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Silver-Free Palladium-Catalyzed C(sp^3)−H Arylation of Saturated Bicyclic Amine Scaffolds

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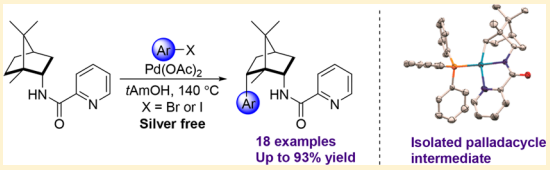
Supporting Information

ABSTRACT: Herein, we report a silver-free Pd(II)-catalyzed C(sp^3)−H arylation of saturated bicyclic and tricyclic amine scaffolds. The reaction provides good yields using a range of aryl iodides and aryl bromides including functionalized examples bearing aldehydes, ketones, esters, free phenols, and heterocycles. The methodology has been applied to medicinally relevant scaffolds. Two of the intermediate palladium complexes in the catalytic cycle have been prepared and characterized, and a mechanism is proposed. Removal of the directing group proceeded with good yield under relatively mild conditions.



INTRODUCTION

Palladium-catalyzed C−H arylation reactions[1,2] have attracted considerable attention as an efficient strategy for carbon−carbon bond formation that avoids the need to prepare prefunctionalized building blocks for a traditional cross-coupling reaction. To date, most attention has been focused on the development of methods for the direct arylation of sp^2 C−H bonds,[1] even though very efficient alternative cross-coupling methods[3] are often available to access the same classes of compounds. The products obtained from direct arylation of sp^3 C−H bonds, in contrast, are often not readily accessible via cross-coupling approaches so such transformations are potentially much more useful.[2] It has been proposed that molecules with an increased proportion of sp^3 centers are more likely to be successful drug candidates, prompting the need for synthetic methods to access functionalized sp^3 rich compounds.[4] We were specifically interested in exploring the direct arylation of amine-containing aliphatic compounds due to the importance of nitrogen functionality in medicinal chemistry (Figure 1).

There have been several recent reports of Pd-catalyzed direct arylation reactions of sp^3 C−H bonds in a range of systems including simple acylic amines,[5] cyclopropanes/cyclobutanes,[6] as well as systems containing five- and six-membered rings.[7] We envisaged that bicyclic amino compounds would be particularly suitable scaffolds for exploring novel Pd-catalyzed C−H arylation reactions as the rigid nature of these ring systems should lead to high regioselectivity in the C−H activation step as well as reducing the propensity of the subsequent σ-organopalladium intermediate to undergo β-hydride elimination. Scaffolds of this type are also important in a range of medicinally useful compounds, Figure 1. To date, there have been a few successful reports of Pd-catalyzed direct arylation of bicyclic scaffolds of this type,[8] but in all cases stoichiometric silver salts were employed. A key aim of our study was to avoid the use of silver salts, as this considerably reduces the efficiency of the process as well as presenting purification difficulties, particularly on scale-up.[9]

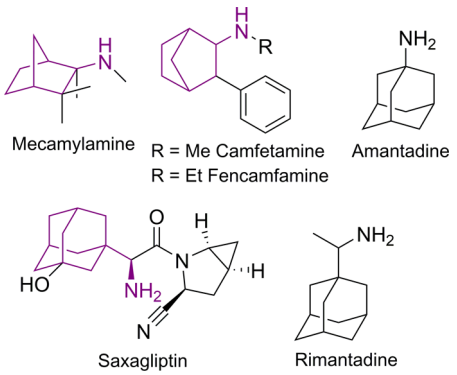


Figure 1. Examples of biologically active saturated bicyclic and tricyclic amines.

RESULTS AND DISCUSSION

We initially selected the 2-pyridyl amide **1**, derived from bornylamine, to examine the proposed Pd-catalyzed C−H arylation reaction (Scheme 1). Initial experiments suggested that the use of Pd(OAc)$_2$ in the presence of a base and CuBr$_2$ as an additive in *t*AmOH solvent[10] led to regioselective and stereoselective arylation at C-3. The choice of base had a

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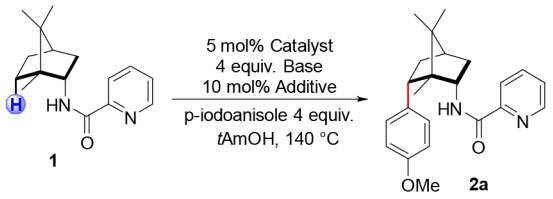
Scheme 1. Optimization of Arylation Conditions



Entry	Catalyst	Base	Additive	Yield[a]
1	$Pd(OAc)_2$	NaOAc	$CuBr_2$	7
2	$Pd(OAc)_2$	K_2CO_3	$CuBr_2$	81 (77[b])
3	$Pd(OAc)_2$	CsOPiv	$CuBr_2$	81
4	**$Pd(OAc)_2$**	**CsOAc**	**$CuBr_2$**	**91[b]**
5	none	CsOAc	$CuBr_2$	-
6	$Pd(OAc)_2$	CsOAc	None	36
7[c]	$Pd(OAc)_2$	CsOAc	$CuBr_2$	72
8[d]	$Pd(OAc)_2$	CsOAc	$CuBr_2$	58
9	$Pd_2(dba)_3$	CsOAc	$CuBr_2$	72
10	$Pd_2(dba)_3$	CsOAc	None	45
11[e]	$Pd(OAc)_2$	CsOAc	$CuBr_2$	88
12[f]	$Pd(OAc)_2$	CsOAc	$CuBr_2$	80

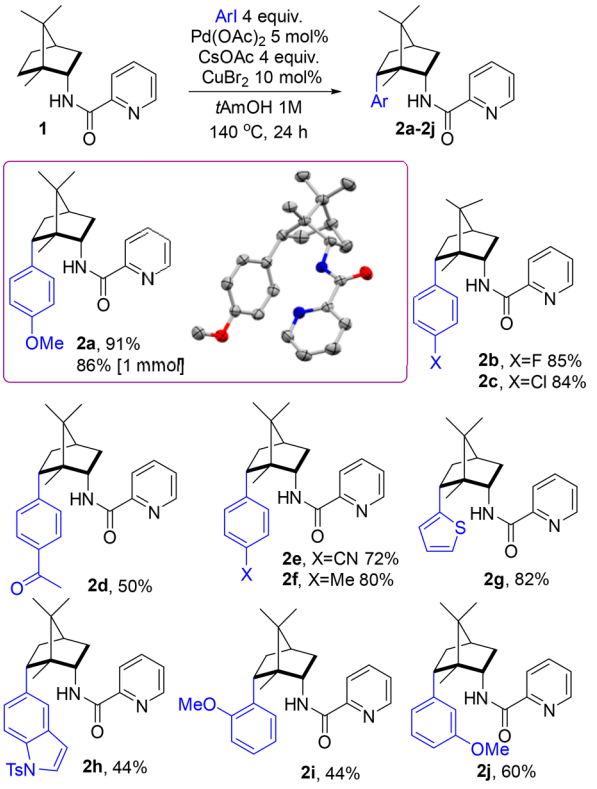
[a]NMR yield. [b]Isolated yield. [c]0.5M concentration. 3 equiv. ArI. [d]1 equiv. ArI. [e]Degassed *t*AmOH. [f]Air atmosphere.

significant effect on the reaction outcome, with cesium carboxylate salts providing the highest yields (entries 3–4). However, it should be noted that inexpensive K_2CO_3 was also very effective, giving the desired product in 77% isolated yield (entry 2). No arylation product was observed in the absence of the palladium catalyst (entry 5), and the yield was significantly reduced in the absence of the copper additive (entry 6). The yield of the product was reduced significantly when fewer equivalents of aryl iodide were employed (entries 7 and 8). A palladium(0) compound could also be employed as the catalyst but gave lower yields (entries 9 and 10). There was no significant change in the yield when reaction was carried out under inert atmosphere with degassed solvent (entry 11), and carrying out the reaction under an atmosphere of air only resulted in a small drop in the yield (entry 12). Our optimized conditions selected for further studies involved the use of 5 mol % of $Pd(OAc)_2$, 10 mol% of $CuBr_2$, and 4 equiv of CsOAc, which gave the arylated product **2a** in 91% isolated yield (entry 4). The structure of **2a** was confirmed by single-crystal X-ray crystallography (Scheme 2).

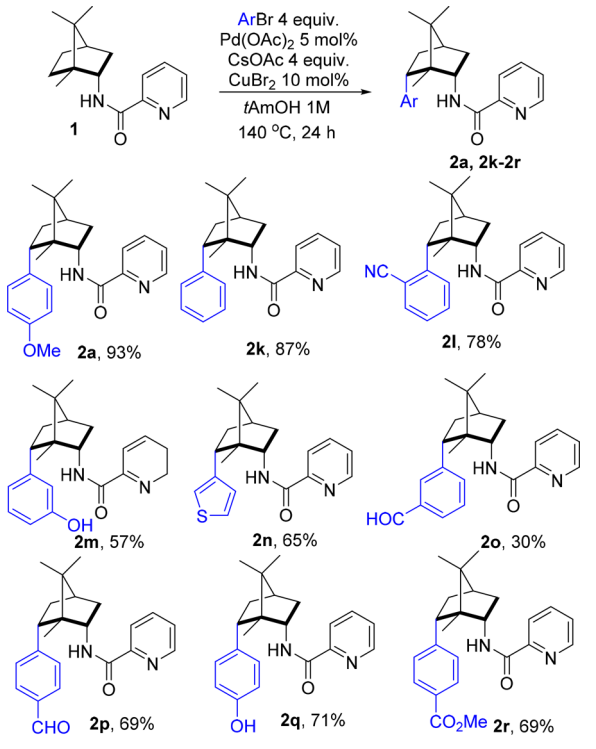
With an effective procedure in hand, we then went on to examine the scope of the reaction with regard to the aryl iodide component (Scheme 2). Pleasingly, the reaction worked well with both electron-rich (**2a**, **2f**, **2i**, **2j**) and electron-deficient (**2b**–**e**) benzene rings. The process could also be extended to direct arylation reactions with electron-rich heterocycles such as thiophene (**2g**) and indole (**2h**). Unsurprisingly, given the sterically crowded nature of the bicyclic ring, arylation with an *ortho*-substituted benzene proceeded in lower yield (**2i**). The arylation was carried out on a 1 mmol scale to give **2a** in comparable yield.

Pleasingly, the chemistry could also be extended to reactions of aryl bromides (Scheme 3) with comparable efficiency. This offers significant advantages in terms of reaction scope as a wider range of bromoarenes are available commercially, and they are usually less expensive than aryl iodides.[11] Thus, arylated product **2a** was obtained in similar yield from the

Scheme 2. Aryl Iodide Scope



Scheme 3. Aryl Bromide Scope



corresponding bromide, and the process was extended to the synthesis of a variety of other arylated products (**2k**–**r**) containing various functional groups including a nitrile (**2l**), free phenols (**2m**, **2q**), aldehydes (**2o**, **2p**), and an ester (**2r**). Notably, a small *ortho* substituent on the aryl bromide was well

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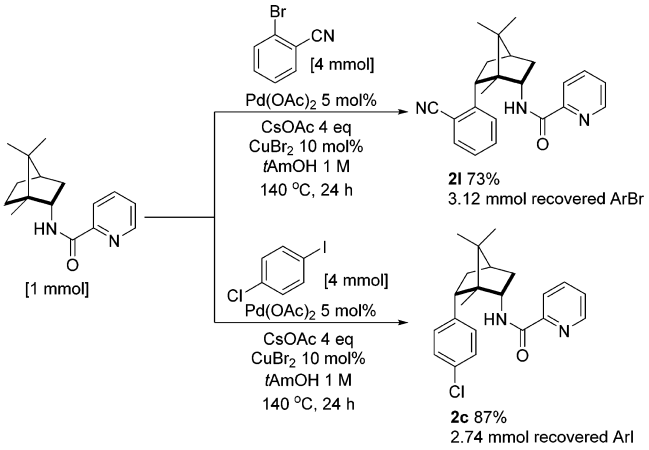
tolerated in the reaction (**2l**). Arylation reactions with *p*-chloroanisole and *p*-methoxyphenyl triflate were unsuccessful.

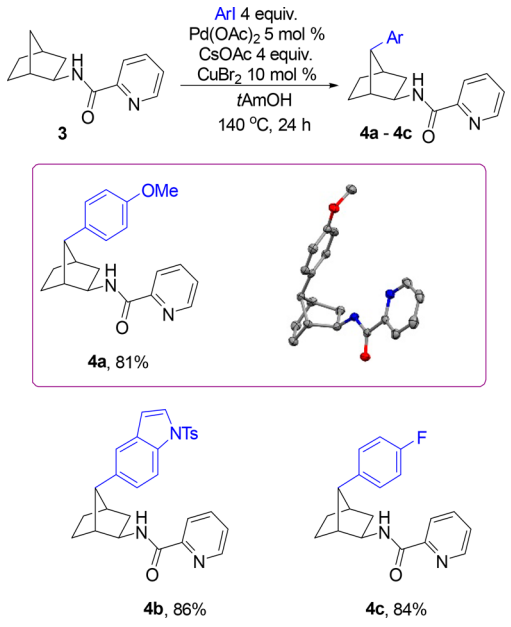
The synthesis of both **2l** and **2c** was also attempted on a 1 mmol scale, and the products were obtained in comparable yields (73% and 87% respectively). Most of the excess unreacted aryl halide could be recovered during purification in each case (Scheme 4).

Scheme 4. Scale-up Arylation and Recovery of the Excess Aryl Bromide



In a further extension of the chemistry, arylation of the 2-pyridyl amide **3** derived from *exo*-2-aminonorbornane led to regioselective and stereoselective arylation at C-7 to give compounds **4a–c** in good yield (Scheme 5). The structure of

Scheme 5. Pd-Catalyzed C–H Arylation of the *exo*-2-Aminonorborane Scaffold



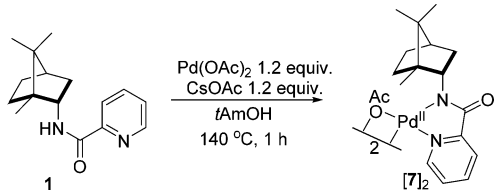
4a was unambiguously confirmed by single-crystal X-ray diffraction. Selective monoarylation of the medicinally relevant adamantane ring in compound **5** proceeded efficiently (Scheme 6).

To probe the mechanism of the C–H arylation reaction, **1** was treated with a stoichiometric quantity of $Pd(OAc)_2$ in the

Scheme 6. Application to Medicinally Relevant Scaffold

presence of CsOAc as a base, which led to the formation of palladium complex $[7]_2$ in which the palladium is coordinated to the deprotonated pyridyl amide (Scheme 7). The formation

Scheme 7. Isolation of a Dimeric Palladium Complex



of dimeric complex $[7]_2$ was accompanied by a dramatic upfield shift of the methine proton adjacent to the nitrogen atom (Figure 2, 4.4 ppm in 1 to 2.6 ppm in $[7]_2$).

By treatment of **1** with $Pd(OAc)_2$/CsOAc in CD_3CN, we were able to prepare the *σ*-organopalladium complex **8a**, showing that the C–H activation step can take place under relatively mild conditions. A simple exchange of the CD_3CN ligand with PPh_3 furnished palladacycle **8b** which was crystallized to provide a sample suitable for X-ray diffraction, enabling unambiguous assignment of the structure (Scheme 8). Complexes $[7]_2$, **8a**, and **8b** were fully characterized by ^1H and ^{13}C NMR spectroscopy.

Treatment of **8a** with 4-iodoanisole and CsOAc in *t*AmOH at 140 °C led to formation of the arylated product **2a**, most likely via the Pd^{IV} intermediate **9**, demonstrating that **8a** is a plausible reaction intermediate. Furthermore, both $[7]_2$ and **8a** could be used effectively as catalysts in the arylation of **1** with *p*-iodoanisole to give the arylated product **2a** in good yield (Scheme 9).

A plausible mechanistic cycle is shown in Scheme 10. Initial deprotonation of the pyridyl amide leads to the formation of complex **7-L**, which undergoes C–H insertion, most likely via a concerted metalation deprotonation (CMD) mechanism, to give *σ*-organopalladium complex **8**. Oxidative addition of the aryl halide generates palladium(IV) complex **9**[12] followed by C–C bond formation by reductive elimination to **10**. Ligand exchange follows to furnish the arylated product and regenerate the active palladium species **7-L**. The exact role of $CuBr_2$ in the reaction is unclear, as evidently all steps of the cycle can take place in its absence. However, it may play a role in re-oxidation of deactivated catalyst species to enable them to re-enter the cycle.

Finally, the pyridyl amides in **2a** and **4a** could be effectively removed from the arylated product in high yield by reductive cleavage with Zn/HCl[13] to give the free amines **11** and **12** (Scheme 11).

In summary, we have developed a novel silver-free Pd-catalyzed method for direct arylation of bicyclic primary amines which is applicable to a wide range of aryl iodides and bromides. The reaction can be carried out on a gram scale and excess unreacted aryl halide recovered. Important palladium

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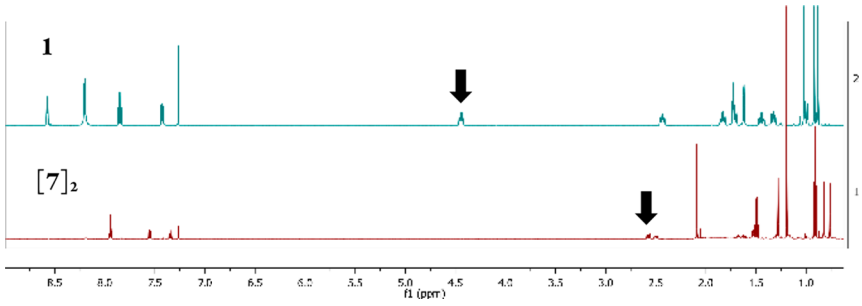
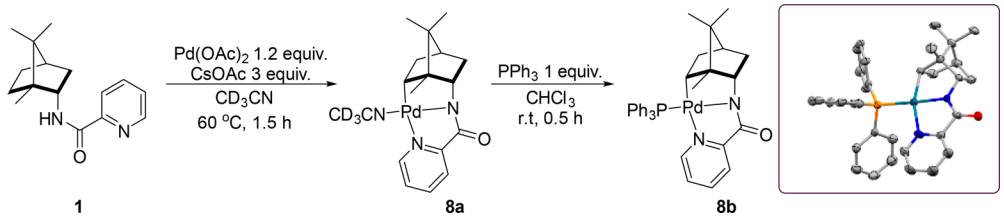
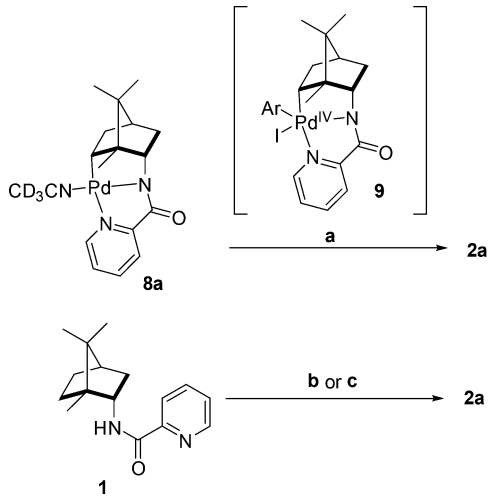


Figure 2. ^{1}H NMR spectra of **1** and $[7]_2$.

Scheme 8. Isolation of Palladacycle Intermediates

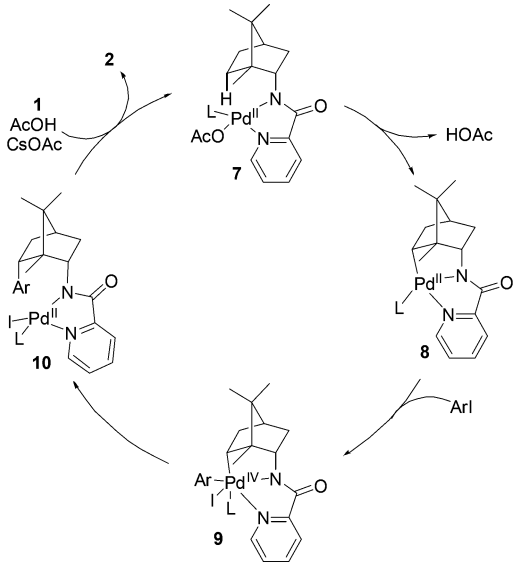


Scheme 9. Mechanistic Investigation

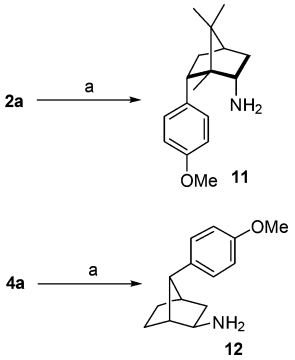


Conditions: (a) CsOAc (1 equiv), 4-iodoanisole (4 equiv), *t*AmOH (1 M), 140 °C, 24 h, 43%; (b) $[7]_2$ (5 mol %), CsOAc 4 (equiv), $CuBr_2$ (10 mol %), 4-iodoanisole (4 equiv), *t*AmOH (1 M), 140 °C, 24 h, 87%. (c) **8a** (5 mol %), CsOAc (4 equiv), $CuBr_2$ (10 mol %), 4-iodoanisole (4 equiv), *t*AmOH (1 M), 140 °C, 24 h, 80%.

Scheme 10. Proposed Mechanistic Cycle



Scheme 11. Removal of the Picolinamide Auxiliary



Conditions: (a) Zn, HCl, THF, H_2O, 81% (**11**), 74% (**12**).

intermediates have been isolated and characterized, and the structures of the arylated products were confirmed by single-crystal X-ray crystallography. Finally, we have demonstrated that the amide directing group can readily be removed under mild conditions to leave the arylated amine products.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents were purchased and used as supplied. $Pd(OAc)_2$ was purchased from Sigma-Aldrich and CsOAc from Fisher Scientific. All reactions were carried out in oven-dried glassware at atmospheric pressure with stirring and under an argon atmosphere unless otherwise indicated. Multiplicities are recorded as s = singlet, d = doublet, t = triplet, dd = doublet of doublets, br s = broad singlet, m = multiplet.

Synthesis of Starting Materials. *N-((1S,2S,4R)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl)picolinamide (**1**).*[8a] DIPEA (0.42 mL, 2.4 mmol, 1.2 equiv) was added dropwise to a solution of (*R*)-(+)-bornylamine (307 mg, 2 mmol, 1 equiv), picolinic acid (295

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mg, 2.4 mmol, 1.2 equiv), and HATU (913 mg, 2.4 mmol, 1.2 equiv) in DMF (10 mL, 0.1 M). The resulting solution was stirred at room temperature for 16 h. Saturated aqueous LiCl (20 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (0−40% EtOAc in petroleum ether) to give the desired amide as a white solid: 387 mg, 1.51 mmol, 75%; mp 78−80 °C; $[\alpha]_D^{18}$ +1.2 (c = 4, $CHCl_3$); ν_{max} (film/cm^{-1}) 3375 (NH), 2982 (CH), 1673 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.23−8.11 (m, 2H, H8), 7.84 (td, J = 7.7, 1.7 Hz, 1H), 7.42 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.48−4.39 (m, 1H), 2.48−2.37 (m, 1H), 1.83 (dtd, J = 12.2, 8.0, 4.0 Hz, 1H), 1.71 (ddd, J = 13.7, 8.2, 3.4 Hz, 2H, H4), 1.49−1.39 (m, 1H), 1.36−1.29 (m, 1H), 1.03−0.96 (m, 4H, H3), 0.92 (s, 3H), 0.88 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.3, 150.3, 148.1, 137.5, 126.1, 122.3, 53.9, 50.0, 48.4, 45.2, 37.7, 28.6, 28.2, 20.0, 18.9, 13.9; LRMS (CI) 259.2 ([M + H]$^+$).

exo-N-(Bicyclo[2.2.1]heptan-2-yl)picolinamide[8a] ***(3)***. DIPEA (0.25 mL, 1.44 mmol, 1.2 equiv) was added dropwise to a solution of *exo*-2-aminonorborane (133 mg, 1.2 mmol, 1 equiv), picolinic acid (178 mg, 1.44 mmol, 1.2 equiv), and HATU (546 mg, 1.44 mmol, 1.2 equiv) in DMF (6 mL, 0.1 M). The resulting solution was stirred at room temperature for 16 h. Saturated aqueous LiCl (15 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The crude residue was purified by flash column chromatography (0−40% EtOAc in petroleum ether) to give the desired amide as a white solid: 225 mg, 1.04 mmol, 87%; mp 61−63 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (ddd, J = 4.7, 1.7, 1.0 Hz), 8.18 (ddd, J = 7.8, 2.4, 1.4 Hz, 1H), 7.88 (s, 1H), 7.83 (tdd, J = 7.7, 3.0, 1.7 Hz, 1H), 7.40 (dddd, J = 7.5, 4.8, 2.5, 1.2 Hz), 3.96−3.88 (m, 1H), 2.33 (m, 2H), 1.88 (ddd, J = 13.1, 8.0, 2.4 Hz, 1H), 1.59−1.53 (m, 1H), 1.52−1.46 (m, 2H), 1.41−1.36 (m, 1H), 1.35−1.30 (m, 1H), 1.27−1.23 (m, 1H), 1.21−1.15 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.5, 150.2, 148.1 , 137.4, 126.1, 122.2, 52.8, 42.6, 40.4, 35.9, 35.9, 28.4, 26.7; LRMS (CI) 217.1 ([M + H]$^+$), 433.2 ([2M + H]$^+$).

N-(((3R,5R,7R)-Adamantan-1-yl)methyl)picolinamide ***(5)***. DIPEA (0.25 mL, 1.44 mmol, 1.2 equiv) was added dropwise to a solution of 1-adamantanemethylamine (198 mg, 1.2 mmol, 1 equiv), picolinic acid (178 mg, 1.44 mmol, 1.2 equiv), and HATU (546 mg, 1.44 mmol, 1.2 equiv) in DMF (6 mL, 0.1 M). The resulting solution was stirred at room temperature for 16 h. Saturated aqueous LiCl (15 mL) was added, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash column chromatography (0−40% EtOAc in petroleum ether) to give the desired amide as a white solid: 302 mg,1.12 mmol, 93%; mp 84−86 °C; ν_{max} (film/cm^{-1}) 3386 (NH), 2969 (CH), 1669 (CO); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, J = 4.7 Hz, 1H), 8.20 (m, 2H), 7.85 (td, J = 7.7, 1.7 Hz, 1H), 7.42 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 3.17 (d, J = 6.7 Hz, 2H), 1.99 (s, 3H), 1.68 (m, 7H), 1.58 (d, J = 2.2 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 150.2, 148.1, 137.5, 126.1, 122.4, 51.1, 40.4, 37.0, 34.2, 28.4; HRMS (ES) m/z [M + H]$^+$ calcd for $C_{17}H_{22}N_2O$ 271.1805, found 271.1804.

Arylation General Procedure. A tube was charged with a picolinamide (0.1 mmol, 1 equiv), $CuBr_2$ (2.2 mg, 0.01 mmol, 10 mol %), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 5 mol %), CsOAc (77 mg, 0.4 mmol), *t*AmOH (0.1 mL), and an aryl iodide or bromide (0.4 mmol, 4 equiv). The tube was sealed with a PTFE-lined cap and heated to 140 °C for 24 h. The reaction mixture was then cooled and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated in vacuo and the resulting crude residue purified by flash column chromatography.

N-((1S,2S,4R,6S)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide ***(2a)***.[8a] Purified using 0−40% EtOAc in petroleum ether: white solid; 33 mg, 0.091 mmol, 91% (aryl iodide), 34 mg, 0.093 mmol, 93% (aryl bromide); mp 113−115 °C; $[\alpha]_D^{18}$ +43.2 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3366 (NH), 2953 (CH), 2928 (CH), 1672 (CO); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21−8.18 (m, 1H), 7.95 (dt, J = 7.8, 1.0 Hz, 1H), 7.74 (d, J = 9.2 Hz, 1H), 7.68 (td, J = 7.7, 1.7 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.26 (ddd, J = 7.6, 4.7, 1.4 Hz, 1H), 6.90 (d, J = 8.8 Hz, 2H), 4.49 (dddd, J = 11.3, 9.3, 6.0, 1.9 Hz, 1H), 3.79 (s, 3H), 3.29 (dd, J = 11.8, 4.8 Hz, 1H), 2.58−2.50 (m, 1H), 2.27−2.19 (m, 1H), 2.00 (dt, J = 12.2, 6.1 Hz, 1H), 1.92 (t, J = 4.6 Hz, 1H), 1.28−1.24 (m, 1H), 1.08 (d, J = 5.6 Hz, 6H), 1.05 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.5, 158.2, 149.9, 147.5, 136.9, 133.8, 129.8, 125.7, 121.8, 114.5, 55.3, 54.5, 53.8, 51.0, 46.8, 43.7, 36.9, 32.9, 20.3, 20.0, 13.8; LRMS (CI) 365.2 ([M + H]$^+$), 729.0 ([2M + H]$^+$).

N-((1S,2S,4R,6S)-6-(4-Fluorophenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)picolinamide ***(2b)***. Purified using 0−50% EtOAc in petroleum ether: off-white solid; 30 mg, 0.085 mmol, 85%; mp 112−115 °C; $[\alpha]_D^{18}$ +24.6 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3364 (NH), 3064 (CH), 2954 (CH), 2924 (CH), 1667 (CO), 1508 (CC); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.26 (ddd, J = 4.7, 1.5, 0.9 Hz, 1H), 7.96 (dt, J = 7.8, 1.0 Hz, 1H), 7.70 (td, J = 7.7, 1.7 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 7.40 (dd, J = 8.4, 5.4 Hz, 2H), 7.29 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.04 (t, J = 8.8 Hz, 2H), 4.50 (dddd, J = 11.4, 9.4, 6.0, 1.9 Hz, 1H), 3.32 (dd, J = 11.8, 5.6 Hz, 1H), 2.59−2.52 (m, 1H), 2.31−2.24 (m, 1H), 2.01 (dd, J = 13.2, 5.8 Hz, 1H), 1.94 (t, J = 4.7 Hz, 1H), 1.25 (dt, J = 8.8, 4.3 Hz, 1H), 1.10 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.4, 161.8 (d, J_{CF} = 243.8 Hz), 149.8, 147.6, 137.7, 136.9, 130.2 (d, J_{CF}= 7.7 Hz), 125.7, 121.7, 115.8 (d, J_{CF} = 21.0 Hz), 54.4, 54.1, 51.0, 47.1, 43.7, 37.0, 33.0, 20.2, 20.0, 13.8; LRMS (ES) 353.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_2OF$ + H 353.2024, found 353.2025.

N-((1S,2S,4R,6S)-6-(4-Chlorophenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)picolinamide ***(2c)***. Purified using 0−40% EtOAc in petroleum ether: pale yellow solid; 31 mg, 0.084 mmol, 84%; mp 130−132 °C; $[\alpha]_D^{18}$ +18.2 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3373 (NH), 2978 (CH), 2950 (CH), 1672 (CO); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 7.96 (dt, J = 7.8, 1.0 Hz, 1H), 7.70 (td, J = 7.7, 1.7 Hz, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.37 (d, J = 8.5 Hz, 2H), 7.34−7.28 (m, 3H, H13), 4.50 (dddd, J = 11.3, 9.4, 6.0, 1.9 Hz, 1H), 3.30 (dd, J = 11.7, 4.9 Hz, 1H), 2.60−2.49 (m, 1H), 2.26 (ddd, J = 16.2, 7.6, 3.9 Hz, 1H), 2.01 (dd, J = 13.2, 5.8 Hz, 1H), 1.94 (t, J = 4.6 Hz, 1H), 1.27−1.21 (m, 1H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (s, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.5, 149.7, 147.9, 140.8, 137.0, 131.9, 129.2, 125.8, 121.7, 56.2, 54.4, 51.1, 47.2, 43.6, 37.0, 32.8, 20.3, 20.0, 13.8; LRMS (ES) 369.2 ([M + H]$^+$) 737.3 ([2M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{25}N_2OCl$ + H 369.1734, found 369.1731.

N-((1S,2S,4R,6S)-6-(4-Acetylphenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)picolinamide ***(2d)***. Purified using 0−60% EtOAc in petroleum ether: off-white solid; 19 mg, 0.050 mmol, 50%; mp 178−181 °C; $[\alpha]_D^{18}$ +21.4 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3367 (NH), 3064 (CH), 2949 (CH), 1667 (CO) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 7.94−7.90 (m, 3H), 7.67 (td, J = 7.7, 1.7 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.8 Hz, 1H), 7.22 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 4.56−4.50 (m, 1H), 3.39 (dd, J = 11.5, 5.7 Hz, 1H), 2.57 (ddd, J = 10.6, 6.9, 3.5 Hz, 1H), 2.54 (s, 3H), 2.32−2.26 (m, 1H), 2.12 (dd, J = 13.3, 5.8 Hz, 1H), 1.98 (t, J = 4.6 Hz, 1H), 1.30 (dd, J = 13.4, 5.9 Hz, 1H), 1.11 (m, 9H, 3 × CH_3); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 198.0, 164.3, 149.6, 148.7, 147.4, 137.0, 135.0, 129.2, 129.0, 125.8, 121.8, 55.4, 54.4, 51.2, 48.0, 43.7, 37.0, 32.6, 26.7, 20.3, 20.0, 14.0; LRMS (ES) 377.2 ([M + H]$^+$) 753.4 ([2M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{28}N_2O_2$ + H 377.2229, found 377.2230.

N-((1S,2S,4R,6S)-6-(4-Cyanophenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)picolinamide ***(2e)***. Purified using 0−50% Et_2O in petroleum ether: off-white solid; 26 mg, 0.072 mmol, 72%; mp 170−172 °C; $[\alpha]_D^{18}$ +55.5 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3374 (NH), 2947 (CH), 2924 (CH), 2222 (CN), 1670 (CO); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.31−8.28 (m, 1H), 7.95 (dd, J = 7.8, 1.0 Hz, 1H), 7.72 (tdd, J = 7.7, 1.7, 1.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.3 Hz, 2H), 7.36−7.29 (m, 2H, H10), 4.52 (dd, J = 15.8, 9.8 Hz, 1H), 3.37 (dd, J = 11.5, 5.6 Hz, 1H), 2.61−2.53 (m, 1H), 2.33−2.25 (m, 1H), 2.07 (dd, J = 13.3, 5.7 Hz, 1H), 1.98 (t, J = 4.6 Hz, 1H),

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1.26 (dd, J = 13.5, 6.0 Hz, 1H), 1.11 (s, 6H), 1.10 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.2, 149.5, 148.7, 147.5, 137.2, 132.7, 129.5, 126.2, 121.7, 119.3, 109.5, 55.6, 54.3, 51.3, 48.1, 43.6, 37.0, 32.5, 20.3, 20.0, 14.0; LRMS (ES) 360.2 ($[M + H]^+$) 719.4 ($[2M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{25}N_3O$ + H 360.2076, found 360.2071.

1,7,7-Trimethyl-6-(p-tolyl)bicyclo[2.2.1]heptan-2-yl)picolinamide (**2f**). Purified using 0−40% EtOAc in petroleum ether: white solid; 28 mg, 0.080 mmol, 80%; mp 150−153 °C; $[\alpha]_D^{18}$ +37.5 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3354 (NH), 3054 (CH), 2951 (CH),1668 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 7.95 (dt, J = 7.8, 1.0 Hz, 1H), 7.74 (d, J = 9.4 Hz, 1H), 7.69 (td, J = 7.7, 1.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.28−7.25 (m, 1H), 7.15 (d, J = 7.8 Hz, 2H), 4.51 (dddd, J = 11.4, 9.4, 6.0, 1.9 Hz, 1H), 3.30 (dd, J = 11.7, 5.5 Hz, 1H), 2.58−2.51 (m, 1H), 2.34 (s, 3H), 2.27−2.21 (m, 1H), 2.07−2.03 (m, 1H), 1.93 (t, J = 4.7 Hz, 1H), 1.29 (dd, J = 13.2, 5.9 Hz, 1H), 1.11−1.04 (m, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.5, 150.0, 147.4, 138.9, 136.9, 135.6, 129.8, 128.8, 125.5, 121.8, 54.5, 54.0, 51.0, 47.3, 43.7, 37.0, 32.7, 21.2, 20.3, 20.0, 13.8; LRMS (ES) 349.2 ($[M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{28}N_2O$ + H 349.2274, found 349.2275.

N-((1S,2S,4R,6R)-1,7,7-Trimethyl-6-(thiophene-2-yl)bicyclo[2.2.1]-heptan-2-yl)picolinamide (**2g**). Purified using 0−40% EtOAc in petroleum ether: orange oil; 28 mg, 0.082 mmol, 82%; $[\alpha]_D^{18}$ 91.4 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3355 (NH), 2951 (CH), 1667 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (dt, J = 7.8, 1.1 Hz, 1H), 7.97−7.91 (m, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.29−7.27 (m, 1H), 7.11 (dd, J = 5.2, 0.7 Hz, 1H), 7.06 (dt, J = 3.4, 1.2 Hz, 1H), 7.00 (dd, J = 5.2, 3.5 Hz, 1H), 4.59 (dddd, J = 11.6, 9.9, 5.7, 2.0 Hz, 1H), 3.50 (dd, J = 11.6, 6.0 Hz, 1H), 2.56−2.50 (m, 1H), 2.50−2.44 (m, 1H), 1.96 (dd, J = 13.0, 6.0 Hz, 1H), 1.92 (t, J = 4.7 Hz, 1H), 1.25 (dd, J = 13.3, 5.7 Hz, 1H), 1.19 (s, 3H), 1.10 (s, 3H), 1.05 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.4, 150.1, 147.5, 147.2, 136.9, 127.3, 125.6, 124.4, 124.0, 121.8, 54.1, 54.0, 50.8, 43.8, 43.7, 37.4, 36.2, 20.2, 20.1, 13.6; LRMS (ES) 341.2 ($[M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{24}N_2OS$ + H 341.1688, found 341.1693.

N-((1S,2S,4R,6S)-1,7,7-Trimethyl-6-(1-tosyl-1H-indol-5-yl)bicyclo-[2.2.1]heptan-2-yl)picolinamide (**2h**). Purified using 0−50% Et_2O in petroleum ether: yellow solid; 23 mg, 0.044 mmol, 44%; mp 182−185 °C; $[\alpha]_D^{18}$ + 13.2 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3066 (CH), 2833 (CH), 1669 (CO), 1371 (SO), 1172 (SO); ^1H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 2H), 7.69−7.62 (m, 2H), 7.59−7.55 (m, 2H, H10), 7.42 (s, 1H), 7.35 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.2 Hz, 2H), 7.05−7.00 (m, 1H), 6.64 (d, J = 3.6 Hz, 1H), 4.51 (ddd, J = 15.6, 7.8, 3.0 Hz, 1H), 3.40 (dd, J = 11.6, 5.4 Hz, 1H), 2.59−2.53 (m, 1H), 2.33 (s, 3H), 2.30−2.23 (m, 1H), 2.08 (dd, J = 13.2, 5.8 Hz, 1H), 1.95 (t, J = 4.6 Hz, 1H), 1.31 (dd, J = 13.3, 5.9 Hz, 1H), 1.10 (d, J = 4.4 Hz, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.5, 149.5, 147.4, 145.0, 137.3, 136.5, 135.5, 133.6, 131.9, 130.0, 127.0, 126.5, 126.3, 125.5, 121.4, 120.9, 113.9, 109.5, 54.4, 54.2, 51.1, 47.6, 43.7, 37.0, 33.1, 21.7, 20.3, 20.0, 13.9; LRMS (ES) 528.2 ($[M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{31}H_{33}N_3O_3S$ + H 528.2321, found 528.2322.

N-((1S,2S,4R,6R)-6-(2-Methoxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2i**). Purified using 0−60% EtOAc in petroleum ether: white solid; 16 mg, 0.044 mmol, 44%; mp 177−180 °C; $[\alpha]_D^{18}$ +101.0 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3353 (NH), 3054 (CH), 2951 (CH), 1669 (C═O), 998 (C−O); ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, J = 4.3 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.69 (td, J = 7.7, 1.4 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.28−7.25 (m, 1H), 7.22 (t, J = 7.3 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 4.52 (dd, J = 15.9, 9.8 Hz, 1H), 3.79 (d, J = 12.0 Hz, 4H), 2.60−2.51 (m, 1H), 2.24−2.17 (m, 1H), 2.04 (dd, J = 13.0, 5.8 Hz, 1H), 1.92 (t, J = 4.5 Hz, 1H), 1.42 (dd, J = 13.2, 6.2 Hz, 1H), 1.13 (s, 3H), 1.10 (s, 3H), 0.94 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.6, 158.3, 150.2, 147.4, 136.8, 130.6, 130.3, 126.9, 125.5, 121.8, 121.4, 111.0, 55.0, 54.9, 51.2, 44.1, 41.1, 36.4, 33.5, 20.5, 20.0, 13.9; LRMS (ES) 365.2 ($[M + H]^+$) 729.4 ($[2M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{28}N_2O_2$ + H 365.2229, found 365.2231.

N-((1S,2S,4R,6S)-6-(3-Methoxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2j**). Purified using 0−40% EtOAc in petroleum ether: colorless oil; 22 mg, 0.060 mmol, 60%; $[\alpha]_D^{18}$ +50.9 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3358 (NH), 2951 (CH), 2836 (CH), 1665 (CO), 1509 (CC); ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, J = 4.7 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 10.3 Hz, 1H), 7.70 (td, J = 7.7, 1.7 Hz, 1H), 7.29−7.27 (m, 1H), 7.23 (t, J = 7.9 Hz, 1H), 7.05−6.98 (m, 2H), 6.76 (dd, J = 8.2, 2.3 Hz, 1H), 4.54 (td, J = 9.6, 5.1 Hz, 1H), 3.78 (s, 3H), 3.33 (dd, J = 11.5, 5.4 Hz, 1H), 2.59−2.53 (m, 1H), 2.29−2.23 (m, 1H), 2.04 (dd, J = 13.2, 5.9 Hz, 1H), 1.94 (t, J = 4.6 Hz, 1H), 1.31−1.27 (m, 1H), 1.11 (d, J = 5.0 Hz, 3H), 1.09 (s, 3H), 1.08 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.5, 160.3, 154.1, 150.0, 147.3, 143.8, 136.9, 130.3, 129.9, 125.6, 121.8, 111.6, 55.2, 54.4, 54.4, 51.1, 47.8, 43.7, 37.1, 32.9, 20.3, 20.0, 13.9; LRMS (ES) 365.2 ($[M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{28}N_2O_2$ + H 365.2229, found 365.2230.

N-((1S,2S,4R,6S)-1,7,7-Trimethyl-6-phenylbicyclo[2.2.1]heptan-2-yl)picolinamide (**2k**). Purified using 0−40% EtOAc in petroleum ether: colorless oil; 29 mg, 0.087 mmol, 87%; $[\alpha]_D^{18}$ +86.8 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3012 (CH), 2951 (CH),1667 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 4.7 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.75−7.65 (m, 2H), 7.45 (dd, J = 9.2, 4.4 Hz, 2H), 7.34 (t, J = 7.7 Hz, 2H), 7.26−7.24 (m, 1H), 7.22 (t, J = 7.4 Hz, 1H), 4.53 (dddd, J = 11.3, 9.5, 6.0, 1.8 Hz, 1H), 3.35 (dd, J = 11.6, 5.5 Hz, 1H), 2.60−2.52 (m, 1H), 2.26 (tt, J = 12.7, 3.9 Hz, 1H), 2.08 (dd, J = 13.2, 5.8 Hz, 1H), 1.95 (t, J = 4.6 Hz, 1H), 1.30 (dd, J = 13.3, 5.9 Hz, 1H), 1.09 (dd, J = 17.6, 6.5 Hz, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.5, 149.9, 148.1, 147.4, 142.1, 137.6, 136.9, 131.2, 129.1, 125.9, 125.5, 121.7, 54.3, 51.1, 47.7, 43.7, 37.0, 32.6, 28.6, 20.3, 20.0, 13.8; LRMS (ES) 336.2 ($[M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{26}N_2O$ + H 335.2123, found 335.2111.

N-((1S,2S,4R,6S)-6-(2-Cyanophenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)picolinamide (**2l**). Purified using 0−40% EtOAc in petroleum ether: orange solid; 28 mg, 0.078 mmol, 78%; mp 185−186 °C; $[\alpha]_D^{18}$ +151.8 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3378 (NH), 3060 (CH), 2954 (CH), 2222 (CN), 1669 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.20−8.17 (m, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 7.7, 1.7 Hz, 2H), 7.65−7.61 (m, 2H), 7.33 (dd, J = 11.1, 4.1 Hz, 1H), 7.30 (ddd, J = 7.5, 4.8, 1.1 Hz, 1H), 4.56−4.50 (m, 1H), 3.82 (dd, J = 11.8, 4.7 Hz, 1H), 2.69−2.62 (m, 1H), 2.45−2.39 (m, 1H), 2.01 (t, J = 4.6 Hz, 1H), 1.95 (dd, J = 13.3, 5.6 Hz, 1H), 1.43 (dd, J = 13.5, 6.3 Hz, 1H), 1.18 (s, 3H), 1.13 (s, 6H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.4, 149.7, 147.3, 146.6, 137.2, 134.1, 133.5, 130.1, 126.3, 125.9, 121.9, 119.2, 114.9, 57.1, 55.0, 51.7, 46.6, 43.8, 36.6, 35.1, 20.4, 20.0, 14.0; LRMS (ES) 360.2 ($[M + H]^+$) 719.4 ($[2M + H]^+$); HRMS (ES-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{25}N_3O$ + H 360.2076, found 360.2079.

N-((1S,2S,4R,6S)-6-(3-Hydroxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2m**). Purified using 0−50% EtOAc in petroleum ether: brown solid; 20 mg, 0.057 mmol, 57%; mp 137−140 °C; $[\alpha]_D^{18}$ +40.6 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3326 (NH), 2951 (CH), 1651 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.32−8.28 (m, 1H), 8.03 (d, J = 9.7 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.64 (td, J = 7.7, 1.6 Hz, 1H), 7.23 (dd, J = 6.8, 4.8 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.92 (d, J = 2.1 Hz, 2H), 6.78−6.74 (m, 1H), 4.53−4.45 (m, 1H), 3.22 (dd, J = 11.5, 5.3 Hz, 1H), 2.48−2.40 (m, 1H), 2.21−2.14 (m, 1H), 1.92 (dd, J = 13.2, 5.7 Hz, 1H), 1.81 (t, J = 4.6 Hz, 1H), 1.13 (dd, J = 13.3, 5.9 Hz, 1H), 1.03 (s, 3H, 1.02 (s, 3H), 0.92 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.8, 157.0, 149.8, 147.6, 143.9, 137.0, 130.2, 125.8, 121.8, 121.3, 115.7, 113.2, 54.4, 54.3, 51.0, 47.6, 43.6, 36.8, 32.8, 20.2, 19.9, 13.7; LRMS (ES) 351.2 ($[M + H]^+$) 725.5 ($[2M + H]^+$); HRMS (ES) m/z $[M + H]^+$ $C_{22}H_{26}N_2O_2$ + H 351.2076, found 351.2072.

N-((1S,2S,4R,6S)-1,7,7-Trimethyl-6-(thiophene-3-yl)bicycle[2.2.1]-hepten-2-yl)picolinamide (**2n**). Purified using 0−50% EtOAc in petroleum ether: orange oil; 22 mg, 0.065 mmol, 65%; $[\alpha]_D^{18}$ +11.0 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3377 (NH), 3062 (CH), 2953 (CH), 1668 (CO); ^1H NMR (400 MHz, $CDCl_3$) δ 8.35−8.31 (m, 1H, 8.01−

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7.97 (m, 1H), 7.85 (s, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.28 (ddd, J = 7.6, 4.8, 1.2 Hz, 1H), 7.25−7.22 (m, 2H, H12), 7.05 (dd, J = 4.9, 1.5 Hz, 1H), 4.56 (dd, J = 16.3, 10.6 Hz, 1H), 3.33 (dd, J = 11.6, 5.9 Hz, 1H), 2.53 (s, 1H), 2.36 (dd, J = 16.1, 8.4 Hz, 1H), 1.95−1.89 (m, 2H, H5), 1.21 (dd, J = 13.3, 5.8 Hz, 1H), 1.14 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.4, 150.0, 147.6, 144.1, 137.0, 128.5, 126.8, 125.6, 121.8, 120.5, 54.2, 53.6, 50.7, 43.7, 43.7, 37.6, 34.8, 20.2, 20.0, 14.01; LRMS (ES) 341.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{24}N_2OS$ + H 341.1682, found 341.1693.

*N-((1S,2S,4R,6S)-6-(3-Formylphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2o**).* Purified using 0−40% EtOAc in petroleum ether: white solid; 11 g, 0.030 mmol, 30%; mp 108−110 °C; $[\alpha]_D^{18}$ +7.8 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 2952 (CH), 1696 (CO), 1670 (CO), 1518 (CC); ^1H NMR (600 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.06 (d, J = 4.2 Hz, 1H), 8.01 (s, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.67 (td, J = 7.7, 1.7, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.25 (ddd, J = 7.5, 4.8, 1.0 Hz, 1H), 4.56−4.50 (m, 1H), 3.41 (dd, J = 11.5, 5.7 Hz, 1H), 2.62−2.55 (m, 1H), 2.33 (ddd, J = 16.2, 7.7, 3.8 Hz, 1H), 2.14 (dd, J = 13.2, 5.9 Hz, 1H), 2.00 (t, J = 4.6 Hz, 1H), 1.34 (dd, J = 13.4, 5.9 Hz, 1H), 1.12 (m, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 192.8, 164.2, 149.5, 147.3, 143.7, 137.2, 137.0, 135.8, 130.1, 129.5, 126.8, 125.8, 121.8, 54.8, 54.5, 51.3, 47.6, 43.6, 37.2, 32.7, 20.3, 20.0, 14.0; LRMS (ES) 363.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{26}N_2O_2$ + H 363.2073, found 363.2076.

*N-((1S,2S,4R,6S)-6-(4-Formylphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2p**).* Purified using 0−50% EtOAc in petroleum ether: off-white solid; 25 mg, 0.069 mmol, 69%; mp 148−150 °C; $[\alpha]_D^{18}$ +29.4 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3016 (CH), 1662 (CO), 1520 (CC); 3016 (CH), 1662 (CO), 1520 (CC); ^1H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H), 8.04 (d, J = 4.7 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.66 (td, J = 7.7, 1.6 Hz, 1H), 7.62 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 9.0 Hz, 1H), 7.24−7.21 (m, 1H), 4.59−4.48 (m, 1H), 3.40 (dd, J = 11.5, 5.6 Hz, 1H), 2.61−2.52 (m, 1H), 2.36−2.24 (m, 1H), 2.13 (dd, J = 13.3, 5.8 Hz, 1H), 1.99 (t, J = 4.6 Hz, 1H), 1.30 (dd, J = 13.4, 6.0 Hz, 1H), 1.13−1.10 (m, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 192.1, 164.3, 150.5, 149.5, 147.4, 137.0, 134.6, 130.5, 129.4, 125.9, 121.8, 55.7, 54.3, 51.3, 48.3, 43.6, 37.0, 32.6, 20.3, 20.0, 14.0; LRMS (ES) 363.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{26}N_2O_2$ + H 363.2073, found 363.2074.

*N-((1S,2S,4R,6S)-6-(4-Hydroxyphenyl)-1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)picolinamide (**2q**).* Purified using 0−50% EtOAc in petroleum ether: yellow solid; 25 mg, 0.071 mmol, 71%; mp 198−200 °C; $[\alpha]_D^{18}$ +20.2 (c = 1, $CHCl_3$); ν_{max} (film/cm^{-1}) 3327 (OH), 2950 (CH), 2809 (CH), 1651 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.35 (d, J = 4.7 Hz, 1H), 7.96−7.88 (m, 2H), 7.65 (td, J = 7.7, 1.6 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 7.24−7.19 (m, 1H), 6.88 (d, J = 8.1 Hz, 2H), 6.16 (s, 1H), 4.54−4.46 (m, 1H), 3.28 (dd, J = 11.7, 5.4 Hz, 1H), 2.58−2.50 (m, 1H), 2.24 (ddd, J = 12.9, 7.3, 3.7 Hz, 1H), 1.99 (dd, J = 13.1, 5.7 Hz, 1H), 1.91 (t, J = 4.6 Hz, 1H), 1.28−1.23 (m, 1H), 1.07 (d, J = 1.6 Hz, 6H), 1.03 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.9, 154.9, 149.6, 147.9, 136.9, 133.3, 130.0, 125.7, 121.7, 116.1, 54.7, 53.7, 50.9, 46.8, 43.7, 36.9, 32.9, 20.3, 20.0, 13.8; LRMS (ES) 351.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{22}H_{26}N_2O_2$ + H 351.2072, found 351.2055.

*Methyl 4-((1S,2S,4R,6S)-1,7,7-Trimethyl-6-(picolinamido)bicyclo-[2.2.1]heptan-2-yl)benzoate (**2r**).* Purified using 0−50% EtOAc in petroleum ether: white solid; 27 mg, 0.069 mmol, 69%; mp 114−115 °C; $[\alpha]_D^{18}$ +43.8 (c = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 3016 (CH), 2953 (CH), 1714 (CO), 1660 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.12−8.10 (m, 1H), 8.00 (d, J = 8.3 Hz, 2H), 7.91 (d, J = 7.8 Hz, 1H), 7.66 (td, J = 7.7, 1.7 Hz, 1H), 7.52 (d, J = 8.0 Hz, 3H), 7.22 (ddd, J = 7.5, 4.8, 1.0 Hz, 1H), 4.56−4.49 (m, 1H), 3.92 (s, 3H), 3.38 (dd, J = 11.5, 5.5 Hz, 1H), 2.58−2.52 (m, 1H), 2.28 (ddd, J = 16.1, 7.6, 3.8 Hz, 1H), 2.11 (dd, J = 13.2, 5.8 Hz, 1H), 1.97 (t, J = 4.6 Hz, 1H), 1.29 (dd, J = 13.4, 6.0 Hz, 1H), 1.12−1.09 (m); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.3, 164.4, 149.6, 148.3, 147.5, 136.9, 130.4, 128.8, 127.8, 125.7, 121.7, 55.3, 54.3, 52.1, 51.2, 48.0, 43.6, 37.0, 32.6, 20.3, 20.0, 13.9; HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{24}H_{28}N_2O_3$ + H 393.2178, found 393.2172.

*N-7-(4-Methoxyphenyl)bicyclo[2.2.1]heptan-2-yl)picolinamide (**4a**).*[8a] Purified using 0−50% EtOAc in petroleum ether: white solid; 26 mg, 0.081 mmol, 81%; mp 99−101 °C; ν_{max} (film/cm^{-1}) 3377 (NH), 2947 (CH), 2862 (CH), 1660 (C═O), 1507 (CC), 1028 (C−O); ^1H NMR (600 MHz, $CDCl_3$) δ 8.23 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 8.04 (dt, J = 7.8, 1.0 Hz, 1H), 7.73 (td, J = 7.7, 1.7 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.28 (ddd, J = 7.6, 4.7, 1.2 Hz), 7.26−7.23 (m, 2H), 6.86−6.83 (m, 2H), 4.12 (td, J = 9.0, 3.7 Hz, 1H), 3.81 (s, 3H), 3.02 (s, 1H), 2.78 (t, J = 4.1 Hz, 1H), 2.73 (d, J = 4.4 Hz, 1H), 1.97 (dd, J = 13.5, 8.6 Hz, 1H), 1.83 (tt, J = 12.0, 4.4 Hz, 1H), 1.75 (ddd, J = 14.5, 9.2, 5.6 Hz, 2H), 1.51−1.46 (m, 1H), 1.36 (ddd, J = 11.9, 9.5, 4.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 162.8, 158.0, 150.1, 147.6, 137.0, 132.3, 129.3, 125.7, 121.8, 114.2, 55.4, 52.9, 52.3, 47.2, 38.2, 38.1, 28.9, 28.2; LRMS (ES) 323.2 ([M + H]$^+$) 645.4 ([2M + H]$^+$); HRMS (ES) m/z [M + H]$^+$ calcd for $C_{20}H_{22}N_2O_2$ + H 323.1760, found 323.1762.

*N-7-(1-Tosyl-1H-indol-5-yl)bicyclo[2.2.1]heptan-2-yl)-picolinamide (**4b**).* Purified using 0−50% EtOAc in petroleum ether: white solid; 42 mg, 0.086 mmol, 86%; mp 149−151 °C; ν_{max} (film/cm^{-1}) 3330 (NH), 2960 (CH), 2919 (CH), 1663 (CO), 1517 (CC), 1365 (SO); ^1H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.2, 1.7 Hz, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.68−7.64 (m, 2H), 7.54 (t, J = 4.3 Hz, 1H), 7.50 (s, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 5.8 Hz, 1H), 7.21 (d, J = 8.3 Hz, 2H), 7.16−7.12 (m, 1H), 6.54 (d, J = 3.6 Hz, 1H), 4.12 (td, J = 9.0, 3.6 Hz, 1H), 3.12 (s, 1H), 2.84 (d, J = 3.7 Hz, 1H), 2.80 (d, J = 4.3 Hz, 1H), 2.33 (s, 3H), 1.99 (dd, J = 13.3, 8.5 Hz, 1H), 1.85 (tt, J = 12.1, 4.3 Hz, 1H), 1.79−1.71 (m, 2H, H3), 1.54−1.48 (m, 1H), 1.38 (ddd, J = 13.6, 9.5, 4.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 162.8, 149.6, 147.7, 145.0, 136.8, 135.5, 135.4, 133.5, 131.4, 130.0, 127.0, 126.4, 125.6, 125.2, 121.5, 121.0, 113.8, 109.2, 53.0, 52.8, 47.3, 38.3, 38.2, 28.9, 28.1, 21.7; LRMS (ES) 486.2 ([M + H]$^+$); HRMS (ES-TOF) m/z [M + H]$^+$ calcd for $C_{28}H_{27}N_3O_3S$ + H 486.1852, found 486.1830.

*N-7-(4-fluorophenyl)bicyclo[2.2.1]heptan-2-yl)picolinamide (**4c**).* Purified using 0−50% EtOAc in petroleum ether: white solid; 26 mg, 0.084 mmol, 84%; mp 125−128 °C; ν_{max} (film/cm^{-1}) 3362 (NH), 2951 (CH), 2871 (CH), 1667 (CO), 1506 (CC), 1219 (CF); ^1H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, J = 4.6 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.33−7.23 (m, 4H), 6.98 (t, J = 8.7 Hz, 2H), 4.11 (td, J = 8.9, 3.8 Hz, 1H), 3.03 (s, 1H), 2.79 (s, 1H), 2.75 (d, J = 4.2 Hz, 1H), 1.99 (dd, J = 13.3, 8.6 Hz, 1H), 1.84 (tt, J = 12.0, 4.4 Hz, 1H), 1.79−1.69 (m, 2H), 1.54−1.47 (m, 1H), 1.40−1.34 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 162.8, 161.5 (d, J_{CF} = 244.0 Hz), 160.7, 149.8, 147.8, 137.1, 136.0, 136.0, 129.9 (d, J_{CF} = 7.8 Hz), 125.9, 121.8, 115.5 (d, J_{CF} = 21.1), 52.8, 52.4, 47.4, 38.1, 38.1, 28.9, 28.1; LRMS (ES) 311.2 ([M + H]$^+$); HRMS (ES) m/z [M + H]$^+$ calcd for $C_{19}H_{19}N_2OF$ + H 311.1560, found 311.1557.

*N-2-(4-Methoxyphenyl)adamantan-1-yl)methyl)picolinamide (**6**).* Purified using 0−40% EtOAc in petroleum ether: colorless oil; 28 mg, 0.074 mmol, 74%; ν_{max} (film/cm^{-1}) 3389 (NH), 2902 (CH), 2850 (CH), 1675 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 8.56−8.52 (m, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 27.7 Hz, 1H), 7.82 (td, J = 7.7, 1.7 Hz, 1H), 7.47−7.43 (m, 2H), 7.40 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 6.90−6.85 (m, 2H), 3.81 (s, 3H), 3.26 (dd, J = 13.7, 7.6 Hz, 1H), 2.95 (dd, J = 13.7, 5.8 Hz, 1H), 2.89 (s, 1H), 2.25 (t, J = 12.2 Hz, 1H), 2.21 (d, J = 13.3 Hz, 1H), 2.14 (d, J = 14.0 Hz, 1H), 2.08−2.05 (m, 1H), 1.92 (s, 1H), 1.91−1.83 (m, 2H), 1.81−1.75 (m, 2H), 1.72 (dd, J = 12.5, 1.7 Hz, 2H), 1.59−1.54 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.5, 158.1, 150.2, 148.1, 137.4, 136.4, 130.6, 126.0, 122.3, 113.9, 55.3, 53.9, 48.5, 43.8, 40.1, 38.1, 37.7, 35.5, 35.4, 31.1, 28.9, 28.0; HRMS (ES) m/z [M + H]$^+$ calcd for $C_{24}H_{28}N_2O_2$ + H 377.2224, found 377.2222.

Scale-up Arylation Procedure and Recovery of Aryl Bromide. A tube was charged with a picolinamide (258 mg, 1.0 mmol, 1 equiv), $CuBr_2$ (22 mg, 0.1 mmol, 10 mol %), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol %), CsOAc (767 mg, 4.0 mmol), t-AmOH (1.0 mL), and 2-bromobenzonitrile (728 mg, 4.0 mmol, 4 equiv). The tube was sealed with a PTFE-lined cap and heated to 140 °C for 24 h. The

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reaction mixture was then cooled and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated in vacuo and the resulting crude residue purified by flash column chromatography (0−50% EtOAc in petroleum ether) to give the arylated product (262 mg, 0.73 mmol, 73%) and 3.12 mmol (568 mg) of recovered aryl bromide.

Scale-up Arylation Procedure and Recovery of Aryl Iodide. A tube was charged with picolinamide (258 mg, 1.0 mmol, 1 equiv), $CuBr_2$ (22 mg, 0.1 mmol, 10 mol %), $Pd(OAc)_2$ (11 mg, 0.05 mmol, 5 mol %), CsOAc (767 mg, 4.0 mmol), *t*-AmOH (1.0 mL), and 4-chloroiodobenzene (954 mg, 4.0 mmol, 4 equiv). The tube was sealed with a PTFE-lined cap and heated to 140 °C for 24 h. The reaction mixture was then cooled and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated in vacuo, and the resulting crude residue purified by flash column chromatography (0−40% EtOAc in petroleum ether), to give the arylated product (321 mg, 0.871 mmol, 73%) and 2.74 mmol (566 mg) of recovered aryl iodide.

Mechanistic Investigation. *Palladium Complex (**7**).* A sealed tube was charged with amide **1** (26 mg, 0.1 mmol, 1 equiv), $Pd(OAc)_2$ (27 mg, 0.12 mmol, 1.2 equiv), and CsOAc (23 mg, 0.12 mmol, 1.2 equiv) in *t*-AmOH (0.05 mL). The resulting mixture was heated at 140 °C for 1 h, cooled, and filtered through Celite washing with $CDCl_3$ and concentrated to give the palladium complex as an orange solid in quantitative yield: 42 mg; $[\alpha]_D^{18}$ +35.4 (*c* = 1, $CHCl_3$); ν_{max} (film/cm^{-1}); 2949 (CH), 2924 (CH), 1673 (CO), 1516 (CC); ^1H NMR (600 MHz, $CDCl_3$) δ 7.97−7.92 (m, 2H), 7.57−7.53 (m, 1H), 7.35 (ddd, *J* = 7.2, 5.8, 1.6 Hz, 1H), 2.57 (dd, *J* = 12.0, 5.2 Hz, 1H), 2.50 (ddd, *J* = 11.6, 5.1, 2.3 Hz, 1H), 2.09 (s, 3H), 1.70−1.65 (m, 1H), 1.65−1.60 (m, 1H), 1.57−1.52 (m, 2H), 1.32−1.29 (m, 1H), 1.28 (s, 3H), 1.18−1.14 (m, 1H), 0.83 (d, *J* = 5.9 Hz, 3H), 0.76 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 184.3, 170.2, 157.0, 145.8, 140.3, 126.4, 125.9, 71.3, 64.8, 53.0, 46.9, 30.1, 29.9, 28.8, 27.3, 19.8, 18.9, 14.6; HRMS (monomer) (ASAP) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}N_2O_3Pd$ + H 423.0902, found 423.0895

*Palladacycle (**8a**).* A sealed tube was charged with amide **1** (52 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (54 mg, 0.24 mmol, 1.2 equiv), and CsOAc (115 mg, 0.3 mmol, 3 equiv) in CD_3CN (1 mL). The reaction mixture was heated at 60 °C for 1.5 h before being filtered through Celite and concentrated. The crude complex was dissolved in chloroform and washed with water (3 × 1 mL) before being concentrated to give the product as a bright yellow solid (77 mg, 95%): mp > 200 °C dec; $[\alpha]_D^{18}$ +141.1 (*c* = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 2942 (CH), 2920 (CH), 1665 (CO); ^1H NMR (600 MHz, CD_3CN) δ 8.30−8.28 (m, 1H), 7.97 (td, *J* = 7.7, 1.6 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.48 (ddd, *J* = 7.5, 5.0, 1.3 Hz, 1H), 3.99 (dt, *J* = 9.5, 2.9 Hz, 1H), 2.63 (dt, *J* = 10.8, 3.3 Hz, 1H), 2.35 (ddt, *J* = 13.0, 9.4, 3.9 Hz, 1H), 1.85 (ddt, *J* = 14.1, 10.8, 3.7 Hz, 1H), 1.71 (d, *J* = 2.3 Hz, 1H), 1.62 (dd, *J* = 13.6, 3.2 Hz, 1H), 1.14 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.04 (s, 3H), 0.96 (s, 3H), 0.85 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, CD_3CN) δ 174.8, 168.0, 157.8, 148.5, 139.8, 127.0, 124.5, 68.3, 64.0, 48.0, 47.5, 47.3, 41.0, 36.7, 22.5, 19.3, 15.2. *It was not possible to obtain mass spectrometry data for this compound.*

*Palladacycle (**8b**).* PPh_3 (26 mg, 0.1 mmol, 1 equiv) was added to a solution of palladacycle **8a** (40 mg, 0.1 mmol, 1 equiv) in $CHCl_3$ (0.5 mL), and the resulting solution stirred at room temperature for 30 min before being filtered through Celite. The filtrate was concentrated to give the desired palladacycle as a yellow solid in quantitative yield: 63 mg; mp 190 °C dec; $[\alpha]_D^{18}$ +28.8 (*c* = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 2942 (CH), 2920 (CH), 1587 (CC), 1095 (CP); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.8 Hz, 1H), 7.78−7.72 (m, 1H), 7.71−7.65 (m, 6H), 7.47 (t, *J* = 7.4 Hz, 3H), 7.43−7.39 (m, 6H), 7.07−7.03 (m, 1H), 6.91−6.86 (m, 1H), 4.28−4.20 (m, 1H), 2.49 (qd, *J* = 8.5, 3.5 Hz, 1H), 2.04 (tdd, *J* = 8.2, 5.8, 2.4 Hz, 1H), 1.57 (t, *J* = 4.0 Hz, 1H), 1.51−1.44 (m, 1H), 1.30 (dd, *J* = 12.8, 2.1 Hz, 1H), 1.13−1.07 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H), 0.47 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.5, 159.7, 148.4, 138.1, 134.4 (d, J_{CP} = 13.2 Hz), 132.1 (d, J_{CP} = 42.1), 130.7 (d, J_{CP} = 1.9 Hz), 128.7 (d, *J* = 10.1 Hz), 124.9, 124.6, 65.7, 65.1, 56.7, 47.2, 46.6, 40.1, 35.6, 22.2, 18.8, 15.2; ^{31}P NMR (300 MHz, $CDCl_3$) δ 33.68; HRMS (ASAP) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{35}N_2OPPd$ + H 625.1607, found 625.1594.

Arylation of Palladacycle (8a). A tube was charged with palladacycle **8a** (41 mg, 0.1 mmol, 1 equiv), CsOAc (19 mg, 0.1 mmol, 1 equiv), *t*AmOH (0.1 mL), and 4-iodoanisole (94 mg, 0.4 mmol, 4 equiv). The tube was sealed with a PTFE-lined cap and heated to 140 °C for 24 h. The reaction mixture was then cooled and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated in vacuo, and the resulting crude residue purified by flash column chromatography to give the arylated product **2a** (16 mg, 0.043 mmol, 43%).

Arylation Using Palladium Complexes as Catalysts. A tube was charged with picolinamide **1** (26 mg, 0.1 mmol, 1 equiv), $CuBr_2$ (2.2 mg, 0.01 mmol, 10 mol %), palladium complex **7** or **8a** (0.005 mmol, 5 mol %), CsOAc (77 mg, 0.4 mmol, 4 equiv), *t*AmOH (0.1 mL), and 4-iodoanisole (94 mg, 0.4 mmol, 4 equiv). The tube was sealed with a PTFE lined cap and heated to 140 °C for 24 h. The reaction mixture was then cooled and filtered through a pad of Celite, washing with EtOAc. The filtrate was concentrated in vacuo and the resulting crude residue purified by flash column chromatography (0−40% EtOAc in petroleum ether). Yield using **7** as a catalyst 32 mg: 87%. Yield using **8a** as a catalyst 29 mg: 80%.

General Procedure for the Removal of the Picolinamide Auxiliary. The reaction was performed in an air atmosphere. Water (2.0 mL) and HCl (0.50 mL, 12 M) were added to a solution of picolinamide (0.20 mmol, 1 equiv) in THF (2.0 mL), and the solution was stirred for 5 min. Zinc dust (196 mg, 3.0 mmol, 15 equiv) was added portionwise over 30 min, and the resulting suspension was stirred for 16 h. The reaction mixture was filtered through Celite, and saturated $NaHCO_3$ (50 mL) was added to the filtrate. The organic layer was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic layers were washed with aqueous HCl (1 M, 50 mL). Saturated aqueous $NaHCO_3$ was added to the aqueous layer to adjust the pH to ∼8 and the product extracted into $CHCl_3$. The organic layer was washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated to give the free amine.

*(1S,2S,4R,6S)-6-(4-Methoxyphenyl)-1,7,7-trimethylbicyclo[2.2.1]-heptan-2-amine (**11**).* Yellow oil: 42 mg, 0.16 mmol, 81%; $[\alpha]_D^{18}$ +14.6 (*c* = 0.5, $CHCl_3$); ν_{max} (film/cm^{-1}) 2981 (CH), 2948 (CH), 1512 (CC); ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.21 (dd, *J* = 11.6, 5.7 Hz, 1H), 3.10 (dd, *J* = 10.5, 6.2 Hz, 1H), 2.43−2.36 (m, 1H), 2.22−2.16 (m, 1H), 1.94 (dd, *J* = 13.1, 5.9 Hz, 1H), 1.82 (t, *J* = 4.7 Hz, 1H), 1.13−1.10 (m, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.91 (s, 3H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 158.0, 134.8, 129.5, 114.0, 58.6, 55.4, 53.4, 51.0, 46.6, 43.4, 39.0, 32.9, 20.6, 19.8, 13.6; LRMS (ES) 260.2 ($[M + H]^+$); HRMS (ES-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{25}NO$ + H 260.2014, found 260.2012.

*7-(4-Methoxyphenol)bicyclo[2.2.1]heptan-2-amine (**12**).* Yellow oil: 32 mg, 0.015 mmol, 74%; ν_{max} (film/cm^{-1}) 2946 (CH), 1832 (CH), 1510 (CC) 1244 (CO); ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 2.88 (s, 1H), 2.82 (s, 1H), 2.69 (m, 1H), 2.50 (d, *J* = 2.6 Hz, 1H), 1.83 (dd, *J* = 12.8, 8.2 Hz, 1H), 1.72 (s, 1H), 1.68−1.61 (m, 1H), 1.56−1.38 (m, 3H), 1.25−1.21 (m, 2H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 157.7, 133.0, 129.4, 113.9, 57.1, 55.3, 51.8, 49.7, 40.7, 38.1, 28.8, 28.7; LRMS (ES) 218.65 ($[M + H]^+$); HRMS (ES-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}NO$ + H 218.1539, found 218.1539.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02665.

^1H and ^{13}C data for all compounds and X-ray crystallography data for **2a**, **4a** and **8b** (PDF)

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Notes

The authors declare no competing financial interest.
CCDC 1553200−1553202 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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