1 H), 1.86 - 2.08 (m, 7 H), 2.78 (dd, J=12.21, 3.66 Hz, 2 H), 3.03 (br s, 2 H), 7.06 (br s, 2 H), 7.22 - 7.29 (m, 4 H), 7.32 (br d, J=7.32 Hz, 4 H). $^{19}$F NMR (471 MHz, $CDCl_3$) $\delta$ ppm <-143.82> - <-143.55> (m, 2 F), <-141.88> - <-141.58> (m, 2 F), -55.96 (t, J=21.5 Hz, 3 F). $^{13}$C{$^1$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 175.6, 143.4, 129.9, 127.8, 126.3, 61.4, 54.1, 47.8, 46.4, 45.8, 33.2, 30.7, 26.9. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{32}H_{31}F_7N_2O$ 593.2398; Found 593.2387.

**Representative Experimental Procedure for Directing Group Removal Using $SmI_2$.** Under nitrogen atmosphere, to a 20 mL microwave vial charged with compound **4** (0.1 mmol, 48.9 mg, 1.0 eq) was added methanol (50 eq, 202.8 uL), triethylamine (50 eq, 693.1 uL) and DMPU (11 eq, 133.0 uL). To the mixture was added $SmI_2$ (0.1M in THF, 10 eq, 10.0 mL) in one portion at room temperature and then the mixture was stirred at the same temperature for 1h until dim blue color disappeared. The reaction was quenched by addition of tosyl chloride (3 eq, 57.2 mg) and triethylamine (10 eq, 138.6 uL) and then stirred at room temperature for 2h. The mixture was filtered through Celite to remove the solid waste and the solid was rinsed with EtOAc (10 mL * 2).

The filtrate was concentrated under vacuum and the crude mixture was subjected to flash chromatography purification (EtOAc/EtOH=3/1 <v/v> in Heptane from 0% to 50%) to afford 16.6 mg desired product **46** as white solid.

*(1R,5S,6s)-6-(1-methyl-1H-pyrazol-3-yl)-3-tosyl-3-azabicyclo[3.1.0]hexane* (***46**, 16.6 mg, white solid, Yield: 52% over two steps*). $^{1}$H NMR (500 MHz, $CDCl_3$) $\delta$ ppm 1.87 - 1.93 (m, 2 H), 2.04 (t, *J*=7.94 Hz, 1 H), 2.43 (s, 3 H), 3.28 - 3.33 (m, 2 H), 3.58 (d, *J*=9.16 Hz, 2 H), 3.81 (s, 3 H), 6.09 (d, *J*=1.83 Hz, 1 H), 7.20 (d, *J*=1.83 Hz, 1 H), 7.25 (d, *J*=7.94 Hz, 2 H), 7.51 (d, *J*=7.94 Hz, 2 H). $^{13}$C{$^{1}$H} NMR (126 MHz, $CDCl_3$) $\delta$ ppm 145.5, 142.9, 134.6, 130.5, 129.3, 127.3, 105.2, 47.2, 38.8, 21.5, 21.3, 17.2. HRMS (ESI+) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_3O_2S$ 318.1271; Found 318.1273.

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## *Supporting Information*

Initial investigation, ligand screening, conditions optimizations, structures of S-1 & S-2, unsuccessful heteroaryl iodides, representative ligands, copies of $^{1}H$, $^{19}F$, $^{13}C\{^{1}H\}$ NMR spectra.

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