JOC The Journal of Organic Chemistry

Article

Pd(II)-Catalyzed Direct Sulfonylation of Benzylamines using Sodium Sulfinates

Ujjwal Karmakar, and Rajarshi Samanta

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b03098 • Publication Date (Web): 05 Feb 2019

Just Accepted

ACS Publications

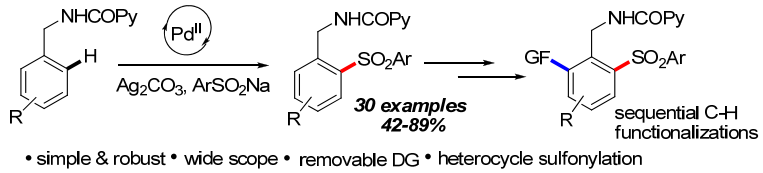
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Pd(II)-Catalyzed Direct Sulfonylation of Benzylamines using Sodium Sulfinates

Ujjwal Karmakar and Rajarshi Samanta*

Department of Chemistry, Indian Institute of Technology Kharagpur, Kharagpur 721302, India.

Supporting Information



ABSTRACT: A Pd(II)-catalyzed direct sulfonylation of benzylamines with sodium sulfinates using removable bidentate directing group is illustrated. The transformation is highly regioselective and tolerates wide functional groups. The mechanistic study reveals that radical species are involved in this reaction. This method delivers a direct synthetic strategy to obtain highly functionalized sulfonylated benzylamines.

INTRODUCTION

Sulfones represent a ubiquitous structural motif having rich pharmaceutical and advanced materials applications.[1] Further, this scaffold is also a well-admired precursor for important synthetic transformations like Julia olefination or Ramberg-Bäcklund reaction.[2] Though there is a significant advancement in the synthesis of sulfones in different ways[3], straightforward introduction of sulfone group in direct C-H bonds attracts more attention due to its simplicity, step-economic nature and avoiding of drastic reaction conditions.[4] Since the pioneering work by Dong group on Pd(II)-catalyzed sulfonylation[5], site-selective sulfonylation of C-H bonds has been explored on different type of substrates using transition metals like Pd,[5,6] Rh,[7] Ru,[8] Cu[9]and Ni.[10] Importantly, a significant progress has been achieved in the transition metal catalyzed sulfonylation of benzamide derivatives with the aid of bidentate directing group. However, due to the omnipresence of *ortho*-sulfonylated benzylamine scaffolds in biologically important compounds (Figure 1), a direct, catalytic, site-selective method for the preparation of these moieties is highly required. In general, the flexible geometry of the substrate and its poor stability under the oxidizing conditions make the task more challenging.

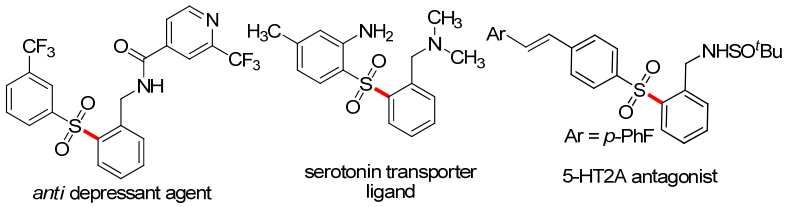
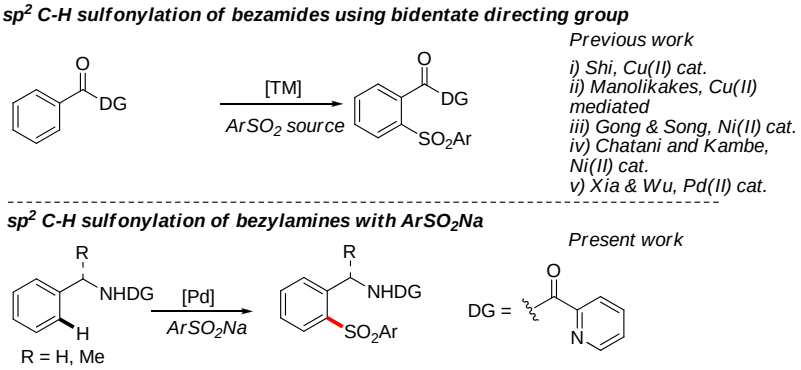


Figure 1: Biologically relevant sulfonylated benzylamine scaffolds

Recently, Shi and co-workers developed a copper(II)-catalyzed direct sulfonylation of benzamide derivatives using sodium sulfinate as coupling partner (Scheme 1i).[9d] Manolikakes and co-workers also developed a copper-mediated sulfonylation with sodium sulfinate using an amide tethered oxazoline directing group.[9e] Chatani's and Kambe's group independently exhibited Ni(II)-catalyzed sulfonylation of benzamide derivative using 8-aminoquinoline based bidentate directing group.[10a-b] Recently, Gong and Song's group revealed Ni(II)-catalyzed version of this transformation (Scheme 1ii).[10c] Very recently, Xia and Wu's group explored a Pd(II)-catalyzed sulfonylation of benzamide derivative having 8-aminoquinoline based bidentate directing group.[6f] Notably, previous reports of sulfonylation are limited with structurally rigid, electron–deficient benzamide moieties. Nevertheless, sodium sulfinates were selected as the strategic sulfonylating reagent due to its easy accessibility and firm stability.[3d, 3i] Since the pioneering development of arylation of benzylamine substrates[11], other important transformations like alkenylation[12], alkynylation[13], alkylation[14], trifluoromethylation[15], and carbonylation[16] were illustrated in the literature. Despite the elegance of the approaches mentioned above, as per our best of knowledge, a direct, catalytic, site-selective sulfonylation of benzylamines remains a strategic challenge.

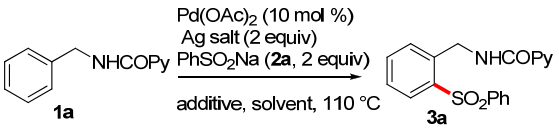
Scheme 1. Pd(II)-Catalyzed Direct C(sp^2)-H Sulfonylation of Benzylamine



Intrigued by our recent studies on transition metal catalyzed C-H functionalizations[17] and related Pd(II)-catalyzed sulfonylation studies[5,6], we hypothesized that Pd(II)-catalyst might help in our desired sulfonylation on benzylamine scaffold. Bidentate directing-group in C-H activation is well appreciated due to its ability towards stabilizing the higher oxidation state of transition metals and delivering the active catalytic site to a nearest C-H bond. Herein, we report a Pd(II)-catalyzed *ortho*-sulfonylation of benzylamines guided by removable bidentate picolinamide group[18] with the sodium sulfinates as sulfonylating agent.

RESULTS AND DISCUSSION

Table 1. Optimization of Reaction Conditions[a]



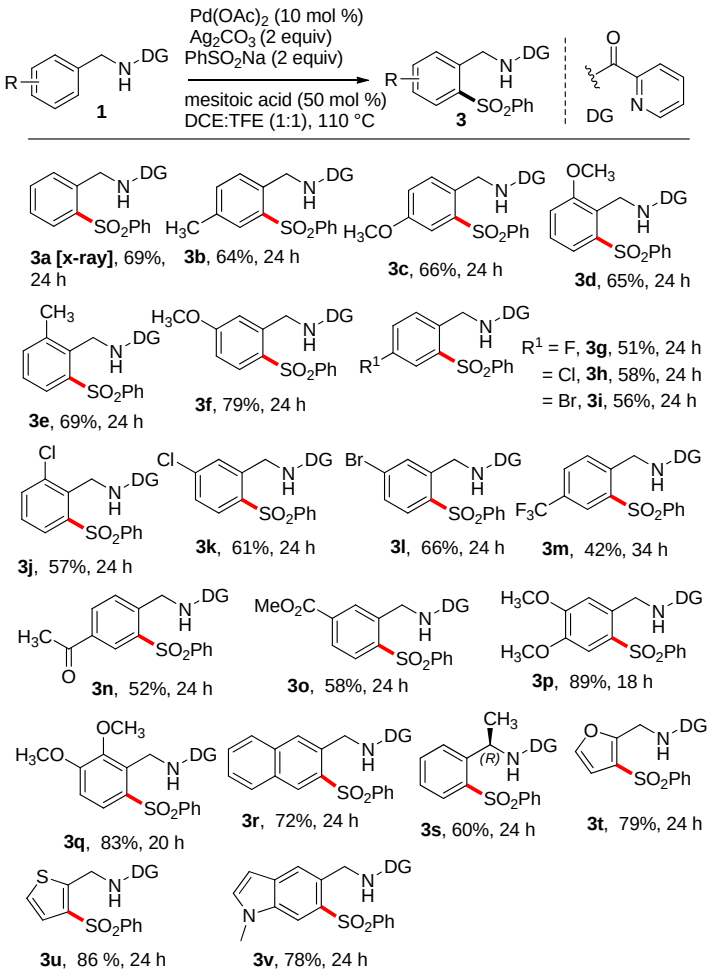
entry	solvent	oxidant	additive (mol %)	yield[b]
1	DCE	-	-	n.d.
2	DCE	Ag_2CO_3	-	31
3	toluene	Ag_2CO_3	-	n.d.
4	butanol	Ag_2CO_3	-	n.d.
5	HFIP	Ag_2CO_3	-	28
6	TFE	Ag_2CO_3	-	38
7	DCE/TFE (1:1)	Ag_2CO_3	-	42
8	DCE/TFE(1:1)	AgOAc	-	36

9	DCE/TFE(1:1)	$AgNO_3$	-	n.d.
10	DCE/TFE(1:1)	Ag_2O	-	n.d.
11	DCE/TFE(1:1)	Ag_2CO_3	LiOAc.$2H_2O$(100)	53
12	DCE/TFE(1:1)	Ag_2CO_3	NaOAc (100)	58
13	DCE/TFE(1:1)	Ag_2CO_3	KOAc (100)	56
14	DCE/TFE(1:1)	Ag_2CO_3	BzOH (50)	52
15	DCE/TFE(1:1)	Ag_2CO_3	4-MeBzOH (50)	52
16	DCE/TFE(1:1)	Ag_2CO_3	2,6-OMeBzOH (50)	58
17	**DCE/TFE(1:1)**	**Ag_2CO_3**	**mesitoic acid (50)**	**69**
18	DCE/TFE(1:1)	Ag_2CO_3	1-AdCO_2H (50)	60
19	DCE/TFE(1:1)	Ag_2CO_3	mesitoic acid (20)	54

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), oxidant (0.2 mmol), additive, solvent (0.1 M), 110 °C, 24 h. [b]Isolated yields. n.d. = not detected. TFE = 2,2,2-trifluoroethanol.

Our investigation commenced with a possible Pd(II)-catalyzed sulfonylation of picolinamide protected benzylamine (**1a**) with sodium sulfinate (**2a**) as a coupling partner (Table 1). Initially, in the absence of any silver salt, there was no desired product formation (Table1, entry 1). Gratifyingly, the acceptable yield of desired product **3a** was isolated when the reaction was performed with Ag_2CO_3 oxidant in DCE solvent (Table 1, entry 2). Screening of other solvents provided an improved yield of **3a** in 1:1 solvent mixture of DCE and 2,2,2-trifluoroethanol with 42% of **3a** (Table 1, entries 3-7). Examination of other silver salts (Table 1, entries 8-10) and different oxidants were tested (see supporting information) with no better results. Considering the significant role of the acetates in direct C-H bond functionalizations[19], relevant acetates were screened. Pleasingly, the yield of the desired product was improved (Table 1, entries 11-13). Furthermore, a thorough investigation of versatile carboxylic acids in 50 mol% (see supporting information) as additives revealed that the reaction proceeded efficiently with mesitoic acid to afford the desired product **3a** in 69% isolated yield (Table 1, entries 14-18). However, lowering the loading of additive decreased the yield of the desired product (Table 1, entry 19). Finally, the structure of **3a** was unequivocally determined through single crystal x-ray analysis.

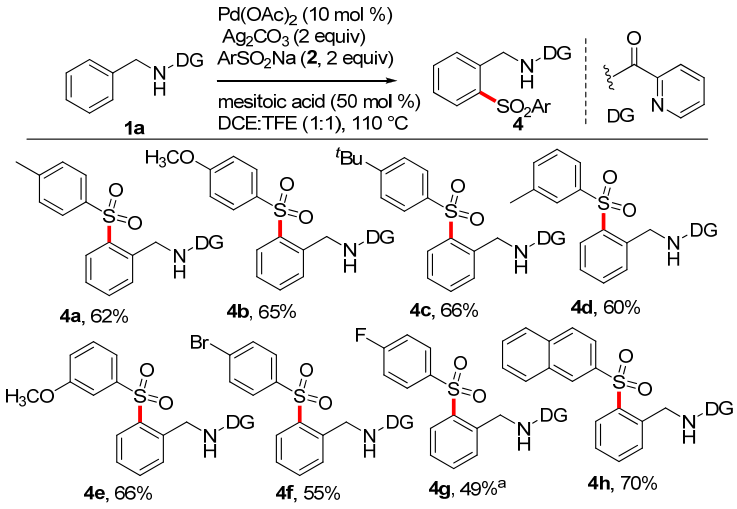
Scheme 2. Scope of Benzylamine Derivatives:



Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.2 mmol), mesitoic acid (50 mol %), DCE:TFE (1:1; 0.1 M), 110 °C

With the optimized reaction protocol, we investigated the broadness in the scope of the reaction (Scheme 2). Synthetically acceptable yields of the sulfonylated products were obtained for substrates containing electron donating groups at its *ortho*, *meta* or *para* position (Scheme 2, **3a**-**3f**). Interestingly, *meta*-methoxy substrate afforded single sulfonylated regioisomer **3f** in 79% yield. Halogen substitutions at the *ortho*, *meta,* and *para*-position of benzylamines were also well tolerated with moderate to good yields (Scheme 2, **3g**-**3l**). Notably, halogens were survived under Pd(II)-catalyzed conditions without proceeding through the expected oxidative addition. Furthermore, the relatively lower yield of the desired product was achieved when electron-withdrawing CF_3, keto or ester groups were tethered at benzylamines (Scheme 2, **3m**-**3o**). Next, highly electron-rich substrates with dimethoxy group worked better with excellent yields (Scheme 2, **3p**-**3q**). Interestingly, naphthalen-2-ylmethanamine derivative (**1r**) provided sulfonylation at the sterically less crowded position in very good yield (Scheme 2, **3r**). It is noteworthy that the optical purity of the benzylamine derivative (**1s**) was firmly tolerated under the developed conditions to provide enantiopure compound **3s** (see supporting information). Significantly, heterocyclic scaffolds like furan and thiophene derivatives provided expected sulfonylated products (Scheme 2, **3t**-**3u**). Appreciating yield and regioselectivity was observed with indole derivative during desired sulfonylation (Scheme 2, **3v**).

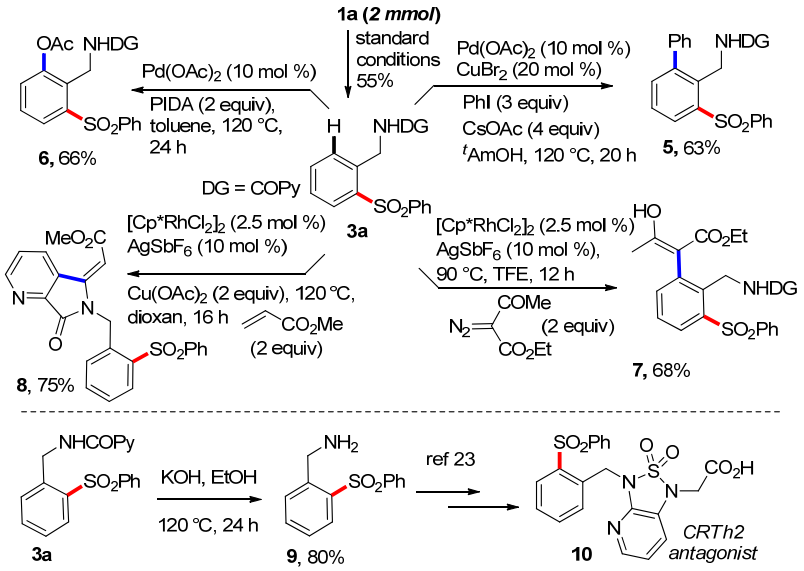
Scheme 3. Scope Using Various Sulfinates:



Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.2 mmol), DCE:TFE (1:1; 0.1 M), 110 °C, 24 h. [a]30 h.

The reaction was explored with various sodium sulfinates having different electronic and steric properties (Scheme 3, **4a**-**4h**). Various functional groups like alkyl, methoxy, halogens were well accommodated during transformation. It is important to mention that the survival of halides during transformation provided the synthetic post modification opportunity (Scheme 3, **4f**-**4g**). Next, a bulky naphthylsulfinate also afforded desired product in very good yield (Scheme 3, **4h**). Unfortunately, there was no desired products formation when the reactions were carried out with *meta*-CF_3 benzene sulfinate salt or alkyl sulfinate salt, CH_3SO_2Na under optimized conditions.

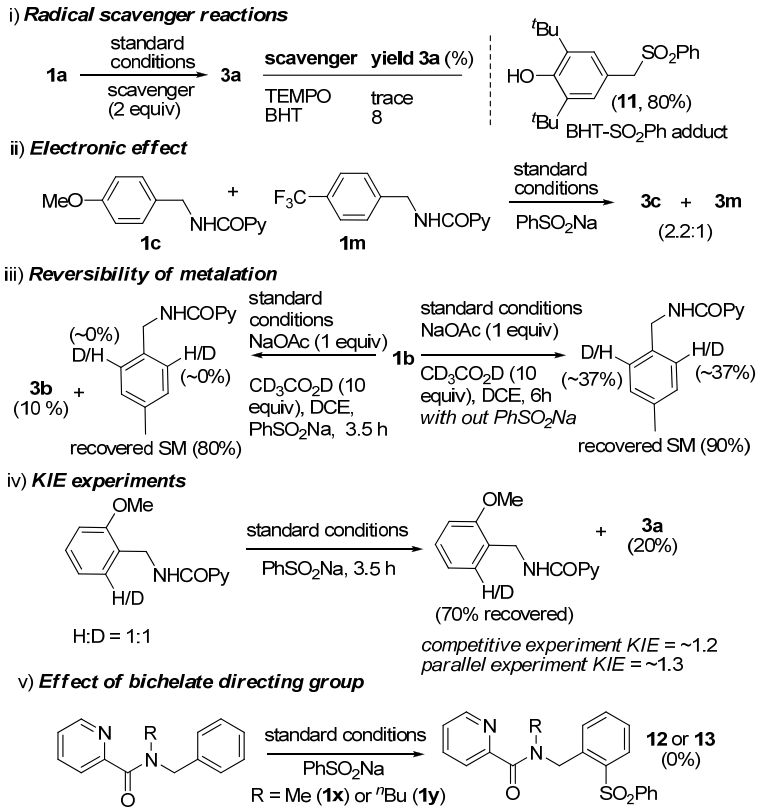
Scheme 4. Product modifications and applications:



The diverse applicability of the developed method was explored through the post-operation modifications of **3a** (Scheme 4). Treatment of **3a** with iodobenzene under $Pd(OAc)_2$ catalyzed conditions offered *ortho*-phenylated product **5**.[20] Next, **3a** was undergone through $Pd(OAc)_2$ catalyzed *ortho*-acetoxylation using $PhI(OAc)_2$ to provide compound **6** in 66% yield.[21] Further, *ortho*-alkylation was carried out with the diazo compound under Rh(III)-catalyzed conditions to provide compound **7.** Furthermore, Rh(III)-catalyzed regio-selective, oxidative olefination at pyridine core of **3a** and subsequent cyclization afforded

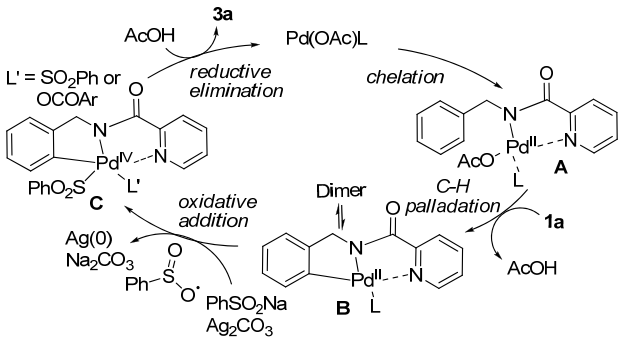
compound **8**.[22] Deprotection of **3a** furnished compound **9** which could be transformed to a pharmaceutically active compound **10** via literature known method.[23]

Scheme 5. Control experiments:



To delineate the probable mechanistic pathway of the reaction, required control experiments were conducted (Scheme 5). To reveal the radical intermediate's involvement, the reaction was carried in the presence of radical quenchers like 2,2,6,6-tetramethylpiperidin-1-yl-)oxidanyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT). Incidentally, a significant amount of inhibition in the formation of the desired product was noticed (Scheme 5i) with the isolation of radical trapped adduct **11.** Next, the reaction rate (Scheme 5ii) for electron-rich benzylamine (**1c**) was found faster over electron-deficient benzylamine (**1m**). The H/D scrambling experiment on **1b** in the absence of sodium sulfinate (**2a**) revealed that the C-H metalation was largely reversible. However, no deuterium incorporation was found when the reaction was carried out in the presence of sodium sulfinate (**2a**). This result indicated that steps following the C-H metalation were not reversible (Scheme 5iii). A KIE value ~1.2 was determined *via* ^{1}H NMR analysis of the recovered picolinamide mixture from the intermolecular competitive experiment. Further, in a competitive parallel experiment, the KIE value of ~1.3 was measured *via* the starting material recovery (see supporting information). These findings proposed that the C–H bond activation at the benzylamine derivative was not the rate-determining step (Scheme 5iv). Reactions of *N*-alkyl protected benzylamines (**1x** or **1y**) with $PhSO_2Na$ (**2a**) did not furnish the corresponding target products **12** or **13** (Scheme 5v). This result exhibited the crucial bichelate-directing role of pyridyl and amide "N" in enabling the site-selective sulfonylation reaction. Based on the above observations and related literature,[5,6, 11-16] a probable mechanism based on Pd(II)/Pd(IV) catalytic cycle is proposed (Scheme 6).

Scheme 6: Plausible mechanism for sulfonylation:



Initially, *N,N'*-bidentate directing group of **1a** coordinates with Pd(II)-catalyst to form **A**. Next; carboxylic acid assisted C-H bond metalation provides 5-membered palladacycle **B** which could be in equilibrium with its dimer. Subsequently, silver salt mediated single-electron oxidation of sodium sulfinate affords the corresponding sulfonyl radical which further leads to the formation of Pd(IV)-complex **C**.[4c,9d,10a] Finally, the reductive elimination of **C** and subsequent protonation provides the sulfonylated product **3a** with the regeneration of active Pd(II)-catalyst. However, the possibility of bimetallic Pd(II)/Pd(III) catalytic cycle cannot be totally ruled out at this stage. [24]

CONCLUSION

In summary, we have developed a direct Pd(II)-catalyzed site-selective sulfonylation of benzylamines using sodium sulfinates as coupling partner and guided by the removable bidentate picolinamide group. The method was explored with diverse functional group tolerance. The involvement of radical species in the catalytic cycle was revealed. The H/D scrambling study showed that C-H bond cleavage was reversible. Moreover, the sulfonylated benzylamines were further explored with sequential functional groups incorporation.

EXPERIMENTAL SECTION

General:

All commercially available compounds were used without further purification. Solvents for elution in the column were distilled. Analytical thin layer chromatography (TLC) was performed on pre- coated silica gel 60 F_{254}. Visualization on TLC was achieved by the use of UV light (254 nm). Column chromatography was undertaken on silica gel (230-400 mesh). ^{1}H NMR spectra were recorded on BRUKER ULTRA SHIELD machine (400 MHz, 500 MHz, and 600 MHz). ^{13}C NMR spectra were recorded on BRUKER machine (150, 125 and 100 MHz) and were fully decoupled by broadband proton decoupling. Chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: s= singlet, d= doublet, t= triplet, q= quartet, dd= doublet of doublet, dt= doublet of triplet, m= multiplet. Coupling constants, *J*, were reported in hertz unit (Hz). Chemical shifts were reported in ppm referenced to the center of a triplet at 77.16 ppm of $CDCl_3$. ^{19}F NMR spectra were recorded on BRUKER machine (376 MHz). Fourier Transform Infrared Spectroscopy (FT-IR) was obtained with a Bruker Alpha ATR spectrometer and selected absorbance peaks are reported in terms of frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from waters XEVO-G2QTOF by using TOF MS ESI+ method. Materials were obtained from commercial suppliers or prepared according to standard procedures unless otherwise noted. HPLC analysis was performed on SHIMADZU LC 20 AD having PDA detector and chiralcel OD-H column under mobile phase (hexane: isopropanol = 9:1) 1mL/min flow rate.

General procedure for the synthesis of substituted Benzylamine compounds:[25]

Substituted aromatic aldehydes (1 mmol) were taken in a 50 mL round bottom flask and hydroxylamine hydrochloride (1.2 mmol) was added to it. Ethanol and water (1:4) mixture were (6 mL) added to the reaction mixture. Sodium carbonate (1.2 mmol) was added and the reaction mixture stirred for 6 h at room temperature. The solvent was removed by using rotary evaporator. The product was partitioned between ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and directly taken for next step without further modification. Most of the benzylamines were procured from commercially available sources. The remaining benzylamines were prepared by following procedures and the analytical data matched with reported values.

Procedure A: Corresponding oxime product (1 mmol) was taken in 10 mL acetic acid. Subsequently, zinc dust (6 equiv) was added to the reaction flask and heated 100 °C for 12 to 24 h and monitored by TLC. Upon completion, sodium bicarbonate was added to the reaction mixture. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography to get pure benzylamine compounds. The analytical data prepared compounds matched with reported value.

Procedure B: Corresponding oxime product (1 mmol) was taken in 10 mL dry THF and cooled to 0 °C. Lithium aluminum hydride (1.5 mmol) was added to it very slowly, and the reaction mixture was stirred for 12 h at room temperature. Upon completion, a saturated ammonium chloride solution was added to the reaction mixture. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The product was purified by column chromatography to get pure benzylamine compounds.

General procedure for the synthesis of substituted *N*-Benzylpicolinamide compounds:[26, 13d, 14a]

Procedure A: Substituted benzylamine derivatives (1 mmol), picolinic acid (1.2 mmol), EDC.HCl (1.2 mmol), HOBT (1.2 mmol), *N,N*-diisopropylethylamine (DIPEA) (2.5 mmol) were taken in a 50 mL round bottom flask containing 10 mL anhydrous DMF. The reaction mixture was stirred for 24 h at room temperature. Upon completion, the reaction mixture was partitioned between ethyl acetate and water. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography to get pure product (**1a-1n, 1p-1s, 1v).** The analytical data of the compounds found similar with reported value.[26, 13d, 14a] The analytical data of new compound **1v** was given**.**

Procedure B: A 50 mL round-bottomed flask was charged with picolinic acid (1 mmol) and dry dichloromethane (10 mL) was added to it. It was cooled to 0 °C in an ice water bath. To the stirred suspension oxalyl chloride (1.1 mmol), was added dropwise followed by addition of DMF (catalytic amount) in one portion. The mixture was kept in the cooling bath for 1 h and then allowed to warm to room temperature. The mixture was cooled to 0 °C and NEt_3 (2 mmol) was added dropwise followed by substituted benzylamine (1.1 mmol). The mixture was left in the cooling bath for 30 minutes and then allowed to warm to room temperature. Stirring was continued at room temperature for 2 h. Removal of solvent in vacuo gave the crude product that was partitioned between DCM and water. The organic phases were combined dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography to give corresponding *N*-Benzylpicolinamide compounds. (**1t-1u**). The Analytical data of **1t** was matched with reported value.[13d] Analytical data of newly synthesized compound **1u** was reported here.

Procedure for the synthesis of Methyl 3-(picolinamidomethyl)benzoate (1o)

3-cyanobenzoic acid (1g, 6.8 mmol) was dissolved in dry methanol (20 mL). The solution was cooled to 0 °C. Then thionyl chloride (0.5 mL, 1.5 equiv) was added to the reaction mixture drop-wise and stirred for 10 h at room temperature. After completion of the reaction the solvent was evaporated and the crude reaction mixture was partitioned between ethyl acetate

and water. The organic layer was dried over Na_2SO_4, concentrated under reduced pressure and directly taken for next step without further purification. (910 mg, yield: 83 %)

Corresponding 3-cyanobenzoic acid ester compound (400 mg, 2.48 mmol) was taken in dry methanol (10 mL) and cooled to 0 °C. To this reaction mixture concentrated HCl (0.3 mL) followed by Pd/C (10 wt %) was added and kept it under hydrogen atmosphere by using a H_2 balloon and stirred for 24 h at room temperature. After completion of the reaction, the reaction mixture was filtered through celite and was washed with methanol. The solvent was concentrated under reduced pressure and directly taken for next step without further purification.

The corresponding benzylamine product (1 mmol) was dissolved in dry dichloromethane and cooled to 0 °C. To this reaction mixture 2-picolinic acid (1.2 mmol), followed by EDC.HCl (2.1mmol) and DMAP (2 mmol) were added. The reaction mixture was stirred for 6 h at room temperature. After completion of the reaction, the reaction mixture was partitioned between DCM and water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and purified by column chromatography to give methyl 3-(picolinamidomethyl)benzoate (**1o**) as a white solid product in 56% yield (151.3 mg).

General procedure for the synthesis of substituted aryl sulfinates salts: [9c, 27]

Substituted aromatic sulfonyl chloride (1 mmol) was taken in a 50 mL round bottom flask. Subsequently, Na_2SO_3 (2 mmol), sodium bicarbonate (2 mmol) and distilled water (10 mL) were added to the flask. Next, the reaction mixture was stirred for 8 h at 80 °C. Water was removed under reduced pressure. The solid white product was recrystallized by ethanol and dried in *vaccuo*. The products were compared with known literature data[9c, 27] and used directly without further modification.

General procedure for $Pd(OAc)_2$-catalyzed *N*-(2(Phenylsulfonyl)benzyl)picolinamide synthesis:

N-Benzylpicolinamide derivative **1** (0.1 mmol) was dissolved in 0.5 mL 2,2,2-trifluroethanol and 0.5 mL DCE (1:1) in a 10 mL screw cap vial. Then $Pd(OAc)_2$ (10 mol %, 2.24 mg), Ag_2CO_3(2 equiv, 54 mg), mesitoic acid (50 mol %, 8.2 mg) and sodium sulfinate (2 equiv, 33 mg) **2a** were added to the reaction mixtures at room temperature and the reaction mixture was stirred for 18-34 h at 110 °C. After completion of the reaction, the solvent was evaporated, and the crude product was partitioned between ethyl acetate and water. Saturated sodium bicarbonate solution was added. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure and directly loaded to the column to obtain a pure product with hexane/ethyl acetate as eluent (40-60 % EA/PE).

Large scale experiment:

In a 50 mL round bottom flask **1a** (424.5 mg, 2 mmol) was dissolved in 5 mL 2,2,2- trifluroethanol and 5 mL DCE (1:1). Then $Pd(OAc)_2$ (10 mol %, 45 mg), Ag_2CO_3 (2 equiv, 1.1 g), mesitoic acid (50 mol %, 164.2 mg) and sodium sulfinate (2 equiv, 656.6 mg) **2a** were added to the reaction mixture at room temperature and the reaction mixture was stirred for 24 h at 110 °C. After completion of the reaction, the solvent was evaporated and the crude product was partitioned between ethyl acetate and water. Saturated sodium bicarbonate solution was added. The organic layer dried over Na_2SO_4 and concentrated under reduced pressure and directly loaded to the column to obtain pure product **3a** with hexane/ethyl acetate as eluent with 55 % yield (387.4 mg).

SYNTHETIC APPLICATION

Procedure for aryalation of 3a:

Compound **3a** (0.1 mmol, 35.2 mg) was dissolved in 1 mL of *tert* amyl alcohol in a 10 mL screw cap vial. Then $Pd(OAc)_2$ (10 mol %, 2.24 mg), $CuBr_2$ (20 mol %, 4.5 mg), CsOAc (4 equiv, 76 mg) and iodobenzene (3 equiv, 61 mg) were added to the reaction mixture. The reaction mixture was allowed to stir at 120 °C for 20 h. After completion of the reaction, the reaction mixture was concentrated and directly purified by flash column chromatography to obtain product **5**.

Procedure for acetoxylation of 3a:

Compound **3a** (0.1 mmol, 35.2 mg) was dissolved in 1 mL of toluene in a 10 mL screw cap vial. Then $Pd(OAc)_2$ (10 mol %, 2.24 mg), diacetoxyiodobenzene (2 equiv, 66 mg) were added to the reaction mixture. The reaction mixture was allowed to stir at 120 °C for 24 h. After completion of the reaction, the reaction mixture was concentrated and directly purified by flash column chromatography to obtain product **6.**

Procedure for Rh(III)-catalysed alkylation of 3a with diazoketo ester:

Compound **3a** (0.1 mmol, 35.2 mg) was dissolved in 1mL 2,2,2- trifluoroethanol in a 10 mL screw cap vial. Then $[(Cp^*RhCl_2)_2]$ (2.5 mol%, 1.5 mg), $AgSbF_6$ (10 mol%, 3.5 mg) and diazoketoester (2 equiv, 32 mg) were added to the reaction mixture at room temperature. Then the reaction mixture was stirred at 90 °C for 12 h. After completion of the reaction, it was concentrated and directly loaded to the column to obtain pure product **7**.

Procedure for Rh(III)-catalyzed alkenylation of 3a:

Compound **3a** (0.1 mmol, 35.2 mg) was dissolved in 1 mL of 1,4-dioxane in a 10 mL screw cap vial. Then $[(Cp^*RhCl_2)_2]$ (2.5 mol%, 1.5 mg), $AgSbF_6$ (10 mol%, 3.5 mg) and methyl acrylate (2 equiv, 0.018 mL) were added to the reaction mixture at room temperature. The reaction mixture was warmed to 120 °C and stirred for 16 h. After completion of the reaction, it was concentrated and directly loaded to the column to get the product **8** after purification.

Removal of picolinamide directing group:

Compound **3a** (0.1 mmol, 35.2 mg) and KOH (60.0 equiv, 336 mg) were taken in a 20 mL reaction vessel. Then it was sealed with a Teflon lined cap and ethanol (4 mL) was added via syringe. The resulting mixture was stirred at 120 °C for 24 h. After completion of the reaction, the reaction mixture was cooled down to room temperature, diluted by 30 mL of ethyl acetate and washed with water (2 × 20 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo and the crude product was purified by column chromatography to give corresponding amine product **9** in 80% yield (19.8 mg) as a yellow oil. The analytical data of the compound was compared with known literature data.[23]

Analytical data of new *N*-Benzylpicolinamide compounds:

N-(4-Acetylbenzyl)picolinamide (**1n**); white solid, (66%, 167.8 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.1 Hz, 1H), 8.48 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.93 (dd, *J* = 8.2, 1.7 Hz, 2H), 7.85 (m, 1H), 7.44 (t, *J* = 6.9 Hz, 3H), 4.73 (d, *J* = 6.4 Hz, 2H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 197.7, 164.5, 149.8, 148.2, 143.9, 137.6, 136.6, 128.9, 127.9, 126.5, 122.6, 43.3, 26.7; FT-IR: $\tilde{\nu}$ = 3052, 2924, 1670, 1608, 1570, 1521, 1465, 1415, 1359, 1268, 1162, 1117, 1089 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{15}H_{15}N_2O_2$: 255.1128, found 255.1125.

Methyl 3-(picolinamidomethyl)benzoate (**1o**); white solid, (56%, 151.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.4 Hz, 1H), 8.45 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.03 (s, 1H), 7.95 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.42 (q, *J* = 7.6 Hz, 2H), 4.72 (d, *J* = 6.2 Hz, 2H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 167.0, 164.5, 149.8, 148.2, 138.8, 137.6, 132.6, 130.7, 129.0, 128.9, 128.8, 126.5, 122.6, 52.3, 43.3; FT-IR: $\tilde{\nu}$ = 3058, 2924, 2854, 1719, 1668, 1591, 1522, 1465, 1435, 1357, 1287, 1207, 1108, 1088 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{15}H_{15}N_2O_3$: 271.1077, found 271.1093.

N-(2,3-Dimethoxybenzyl)picolinamide (**1q**); gray solid, (76%, 206.9 mg); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 3.9 Hz, 1H), 8.42 (s, 1H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 7.6, 1.7 Hz, 1H), 7.38 (m, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 6.98 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.87 (dd, *J* = 8.0, 1.7 Hz, 1H), 4.69 (d, *J* = 6.1 Hz, 2H), 3.92 (s, 3H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 164.3, 152.9, 150.3, 148.2, 147.6, 137.4, 132.1, 126.2, 124.3, 122.4, 121.6, 112.2, 61.0, 56.0, 38.9; FT-IR: $\tilde{\nu}$ = 3056,

2924, 2850, 1674, 1590, 1524, 1482, 1434, 1356, 1275, 1223, 1170, 1081 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{15}H_{17}N_2O_3$: 273.1234, found 273.1256.

N-(Thiophen-2-ylmethyl)picolinamide (**1u**); brown solid, (63%, 137.5 mg); ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.6 Hz, 1H), 8.41 (s, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 7.86 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 (m, 1H), 7.23 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.05 (m, 1H), 6.97 (dd, *J* = 5.1, 3.4 Hz, 1H), 4.84 (d, *J* = 6.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1, 149.8, 148.2, 140.9, 137.6, 127.0, 126.4, 126.3, 125.3, 122.6, 38.4; FT-IR: $\tilde{\nu}$ = 3058, 2924, 1668, 1570, 1519, 1465, 1436, 1368, 1290, 1168, 1088 cm^{-1}; HRMS: calculated for $[M+Na]^+$ $C_{11}H_{10}N_2NaOS$: 241.0406 found 241.0413.

N-((1-Methyl-1*H*-indol-5-yl)methyl)picolinamide (**1v**); reddish solid, (68%, 180.4 mg); ^1H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.2 Hz, 1H), 8.35 (s, 1H), 8.25 (d, *J* = 7.8 Hz, 1H), 7.86 (m, 1H), 7.63 (s, 1H), 7.40 (m, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.25 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.06 (d, *J* = 3.0 Hz, 1H), 6.46 (d, *J* = 3.0 Hz, 1H), 4.76 (d, *J* = 5.9 Hz, 2H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.1, 150.2, 148.1, 137.4, 136.3, 129.5, 129.1, 128.8, 126.2, 122.4, 122.2, 120.6, 109.6, 101.0, 44.3, 33.0; FT-IR: $\tilde{\nu}$ = 3055, 2924, 2855, 1667, 1569, 1515, 1464, 1434, 1338, 1305, 1245, 1156, 1086 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{16}H_{16}N_3O$: 266.1288, found 266.1286.

Analytical data of *N*-(2(Phenylsulfonyl)benzyl)picolinamide:

N-(2-(Phenylsulfonyl)benzyl)picolinamide (**3a**); Crystalline solid, m.p. 134 - 136 °C, (69%, 24.3 mg); R_f = 0.42 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.55 (d, *J* = 3.2 Hz, 1H), 8.15 (t, *J* = 6.9 Hz, 2H), 7.92 (d, *J* = 7.7 Hz, 2H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.51 – 7.45 (m, 3H), 7.39 (m, 1H), 4.84 (d, *J* = 6.7 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.5, 149.8, 148.4, 141.6, 139.0, 137.9, 137.3, 134.4, 133.5, 132.3, 130.0, 129.5, 128.4, 127.5, 126.3, 122.4, 40.6; FT-IR: $\tilde{\nu}$ = 3053, 2924, 2853, 1682, 1591, 1514, 1463, 1434, 1356, 1254, 1238, 1151, 1086 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{17}N_2O_3S$: 353.0954, found 353.0971.

N-(4-Methyl-2-(phenylsulfonyl)benzyl)picolinamide (**3b**); amorphous solid, (64%, 23.5 mg); R_f = 0.38 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 (t, *J* = 6.7 Hz, 1H), 8.54 (d, *J* = 4.6 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.62 – 7.45 (m, 4H), 7.42 – 7.34 (m, 2H), 4.77 (d, *J* = 6.6 Hz, 2H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.4, 149.9, 148.4, 141.9, 138.8, 138.6, 137.3, 135.1, 135.0, 133.4, 132.5, 130.4, 129.5, 127.4, 126.3, 122.4, 40.3, 21.2; FT-IR: $\tilde{\nu}$ = 3061, 2924, 2854, 1674, 1570, 1516, 1463, 1435, 1353, 1303, 1243, 1161, 1084 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_3S$: 367.1111, found 367.1123.

N-(4-Methoxy-2-(phenylsulfonyl)benzyl)picolinamide (**3c**); amorphous solid, (66%, 25.2 mg); R_f = 0.30 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (t, *J* = 5.7 Hz, 1H), 8.54 (d, *J* = 4.6 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 7.3 Hz, 2H), 7.81 (td, *J* = 7.8, 1.7 Hz, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.51 (dd, *J* = 8.3, 6.7 Hz, 1H), 7.40 (m, 1H), 7.07 (dd, *J* = 8.4, 2.8 Hz, 1H), 4.73 (d, *J* = 6.5 Hz, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.4, 159.3, 149.9, 148.4, 141.6, 139.9, 137.3, 134.1, 133.5, 129.7, 129.5, 127.4, 126.3, 122.4, 119.9, 115.1, 55.9, 40.0; FT-IR: $\tilde{\nu}$ = 3062, 2926, 2855, 1665, 1606, 1570, 1522, 1446, 1360, 1290, 1241, 1156, 1043 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_4S$: 383.1060, found 383.1061.

N-(2-Methoxy-6-(phenylsulfonyl)benzyl)picolinamide (**3d**); amorphous solid, (65%, 24.8 mg); R_f = 0.32 (40% EA/PE); ^1H NMR (600 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.6 Hz, 1H), 8.21 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.91 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.81 (td, *J* = 7.7, 1.6 Hz, 1H), 7.53 – 7.42 (m, 4H), 7.37 (m, 1H), 7.17 (d, *J* = 8.3 Hz, 1H), 4.89 (d, *J* = 5.7 Hz, 2H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7, 159.5, 150.2, 148.2, 141.8, 141.5, 137.2, 133.3, 129.4, 129.4,

127.6, 126.0, 125.4, 122.4, 121.6, 116.5, 56.6, 34.1; FT-IR: $\tilde{\nu}$ = 3061, 2922, 2853, 1668, 1608, 1576, 1518, 1445, 1366, 1291, 1239, 1152, 1046 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_4S$: 383.1060, found 383.1071.

N-(2-Methyl-6-(phenylsulfonyl)benzyl)picolinamide (**3e**); amorphous solid, (69%, 25.3 mg); R_f = 0.40 (40% EA/PE) ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 8.48 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 8.09 (d, *J* = 7.7 Hz, 1H), 7.93 – 7.83 (m, 2H), 7.82 (td, *J* = 7.7, 1.7 Hz, 1H), 7.57 – 7.45 (m, 4H), 7.44 – 7.36 (m, 2H), 4.81 (d, *J* = 6.1 Hz, 2H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 163.9, 149.8, 148.4, 141.8, 141.4, 140.7, 137.3, 136.7, 135.2, 133.4, 129.5, 128.3, 128.0, 127.4, 126.2, 122.4, 37.0, 20.1; FT-IR: $\tilde{\nu}$ = 3061, 2923, 2853, 1674, 1570, 1516, 1463, 1354, 1303, 1243, 1161, 1084 cm^{-1}; HRMS calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_3S$: 367.1111, found 367.1078.

N-(5-Methoxy-2-(phenylsulfonyl)benzyl)picolinamide (**3f**); amorphous solid, (79%, 30.2 mg); R_f = 0.38 (40% EA/PE); ^1H NMR (600 MHz, $CDCl_3$) δ 8.71 (t, *J* = 6.8 Hz, 1H), 8.54 (d, *J* = 4.8 Hz, 1H), 8.14 (d, *J* = 9.0 Hz, 2H), 7.89 (d, *J* = 7.3 Hz, 2H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.40 (m, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.9, 2.5 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.5, 164.1, 149.8, 148.4, 142.4, 140.2, 137.3, 133.1, 132.6, 130.3, 129.4, 127.2, 126.3, 122.4, 117.5, 113.2, 55.8, 40.8; FT-IR: $\tilde{\nu}$ = 3061, 2924, 2854, 1674, 1570, 1516, 1463, 1435, 1353, 1303, 1243, 1161, 1084 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_4S$: 383.1060, found 383.1068.

N-(4-Fluoro-2-(phenylsulfonyl)benzyl)picolinamide (**3g**); gummy liquid, (51%, 18.9 mg); R_f = 0.28 (40% EA/PE); ^1H NMR (600 MHz, $CDCl_3$) δ 8.70 (t, *J* = 5.8 Hz, 1H), 8.56 (dt, *J* = 4.8, 1.3 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.95- 7.93 (m, 2H), 7.90 – 7.79 (m, 2H), 7.67 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.62 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 2H), 7.42 (m, 1H), 7.25 (m, 1H), 4.79 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.6, 161.7 (d, *J* = 252.0 Hz), 149.7, 148.4, 140.92, 140.91 (d, *J* = 24.0 Hz), 137.4, 134.5 (d, *J* = 7.4 Hz), 133.88, 133.85 (d, *J* = 3.5 Hz), 129.7, 127.7, 126.4, 122.4, 121.2 (d, *J* = 20.8 Hz), 117.2 (d, *J* = 24.8 Hz), 39.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.98; FT-IR: $\tilde{\nu}$ = 3061, 2924, 2858, 1672, 1570, 1516, 1464, 1425, 1389, 1303, 1219, 1154, 1089 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}FN_2O_3S$: 371.0860, found 371.0873.

N-(4-Chloro-2-(phenylsulfonyl)benzyl)picolinamide (**3h**); amorphous solid, (58%, 22.4 mg); R_f = 0.36 (40% EA/PE); ^1H NMR (600 MHz, $CDCl_3$) δ 8.68 (t, *J* = 6.5 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.83 (t, *J* = 7.8 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.58 – 7.48 (m, 3H), 7.42 (t, *J* = 6.2 Hz, 1H), 4.80 (d, *J* = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.6, 149.6, 148.4, 141.0, 140.6, 137.4, 136.3, 134.5, 134.2, 133.9, 133.7, 129.8, 129.7, 127.7, 126.5, 122.4, 40.0; FT-IR: $\tilde{\nu}$ = 3060, 2924, 2852, 1669, 1570, 1518, 1468, 1435, 1358, 1290, 1245, 1154, 1039 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{35}ClN_2O_3S$: 387.0565, found 387.0571.

N-(4-Bromo-2-(phenylsulfonyl)benzyl)picolinamide (**3i**); amorphous solid (56%, 24.2 mg); R_f = 0.40 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (t, *J* = 6.6 Hz, 1H), 8.55 (d, *J* = 4.5 Hz, 1H), 8.30 (d, *J* = 2.2 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 7.7 Hz, 2H), 7.82 (td, *J* = 7.7, 1.8 Hz, 1H), 7.67 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.63 (m, 1H), 7.55 (dd, *J* = 8.1, 6.5 Hz, 3H), 7.41 (m, 1H), 4.78 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.6, 149.6, 148.4, 140.9, 140.6, 137.4, 137.3, 136.8, 133.9, 132.6, 129.7, 127.7, 126.5, 122.4, 122.2, 40.1; FT-IR: $\tilde{\nu}$ = 3063, 2924, 2853, 1671, 1560, 1517, 1469, 1397, 1361, 1306, 1242, 1153, 1048 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{81}BrN_2O_3S$: 433.0040, found 433.0053.

N-(2-Chloro-6-(phenylsulfonyl)benzyl)picolinamide (**3j**); gummy liquid, (57%, 22.1 mg); R_f = 0.32 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.6 Hz, 1H), 8.24 (s, 1H), 8.19 (t, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.53–7.47 (m, 4H), 7.40 (d, *J* = 6.1 Hz, 1H), 4.98 (d, *J* = 5.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 163.8, 149.7, 148.3, 142.6, 141.1, 138.4, 137.4, 135.7, 134.7, 133.8, 129.7, 129.4, 128.7, 127.7, 126.3, 122.5,

37.7; FT-IR: $\tilde{\nu}$ = 3063, 2923, 2853, 1672, 1574, 1520, 1466, 1446, 1361, 1288, 1246, 1156, 1044 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{35}ClN_2O_3S$: 387.0565, found 387.0577.

N-(5-Chloro-2-(phenylsulfonyl)benzyl)picolinamide (**3k**); amorphous solid, (61%, 23.6 mg); R_f = 0.42 (40% EA/PE) ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (t, *J* = 6.7 Hz, 1H), 8.56 (d, *J* = 4.6 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H),7.91 (d, *J* = 8.3 Hz, 2H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.62 (s, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.46 – 7.41 (m, 2H), 4.81 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.6, 149.6, 148.5, 141.3, 137.43, 137.41, 133.7, 132.0, 131.9, 131.6, 131.5, 129.7, 128.6, 127.5, 126.5, 122.5, 40.3; FT-IR: $\tilde{\nu}$ = 3063, 2923, 2852, 1674, 1588, 1518, 1465, 1435, 1355, 1307, 1246, 1156, 1048 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{35}ClN_2O_3S$: 387.0565, found 387.0566.

N-(5-Bromo-2-(phenylsulfonyl)benzyl)picolinamide (**3l**); amorphous solid, (66%, 28.5 mg); R_f = 0.44 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 6.8 Hz, 1H), 8.57 (d, *J* = 4.7 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 2H), 7.84 (td, *J* = 7.7, 1.7 Hz, 1H), 7.79 (s, 1H), 7.68 – 7.56 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.43 (dd, *J* = 7.5, 4.8 Hz, 1H), 4.81 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.6, 149.6, 148.4, 141.2, 139.8, 138.0, 137.5, 134.9, 133.8, 131.6, 131.5, 129.7, 129.5, 127.5, 126.5, 122.5, 40.2; FT-IR: $\tilde{\nu}$ = 3061, 2923, 2853, 1673, 1557, 1516, 1464, 1390, 1355, 1308, 1244, 1155, 1047 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{79}BrN_2O_3S$: 431.0060, found 431.0060.

N-(2-(Phenylsulfonyl)-4-(trifluoromethyl)benzyl)picolinamide (**3m**); gummy liquid, (42%, 17.7 mg); R_f = 0.26 (40% EA/PE); ^1H NMR (600 MHz, $CDCl_3$) δ 8.70 (s, 1H), 8.57 (d, *J* = 4.7 Hz, 1H), 8.44 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 2H), 7.88 – 7.77 (m, 3H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 6.2 Hz, 1H), 4.89 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.7, 149.4, 148.5, 141.8, 140.7, 140.1, 137.5, 134.1, 132.7, 131.0 (q, *J* = 33.5 Hz) 130.9 (q, *J* = 3.4 Hz), 129.8, 127.7, 127.1 (q, *J* = 3.7 Hz), 126.6, 123.2 (q, *J* = 273.2 Hz), 122.5, 40.3; FT-IR: $\tilde{\nu}$ = 3065, 2923, 2852, 1677, 1616, 1571, 1519, 1448, 1405, 1327, 1229, 1155, 1084 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{16}F_3N_2O_3S$: 421.0828, found 421.0838.

N-(4-Acetyl-2-(phenylsulfonyl)benzyl)picolinamide (**3n**); amorphous solid, (52%, 20.5 mg), R_f = 0.24 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 1.7 Hz, 2H), 8.56 (d, *J* = 4.4 Hz, 1H), 8.33 – 7.98 (m, 2H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.62 (m, 1H), 7.55 (dd, *J* = 8.4, 6.9 Hz, 2H), 7.42 (m, 1H), 4.90 (d, *J* = 6.6 Hz, 2H), 2.64 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.1, 164.7, 149.5, 148.5, 142.6, 141.0, 139.7, 137.5, 137.0, 133.9, 133.5, 132.5, 129.9, 129.7, 127.7, 126.5, 122.5, 40.5, 26.9; FT-IR: $\tilde{\nu}$ = 3060, 2925, 2855, 1679, 1600, 1519, 1447, 1393, 1358, 1308, 1255, 1154, 1095 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{21}H_{19}N_2O_4S$: 395.1060, found 395.1067.

Methyl 4-(phenylsulfonyl)-3-(picolinamidomethyl)benzoate (**3o**); amorphous solid, (58%, 23.8 mg), R_f = 0.34 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.56 (d, *J* = 4.6 Hz, 1H), 8.27 (s, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.19 – 8.07 (m, 2H), 7.99 – 7.87 (m, 2H), 7.83 (td, *J* = 7.6, 1.7 Hz, 1H), 7.62 (m, 1H), 7.53 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.42 (t, *J* = 6.0 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 2H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 165.5, 164.5, 149.6, 148.4, 142.9, 140.8, 138.3, 137.4, 135.3, 133.9, 133.1, 130.2, 129.7, 129.4, 127.7, 126.5, 122.5, 52.9, 40.6; FT-IR: $\tilde{\nu}$ = 3062, 2924, 2856, 1729, 1676, 1614, 1570, 1521, 1464, 1363, 1256 1197, 1156, 1060 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{21}H_{19}N_2O_5S$: 411.1009, found 411.1031.

N-(4,5-Dimethoxy-2-(phenylsulfonyl)benzyl)picolinamide (**3p**); amorphous solid, (89%, 36.8 mg); R_f = 0.34 (60% EA/PE); ^1H NMR (600 MHz, $CDCl_3$,) δ 8.67 (t, *J* = 6.5 Hz, 1H), 8.54 (d, *J* = 4.3 Hz, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 7.89 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.68 (s, 1H), 7.55 (m, 1H), 7.50 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.40 (m, 1H), 7.13 (s, 1H), 4.71 (d, *J* = 6.6 Hz, 2H), 3.96 (s, 3H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 153.4, 149.9, 148.44, 148.42,

142.6, 137.3, 133.2, 132.2, 130.2, 129.5, 127.0, 126.3, 122.4, 115.1, 112.6, 56.6, 56.5, 40.5; FT-IR: $\tilde{\nu}$ = 3057, 2926, 2856, 1662, 1578, 1486, 1452, 1368, 1302, 1264, 1152, 1096 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{21}H_{21}N_2O_5S$: 413.1166, found 413.1181.

N-(2,3-Dimethoxy-6-(phenylsulfonyl)benzyl)picolinamide (**3q**); amorphous solid, (83%, 34.3 mg); R_f = 0.30 (60% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.7 Hz, 1H), 8.47 (s, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.05 (d, *J* = 8.9 Hz, 1H), 7.92 – 7.83 (m, 2H), 7.79 (td, *J* = 7.7, 1.6 Hz, 1H), 7.50 – 7.39 (m, 3H), 7.36 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6, 157.6, 150.1, 149.2, 148.3, 142.2, 137.2, 133.1, 131.8, 131.4, 129.3, 127.22, 127.19, 126.1, 122.3, 111.0, 61.5, 56.2, 34.3; FT-IR: $\tilde{\nu}$ = 3061, 2924, 2852, 1676, 1576, 1478, 1447, 1356, 1309, 1244, 1156, 1086 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{21}H_{21}N_2O_5S$: 413.1166, found 413.1175.

N-((3-(Phenylsulfonyl)naphthalen-2-yl)methyl)picolinamide (**3r**); amorphous solid, (72%, 28.9 mg); R_f = 0.38 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 4.8 Hz, 2H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 8.08 (s, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.95 (d, *J* = 7.7 Hz, 2H), 7.90 – 7.74 (m, 2H), 7.67 – 7.55 (m, 3H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.40 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.91 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 149.9, 148.4, 141.6, 137.4, 136.2, 135.7, 133.5, 132.5, 132.3, 131.9, 131.6, 129.7, 129.6, 129.3, 128.0, 127.8, 127.5, 126.3, 122.4, 40.8; FT-IR: $\tilde{\nu}$ = 3059, 2923, 2853, 1673, 1590, 1519, 1473, 1446, 1364, 1306, 1220, 1153, 1087 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{23}H_{19}N_2O_3S$: 403.1111, found 403.1119.

(*R*)-*N*-(1-(2-(Phenylsulfonyl)phenyl)ethyl)picolinamide (**3s**); amorphous solid, (60%, 21.9 mg); R_f = 0.40 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.9 Hz, 1H), 8.32 (d, *J* = 6.7 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 4.4 Hz, 3H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.52 – 7.36 (m, 5H), 5.98 (m, 1H), 1.58 (d, *J* = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.3, 149.8, 148.1, 144.7, 142.0, 138.2, 137.4, 134.3, 133.2, 130.4, 129.2, 127.9, 127.7, 127.5, 126.3, 122.3, 46.3, 23.8; FT-IR: $\tilde{\nu}$ = 3065, 2923, 2853, 1673, 1570, 1510, 1447, 1307, 1299, 1153, 1087 cm^{-1}. HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_3S$: 367.1111, found 367.1120.

N-((3-(Phenylsulfonyl)furan-2-yl)methyl)picolinamide (**3t**); amorphous solid, (79%, 27.1 mg); R_f = 0.38 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 8.19 (d, *J* = 7.8 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.46 (td, *J* = 8.3, 7.8, 5.8 Hz, 3H), 7.34 (d, *J* = 1.9 Hz, 1H), 6.59 (d, *J* = 1.9 Hz, 1H), 5.00 (d, *J* = 6.4 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.5, 155.3, 149.4, 148.3, 142.7, 141.9, 137.5, 133.6, 129.5, 127.3, 126.6, 124.6, 122.6, 110.3, 35.1; FT-IR: $\tilde{\nu}$ = 3065, 2923, 2853, 1674, 1571, 1516, 1447, 1308, 1216, 1146, 1074 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{17}H_{15}N_2O_4S$: 343.0747, found 343.0754.

N-((3-(Phenylsulfonyl)thiophen-2-yl)methyl)picolinamide (**3u**); amorphous solid, (86%, 30.8 mg); R_f = 0.32 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.57 (d, *J* = 4.7 Hz, 1H), 8.17 (d, *J* = 7.7 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 2H), 7.84 (t, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.43 (dd, *J* = 7.4, 4.9 Hz, 1H), 7.32 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 5.4 Hz, 1H), 5.07 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.5, 149.4, 148.4, 147.5, 142.0, 137.5, 136.6, 133.5, 129.5, 128.2, 127.2, 126.6, 125.1, 122.5, 36.1; FT-IR: $\tilde{\nu}$ = 3061, 2924, 2854, 1672, 1570, 1516, 1446, 1362, 1307, 1218, 1157, 1081 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{17}H_{15}N_2O_3S_2$: 359.0519, found 359.0520.

N-((1-Methyl-6-(phenylsulfonyl)-1*H*-indol-5-yl)methyl)picolinamide (**3v**); brown solid, (78%, 31.6 mg); R_f = 0.36 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (t, *J* = 6.4 Hz, 1H), 8.52 (d, *J* = 4.8 Hz, 1H), 8.34 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.96 – 7.84 (m, 3H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.48 (dt, *J* = 15.6, 7.5 Hz, 3H), 7.35 (m, 1H), 7.27 (s, 1H), 6.51 (d, *J* = 3.0

Hz, 1H), 4.81 (d, *J* = 6.6 Hz, 2H), 3.91 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.2, 150.2, 148.3, 142.8, 137.2, 135.0, 133.6, 132.9, 132.7, 131.1, 129.3, 127.8, 127.1, 126.1, 125.0, 122.3, 112.9, 102.1, 41.0, 33.5; FT-IR: $\tilde{\nu}$ = 3061, 2923, 2858, 1670, 1570, 1517, 1446, 1389, 1303, 1252, 1150, 1085 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{22}H_{19}N_3O_3S$: 406.1220, found 406.1230.

N-(2-Tosylbenzyl)picolinamide (**4a**); amorphous solid, (62%, 22.7 mg); R_f = 0.34 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (t, *J* = 6.6 Hz, 1H), 8.56 (dt, *J* = 4.7, 1.2 Hz, 1H), 8.16 – 8.13 (m, 2H), 7.88 – 7.77 (m, 3H), 7.65 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.5 Hz, 1H), 7.46 (td, *J* = 7.7, 1.4 Hz, 1H), 7.41 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.84 (d, *J* = 6.6 Hz, 2H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.5, 149.9, 148.4, 144.5, 139.4, 138.7, 137.8, 137.3, 134.2, 132.3, 130.1, 129.9, 128.4, 127.6, 126.3, 122.4, 40.6, 21.7; FT-IR: $\tilde{\nu}$ = 3017, 2923, 2853, 1671, 1592, 1516, 1466, 1435, 1361, 1303, 1245, 1152, 1092 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_3S$: 367.1111, found 367.1123.

N-(2-(4-Methoxyphenylsulfonyl)benzyl)picolinamide (**4b**); amorphous solid, (65%, 24.8 mg); R_f = 0.30 (40% EA/PE) ^1H NMR (600 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.55 (d, *J* = 5.3 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 1H), 8.11 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.54 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48 – 7.36 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.86 (d, *J* = 6.6 Hz, 2H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 163.6, 149.8, 148.4, 139.9, 137.6, 137.5, 134.0, 133.0, 132.3, 129.9, 129.7, 128.4, 126.4, 122.5, 114.8, 55.8, 40.6; FT-IR: $\tilde{\nu}$ = 3062, 2923, 2851, 1671, 1593, 1518, 1484, 1435, 1361, 1297, 1261, 1149, 1093 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_4S$: 383.1060, found 383.1068.

N-(2-(4-*tert*-Butylphenylsulfonyl)benzyl)picolinamide (**4c**); amorphous solid, (66%, 26.9 mg); R_f = 0.42 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.79 (t, *J* = 6.7 Hz, 1H), 8.57 (d, *J* = 4.9 Hz, 1H), 8.16 (dd, *J* = 8.0, 3.0 Hz, 2H), 7.94 – 7.78 (m, 3H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.60 – 7.44 (m, 4H), 7.41 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.86 (d, *J* = 6.6 Hz, 2H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.5, 157.5, 149.8, 148.4, 139.4, 138.5, 137.8, 137.4, 134.2, 132.4, 130.0, 128.4, 127.4, 126.6, 126.3, 122.5, 40.7, 35.4, 31.2; FT-IR: $\tilde{\nu}$ = 3062, 2961, 2853, 1675, 1593, 1518, 1465, 1399, 1308, 1239, 1198, 1157, 1088 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{23}H_{25}N_2O_3S$: 409.1580, found 409.1586.

N-(2-(*m*-Tolylsulfonyl)benzyl)picolinamide (**4d**); amorphous solid, (60%, 21.9 mg); R_f = 0.34 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.55 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 7.7 Hz, 2H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.71 (s, 2H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.44 – 7.35 (m, 3H), 4.84 (d, *J* = 6.5 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 149.8, 148.4, 141.5, 139.9, 139.1, 137.9, 137.4, 134.4, 134.3, 132.4, 130.0, 129.4, 128.4, 127.8, 126.3, 124.7, 122.4, 40.6, 21.5; FT-IR: $\tilde{\nu}$ = 3062, 2925, 2853, 1674, 1570, 1519, 1465, 1435, 1361, 1303, 1220, 1152, 1089 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_3S$: 367.1111, found 367.1131.

N-(2-(3-Methoxyphenylsulfonyl)benzyl)picolinamide (**4e**); amorphous solid, (66%, 25.2 mg); R_f = 0.28 (40% EA/PE) ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.55 (d, *J* = 4.6 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 2H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.53 – 7.32 (m, 5H), 7.08 (m, 1H), 4.86 (d, *J* = 6.5 Hz, 2H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.4, 160.2, 149.8, 148.4, 142.8, 138.9, 138.0, 137.4, 134.4, 132.4, 130.6, 130.1, 128.4, 126.3, 122.4, 119.8, 119.7, 112.1, 55.9, 40.6; FT-IR: $\tilde{\nu}$ = 3063, 2924, 2853, 1673, 1593, 1519, 1479, 1435, 1362, 1307, 1249, 1152, 1093 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{20}H_{19}N_2O_4S$: 383.1060, found 383.1072.

N-(2-(4-Bromophenylsulfonyl)benzyl)picolinamide (**4f**); amorphous solid, (55%, 23.9 mg), R_f = 0.38 (40% EA/PE) ^1H NMR (600 MHz, $CDCl_3$) δ 8.63 (t, *J* = 6.5 Hz, 1H), 8.56 (d, *J* = 4.7 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 2H), 7.83 (td, *J* = 7.7, 1.7 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.7 Hz,

1H), 7.42 (dd, *J* = 7.5, 4.7 Hz, 1H), 4.85 (d, *J* = 6.5 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 164.5, 149.7, 148.5, 140.8, 138.5, 138.0, 137.5, 134.6, 132.9, 132.5, 130.2, 129.0, 128.8, 128.6, 126.5, 122.4, 40.7; FT-IR: $\tilde{\nu}$ = 3062, 2924, 2854, 1674, 1570, 1519, 1465, 1386, 1355, 1307, 1156, 1092 cm^{-1} ; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}{}^{81}BrN_2O_3S$: 433.0040, found 433.0012.

N-(2-(4-Fluorophenylsulfonyl)benzyl)picolinamide (**4g**); gummy liquid, (49%, 18.2 mg); R_f = 0.30 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.55 (d, *J* = 3.9 Hz, 1H), 8.21 – 8.06 (m, 2H), 7.95 (dd, *J* = 8.6, 4.7 Hz, 2H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.49 (dd, *J* = 9.2, 6.1 Hz, 1H), 7.42 (dd, *J* = 7.6, 4.5 Hz, 1H), 7.19 (dd, *J* = 10.1, 6.7 Hz, 2H), 4.86 (d, *J* = 6.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) δ 165.6 (d, *J* = 256.4 Hz), 164.5, 149.7, 148.4, 138.8, 137.8, 137.7 (d, *J* = 3.2 Hz), 137.5, 134.5, 132.4, 130.4 (d, *J* = 9.6 Hz), 130.0, 128.5, 126.4, 122.4, 116.9 (d, *J* = 22.8 Hz), 42.3; ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.61; FT-IR: $\tilde{\nu}$ = 3065, 2923, 2853, 1674, 1590, 1520, 1465, 1405, 1362, 1292, 1238, 1152, 1063 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{19}H_{16}FN_2O_3S$: 371.0860, found 371.0870.

N-(2-(Naphthalen-2-ylsulfonyl)benzyl)picolinamide (**4h**); amorphous solid, (70%, 28.2 mg); R_f = 0.40 (40% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (t, *J* = 6.5 Hz, 1H), 8.59 (s, 1H), 8.43 (d, *J* = 4.7 Hz, 1H), 8.22 (dd, *J* = 7.9, 1.4 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.80– 7.76 (m, 2H), 7.72 – 7.55 (m, 4H), 7.50 (td, *J* = 7.7, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.3, 5.1 Hz, 1H), 4.89 (d, *J* = 6.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.4, 149.8, 148.3, 139.1, 138.5, 138.0, 137.3, 135.2, 134.4, 132.6, 132.3, 130.2, 130.0, 129.6, 129.4, 128.9, 128.5, 128.1, 127.9, 126.3, 122.5, 122.4, 40.7; FT-IR: $\tilde{\nu}$ = 3059, 2924, 2853, 1672, 1570, 1518, 1462, 1432, 1349, 1307, 1222, 1154, 1077 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{23}H_{19}N_2O_3S$: 403.1111, 403.1105.

N-((3-(Phenylsulfonyl)biphenyl-2-yl)methyl)picolinamide (**5**); amorphous solid, (63%, 26.9 mg); R_f = 0.42 (60% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 4.7 Hz, 1H), 8.34 (m, 1H), 8.25 (s, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.91 (d, *J* = 7.1 Hz, 2H), 7.78 (t, *J* = 7.7 Hz, 1H), 7.65 – 7.50 (m, 2H), 7.44 (d, *J* = 6.3 Hz, 3H), 7.40 – 7.30 (m, 4H), 7.21 (d, *J* = 6.5 Hz, 2H), 4.65 (d, *J* = 5.1 Hz, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.1, 149.9, 148.2, 146.9, 141.6, 141.1, 139.2, 137.2, 136.4, 134.5, 133.3, 129.7, 129.4, 129.1, 128.4, 128.2, 128.1, 127.6, 126.1, 122.3, 38.1; FT-IR: $\tilde{\nu}$ = 3065, 2922, 2852, 1716, 1652, 1588, 1447, 1368, 1308, 1252, 1209, 1155, 1092 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{25}H_{21}N_2O_3S$: 429.1267, found 429.1273.

3-(Phenylsulfonyl)-2-((pyridin-2-ylmethylamino)methyl)phenyl acetate (**6**); colorless oil, (66%, 26.2 mg); R_f = 0.36 (60% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 5.1 Hz, 2H), 8.21 – 8.03 (m, 2H), 7.93 (d, *J* = 8.0 Hz, 2H).7.80 (t, *J* = 7.8 Hz, 1H), 7.68 – 7.46 (m, 4H), 7.37 (d, *J* = 7.3 Hz, 2H), 4.82 (d, *J* = 6.1 Hz, 2H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 169.5, 163.9, 151.2, 150.2, 148.4, 142.0, 141.6, 137.2, 133.7, 130.2, 129.7, 129.2, 129.1, 127.7, 127.6, 126.1, 122.3, 34.0, 21.1; FT-IR: $\tilde{\nu}$ = 3062, 2852, 1771, 1678, 1591, 1519, 1464, 1368, 1188, 1250, 1160, 1085 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{21}H_{19}N_2O_5S$: 411.1009, found 411.1011.

(*Z*)-Ethyl 3-hydroxy-2-(3-(phenylsulfonyl)-2-((pyridin-2-ylmethylamino)methyl)phenyl)but-2-enoate (**7**); green oil, (68%, 32.6 mg); R_f = 0.26 (60% EA/PE); ^1H NMR (400 MHz, $CDCl_3$) δ 12.12 (s, 1H), 8.44 (d, *J* = 4.6 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.59 (dt, *J* = 9.1, 4.4 Hz, 2H), 7.55 – 7.42 (m, 4H). 7.25 (d, *J* = 6.9 Hz, 1H), 5.26 (d, *J* = 15.1 Hz, 1H), 5.10 (d, *J* = 15.1 Hz, 1H), 4.21– 4.08 (m, 2H), 1.54 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.1, 170.8, 170.4, 154.2, 148.5, 141.9, 139.1, 137.3, 136.5, 133.6, 133.4, 133.0, 129.5, 129.4, 128.0, 127.2, 124.5, 122.5, 108.7, 61.1, 48.3, 18.4, 14.3; FT-IR: $\tilde{\nu}$ = 3065, 2923, 2852, 1735, 1657, 1561, 1446, 1344, 1308, 1252, 1219, 1156, 1092 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{25}H_{25}N_2O_6S$: 481.1428; found 481.1408.

(*E*)-Methyl 2-(7-*oxo*-6-(2-(phenylsulfonyl)benzyl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyridin-5-ylidene)acetate (**8**); green oil, (75%, 32.6 mg); R_f = 0.30 (60% EA/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (d, *J* = 8.1 Hz, 1H), 8.87 (d, *J* = 4.6 Hz, 1H), 8.26 (m, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.66 (m, 1H), 7.62 – 7.53 (m, 3H), 7.53 – 7.47 (m, 2H), 7.03 (d, *J* = 3.3 Hz, 1H), 5.66 (s, 1H), 5.34 (s, 2H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 165.4, 153.2, 148.3, 144.6, 140.9, 138.2, 136.4, 134.7, 134.5, 133.9, 130.1, 129.8, 128.5, 127.7, 127.6, 127.1, 102.4, 52.0, 40.2; FT-IR: $\tilde{\nu}$ = 3067, 2924, 2853, 1738, 1716, 1634, 1592, 1479, 1446, 1403, 1320, 1197, 1158, 1090 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{23}H_{19}N_2O_5S$: 435.1009, found 435.1012.

(2-(Phenylsulfonyl)phenyl)methanamine (**9**); yellow oil, (80%, 19.8 mg); R_f = 0.30 (5% MeOH/DCM); ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.6 Hz, 2H), 7.73 (m, 3H), 7.64 (t, *J* = 7.7 Hz, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 3.99 (s, 2H), 1.90 (s, 2H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d_6) δ 140.9, 137.7, 134.3, 133.8, 130.3, 129.8, 129.2, 128.1, 127.1, 41.2; FT-IR: $\tilde{\nu}$ = 3414, 1652, 1022, 995, 824, 761 cm^{-1}; HRMS: calculated for $[M+H]^+$ $C_{13}H_{14}NO_2S$: 248.0740, found 248.0733.

2,6-di-*tert*-Butyl-4-(phenylsulfonylmethyl)phenol (**11**); red solid, (80%, 28.9 mg); R_f = 0.32 (50% EA/PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.9 Hz, 3H), 7.42 (td, *J* = 7.8, 1.6 Hz, 2H), 6.75 (s, 2H), 5.26 (s, 1H), 4.22 (s, 2H), 1.31 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.4, 138.0, 136.2, 133.5, 129.0, 128.8, 127.8, 118.9, 63.3, 34.3, 30.2.; FT-IR: $\tilde{\nu}$ = 3662, 2956, 2871, 1718, 1585, 1433, 1360, 1315, 1225, 1085 cm^{-1}; HRMS: calculated for $[M+Na]^+$ $C_{21}H_{28}NaO_3S$: 383.1651, found 383.1666.

ASSOCIATED CONTENT

Supporting information:

Procedures along with results from optimization, control, and deuteration experiments. Crystallographic data and NMR spectra. This material is available free of charge via the Internet at **http://pubs.acs.org**.

AUTHER INFORMATION

*E-mail: **rsamanta@chem.iitkgp.ac.in**

Notes:

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support by the CSIR, India [02(0323)/17/EMR-II] is gratefully acknowledged. Authors thank DST, India (SR/FST/CSII-026/2013) for 500 MHz NMR facility, CRF(IIT Kharagpur) for the analytical facility and IIT Kharagpur for fellowship (UK). We sincerely thank Prof. S. Nanda, IIT Kharagpur for HPLC data.

REFERENCES

(1) (a) Shcroft, C. P.; Hellier, P.; Pettman, A.; Wakinson, S. Second-generation process research towards eletriptan: A Fischer Indole Approach. *Org. Process Res. Dev.* **2011**, *15*, 98. (b) Madasu, S. B.; Vekariya, N. A.; Hari Kiran, M. N. V. D.; Gupta, B.; Islam, A.; Douglas, P. S.; Babu, K. R. Synthesis of compounds related to the anti-migraine drug eletriptan hydrobromide. *Beilstein J. Org. Chem.* **2012**, *8*, 1400. (c) Patai, S.; Rappoport, Z.; Stirling, C. J. M. *The Chemistry of Sulfones and Sulfoxides*, Wiley, New York, **1988**. (d) Acton, Q. A. *Sulfones – Advances in Research and Application*, Scholarly Editions, Atlanta, **2013**.

(2) For reviews, see: (a) El-Awa, A.; Noshi, M. N.; du Jourdin, X. M.; Fuchs, P. L. Evolving organic synthesis fostered by the pluripotent phenylsulfone moiety. *Chem. Rev.* **2009**, *109*, 2315. (b) Plesniak, K.; Zarecki, A.; Wicha, J. The Smiles rearrangement and the Julia-Kocienski olefination reaction. *Top. Curr. Chem.* **2007**, *275*, 163. (c) Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp, D. Stereoselective and enantioselective synthesis of five-membered rings via conjugate additions of allylsulfone carbanions. *Pure Appl. Chem.* **2000**, *72*, 1671. (d) Simpkins, N. S. *Sulfones in Organic Synthesis;* Pergamon Press: New York, 1993.

(3) Recent reviews: (a) Liu, N.-W.; Liang, S.; Manolikakes, G. Recent advances in the synthesis of sulfones. *Synthesis* **2016**, *48*, 1939. Few representative examples: (b) Vedovato, V.; Talbot, E. P. A.; Willis, M. C. Copper-catalyzed synthesis of activated sulfonate esters from boronic acids, DABSO, and pentafluorophenol. *Org. Lett.* **2018**, *17*, 5493. (c) Yuan, Z.; Wang, H.-Y.; Mu, X.; Chen, P.; Guo, Y.-L.; Liu, G. Highly selective Pd-catalyzed intermolecular fluorosulfonylation of styrenes. *J. Am. Chem. Soc.* **2015**, *137*, 2468. (d) Tang, X.; Huang, L.; Xu, Y.; Yang, J.; Wu, W.; Jiang, H. Copper-catalyzed coupling of oxime acetates with sodium sulfinates: An efficient synthesis of sulfone derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 4205. (e) Xi, Y.; Dong, B.; McClain, E. J.; Wang, Q.; Gregg, T. L.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. Gold-catalyzed intermolecular C–S bond formation: efficient synthesis of α-substituted vinyl sulfones. *Angew. Chem., Int. Ed.* **2014**, *53*, 4657. (f) Handa, S.; Fennewald, J. C.; Lipshutz, B. H. Aerobic oxidation in nanomicelles of aryl alkynes, in water at room temperature. *Angew. Chem., Int. Ed.* **2014**, *53*, 3432. (g) Lu, Q.; Zhang, J.; Zhao, G.; Qi, Y.; Wang, H.; Lei, A. Dioxygen-triggered oxidative radical reaction: Direct aerobic difunctionalization of terminal alkynes toward β-keto sulfones. *J. Am. Chem. Soc.* **2013**, *135*, 11481. (h) Liu, Q.; Zhang, J.; Wei, F.; Qi, Y.; Wang, H.; Liu, Z.; Lei, A. Aerobic oxysulfonylation of alkenes leading to secondary and tertiary β-hydroxysulfones. *Angew. Chem., Int. Ed.* **2013**, *52*, 7156. (i) Wu, X.-S.; Chen, Y.; Li, M.-B.; Zhou, M.-G.; Tian, S.-K. Direct substitution of primary allylic amines with sulfinate salts. *J. Am. Chem. Soc.* **2012**, *134*, 14694. (j) Pal, T. K.; Dey, S.; Pathak, T. A general route to mono- and disubstituted divinyl sulfones: Acyclic michael acceptors for the synthesis of polyfunctionalized cyclic sulfones. *J. Org. Chem.* **2011**, *76*, 3034.

(4) Recent reviews: (a) Shaaban, S.; Liang, S.; Liu, N.-W.; Manolikakes, G. Synthesis of sulfones via selective C–H-functionalization. *Org. Biomol. Chem.* **2017**, *15*, 1947. (b) Shen, C.; Zhang, P.; Sun, Q.; Bai, S.; Hor, T. S. A.; Liu, X. Recent advances in C–S bond formation via C–H bond functionalization and decarboxylation. *Chem. Soc. Rev.* **2015**, *44*, 291. Representative examples: (c) Zhao, X.; Dong, V. M. Carbon–Sulfur reductive elimination from palladium (IV) sulfinate complexes. *Angew. Chem., Int. Ed.* **2011**, *50*, 932. (d) Li, X.; Xu, Y.; Wu, W.; Jiang, C.; Qi, C.; Jiang, H. Copper-catalyzed aerobic oxidative N–S bond functionalization for C–S bond formation: Regio- and stereoselective synthesis of sulfones and thioethers. *Chem. -Eur. J.* **2014**, *20*, 7911. (e) Wan, Y.; Zhang, J.; Chen, Y.; Kong, L.; Luo, F.; Zhu, G. Palladium-catalyzed tandem cyclization/sulfonylation of homoallenyl amides with sodium sulfinates. *Org. Biomol. Chem.* **2017**, *15*, 7204.

(5) Zhao, X.; Dimitrijević, E.; and Dong, V. M. Palladium-catalyzed C–H bond functionalization with arylsulfonyl chlorides. *J. Am. Chem. Soc.* **2009**, *131*, 3466.

(6) (a) Xu, Y.-H.; Wang, M.; Lu, P.; Loh, T.-P. Palladium-catalyzed alkenyl C–H bond sulfonylation reaction using organosulfonyl chlorides. *Tetrahedron* **2013**, *69*, 4403. (b) Xu, Y.; Liu, P.; Li, S.-L.; Sun, P. Palladium-catalyzed *ortho*-sulfonylation of 2-Aryloxypyridines and subsequent formation of *ortho*-sulfonylated phenols. *J. Org. Chem.* **2015**, *80*, 1269. (d) Zhang, D.; Cui, X.; Zhang, Q.; Wu, Y. Pd-catalyzed direct C–H bond sulfonylation of azobenzenes with arylsulfonyl chlorides. *J. Org. Chem.* **2015**, *80*, 1517. (e) Rao, W.-H.; Zhan, B.-B.; Chen, K.; Ling, P.-X.; Zhang, Z.-Z.; Shi, B.-F. Pd(II)-catalyzed direct sulfonylation of unactivated C(sp^3)–H bonds with sodium sulfinates. *Org. Lett.* **2015**, *17*, 3552. (f) Xia, H.; An, Y.; Zeng, X.; Wu, J. Palladium-catalyzed direct sulfonylation of C–H bonds with the insertion of sulfur dioxide. *Chem. Commun.* **2017**, *53*, 12548. (g) Liu, T.; Zhou, W.; Wu, J. Palladium-catalyzed direct C–H functionalization of indoles with the insertion of sulfur dioxide: Synthesis of 2-sulfonated indoles. *Org. Lett.* **2017**, *19*, 6638. (h) Bai, P.; Sun, S.; Li, Z.; Qiao, H.; Su, X.; Yang, F.; Wu, Y.; Wu, Y. Ru/Cu Photoredox or Cu/Ag catalyzed C4–H sulfonylation of 1‑Naphthylamides at room temperature. *J. Org. Chem.* **2017**, *82*, 12119.

(7) Wang, F.; Yu, X.; Qi, Z.; Li, X. Rhodium-catalyzed C–S and C–N functionalization of arenes: Combination of C–H activation and hypervalent iodine chemistry. *Chem. -Eur. J.* **2016**, *22*, 511.

(8) (a) Saidi, O.; Marafie, J.; Ledger, A. E. W.; Liu, P. M.; Mahon, M. F.; Kociok-Köhn, G.; Whittlesey, M. K.; Frost, C. G. Ruthenium-catalyzed *meta* sulfonation of 2-Phenylpyridines. *J. Am. Chem. Soc.* **2011**, *133*, 19298. (b) Ramesh, B.; Jeganmohan, M. Ruthenium-catalyzed remote C–H sulfonylation of *N*-aryl-2-aminopyridines with aromatic sulfonyl chlorides. *Org. Lett.* **2017**, 19, 6000.

(9) Selected examples: (a) Wu, Z.; Song, H.; Cui, X.; Pi, C.; Du, W.; Wu, Y.; Sulfonylation of quinoline N-Oxides with aryl sulfonyl chlorides via copper-catalyzed C–H bonds activation. *Org. Lett.* **2013**, *15*, 1270. (b) Liang, H.-W.; Jiang, K.; Ding, W.; Yuan, Y.; Shuai, L.; Chen, Y. -C.; Wei, Y. Selective remote C–H sulfonylation of aminoquinolines with arylsulfonyl chlorides via copper catalysis. *Chem. Commun.* **2015**, *51*, 16928. (c) Liu, J.; Yu, L.; Zhuang, S.; Gui, Q.; Chen, X.; Wang, W.; Tan, Z. Copper-mediated *ortho* C–H sulfonylation of benzoic acid derivatives with sodium sulfinates. *Chem. Commun.* **2015**, *51*, 6418. (d) Rao, W.-H.; Shi, B.-F. Copper(II)-catalyzed direct sulfonylation of C(sp^2)–H bonds with sodium sulfinates. *Org. Lett.* **2015**, *17*, 2784. (e) Liang, S.; Liu, N.-W.; Manolikakes, G. Copper-mediated sulfonylation of aryl C(sp^2)–H bonds with sodium and lithium sulfinates. *Adv. Synth. Catal.* **2016**, *358*, 159. (f) Yang, Y.; Li, W.; Xia, C.; Ying, B.; Shen, C.; Zhang, P. Catalyst-controlled selectivity in C−S bond formation: Highly efficient synthesis of C2- and C3-sulfonylindoles. *ChemCatChem* **2016**, *8*, 304. (g) Wei, J.; Jiang, J.; Xiao, X.; Lin, D.; Deng, Y.; Ke, Z.; Jiang, H.; Zeng, W. Copper-catalyzed regioselective C–H sulfonylation of 8-aminoquinolines. *J. Org. Chem.* **2016**, *81*, 946. (h) Du, B.; Qian, P.; Wang, Y.; Mei, H.; Han, J.; Pan, Y. Cu-catalyzed deoxygenative C2-sulfonylation reaction of quinoline N-Oxides with sodium sulfinate. *Org. Lett.* **2016**, *18*, 4144. (i) Liang, S.; Bolte, M.; Manolikakes, G. Copper-catalyzed remote para-C−H functionalization of anilines with sodium and lithium sulfinates. *Chem. -Eur. J.* **2017**, *23*, 96.

(10) (a) Yokota, A.; Chatani, N. Ni(II)-catalyzed sulfonylation of *ortho* C–H bonds in aromatic amides utilizing an N,N-bidentate directing group. *Chem Lett.* **2015**, *44*, 902. (b) Reddy, V. P.; Qiu, R.; Iwasaki, T.; Kambe, N. Nickel-catalyzed synthesis of diarylsulfides and sulfones via C–H bond functionalization of arylamides. *Org. Biomol. Chem.* **2015**, *13*, 6803. (c) Liu, S.-L.; Li, X.-H.; Zhang, S.-S.; Hou, S.-K.; Yang, G.-C.; Gong, J.-F.; Song, M.-P. Nickel-catalyzed sulfonylation of C(sp^2)–H bonds with sodium sulfinates. *Adv. Synth. Catal.* **2017**, *359*, 2241.

(11) (a) Lazareva, A.; Daugulis, O. Direct palladium-catalyzed *ortho*-arylation of benzylamines. *Org. Lett.* **2006**, *8*, 5211. (b) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. Scope and limitations of auxiliary-assisted, palladium-catalyzed arylation and alkylation of sp^2 and sp^3 C–H bonds. *J. Org. Chem.* **2013**, *78*, 9689.

(12) (a) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. Indirect *ortho* functionalization of substituted toluenes through *ortho* olefination of N,N-Dimethylbenzylamines tuned by the acidity of reaction conditions. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (b) Zhao, Y.; He, G.; Nack, W. A. Chen, G. Palladium-catalyzed alkenylation and alkynylation of *ortho*-C(sp^2)–H bonds of benzylamine picolinamides. *Org. Lett.* **2012**, *14*, 2948.

(13) (a) Landge, V. G.; Midya, S. P.; Rana, J.; Shinde, D. R.; Balaraman, E. Expedient cobalt-catalyzed C–H alkynylation of (enantiopure) benzylamines. *Org. Lett.* **2016**, *18*, 5252. (b) Grigorgeva, L.; Daugulis, O. Cobalt-catalyzed, aminoquinoline-directed C(sp^2)–H Bond alkenylation by alkynes. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209. (c) Li, G.; Hu, J.; Zeng, R.; Shi, D. –Q.; Zhao, Y. Direct *ortho*-selective C–H functionalization of carboxybenzyl-protected arylalkylamines via Ir(III)-catalyzed C–H activation. *Org. Lett.* **2018**, *20*, 2454. (d) Martínez, Á. M.; Echavarren, J.; Alonso, I.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. Rh^{I}/Rh^{III} catalyst-controlled divergent aryl/heteroaryl C–H bond functionalization of picolinamides with alkynes. *Chem. Sci.* **2015**, *6*, 5802.

(14) (a) Zhao, Y.; Chen, G. Palladium-catalyzed alkylation of *ortho*-C(sp^2)–H bonds of benzylamide substrates with Alkyl Halides. *Org. Lett.* **2011**, *13*, 4850. (b) Shen, Z.; Cera, G.; Haven, T.; Ackermann, L. Tri-substituted triazole-enabled C–H activation of benzyl and aryl amines by iron catalysis. *Org. Lett.* **2017**, *19*, 3795.

(15) Miura, M.; Feng, C. -G.; Ma, S.; Yu, J. –Q. Pd(II)-catalyzed *ortho*-trifluoromethylation of benzylamines. *Org. Lett.* **2013**, *15*, 5258.

(16) (a) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. Preparation of benzolactams by $Pd(OAc)_2$-catalyzed direct aromatic carbonylation. *J. Am. Chem. Soc.* **2004**, *126*, 14342. (b) Zhang, C.; Ding, Y.; Gao, Y.; Li, S.; Li, G. Palladium-catalyzed direct C–H carbonylation of free primary benzylamines: A synthesis of benzolactams. *Org. Lett.* **2018**, *20*, 2595. (c) Wang, C.; Li Zhang, L.; Chen, C.; Han, J. Yao, Y.; Zhao, Y. Oxalyl amide assisted palladium-catalyzed synthesis of pyrrolidones via carbonylation of γ-C(sp^3)–H bonds of aliphatic amine substrates. *Chem. Sci.* **2015**, *6*, 4610. (d) Hernando, L.; Villalva, J.; Martínez, Á. M.; Alonso, I.; Rodríguez, N.; Arrayás, R. G.; Carretero, J. C. Palladium-catalyzed carbonylative cyclization of amines via γ-C(sp^3)–H activation: Late-stage diversification of amino acids and peptides. *ACS Catal.* **2016**, *6*, 6868.

(17) (a) Maity S.; Das, D.; Sarkar, S.; Samanta, R. Direct Pd(II)-catalyzed site-selective C5-arylation of 2-pyridone using aryl iodides.*Org. Lett.* **2018**, *20*, 5167. (b) Ghosh, B.; Biswas, A.; Chakraborty, S.; Samanta, R. Rh^{III}-catalyzed direct C8-arylation of quinoline N-Oxides using diazonaphthalen-2(1H)-ones: A practical approach towards 8-aza BINOL. *Chem Asian J* **2018**, *13*, 2388. (c) Das, D.; Samanta, R. Iridium(III)-catalyzed regiocontrolled direct amidation of isoquinolones and pyridones. *Adv. Synth. Catal.* **2018**, *360*, 379. (d) Maity S.; Karmakar, U.; Samanta R. Regiocontrolled direct C4 and C2-methyl thiolation of indoles under rhodium-catalyzed mild conditions. *Chem. Commun.* **2017**, *53*, 12197. (e) Karmakar, U.; Das, D.; Samanta, R. Iridium-catalysed cascade synthesis of Oxindoles using diazo compounds: A quick Entry to C-7-functionalized oxindoles. *Eur. J. Org. Chem.* **2017**, 2780. (f) Biswas, A.; Karmakar, U.; Nandi, S.; Samanta, R. Copper catalyzed direct, regioselective arylamination of N-Oxides: studies to access conjugated π-systems. *J. Org. Chem.* **2017**, *82*, 8933. (g) Biswas, A.; Karmakar, U.; Pal, A.; Samanta, R. Copper-catalyzed regioselective cascade alkylation and cyclocondensation of quinoline N-Oxides with diazo Esters: direct access to conjugated π-systems. *Chem. -Eur. J.* **2016**, *22*, 13826.

(18) Zaitsev, V. G.; Shabashov, D.; Dauguis, O. Highly Regioselective Arylation of sp^3 C–H Bonds Catalyzed by Palladium Acetate *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(19) (a) Li, L.; Brennessel, W. W.; Jones, W. D. An efficient low-temperature route to polycyclic isoquinoline salt synthesis via C–H activation with $[Cp^*MCl_2]_2$ (M = Rh, Ir). *J. Am. Chem. Soc.* **2008**, *130*, 12414. (b) Li, L.; Brennessel, W. W.; Jones, W. D. C–H activation of phenyl imines and 2-Phenylpyridines with $[Cp^*MCl_2]_2$ (M = Ir, Rh): regioselectivity, kinetics, and mechanism. *Organometallics* **2009**, *28*, 3492. (c) Ackermann, L. Carboxylate-assisted transition-metal-catalyzed C–H bond functionalizations: mechanism and scope. *Chem. Rev.* **2011**, *111*, 1315.

(20) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. Scope and limitations of auxiliary-assisted, palladium-catalyzed arylation and alkylation of sp^2 and sp^3 C–H bonds. *J. Org. Chem.* **2013**, *78*, 9689.

(21) He, G.; Lu, G.; Guo, Z.; Liu, P.; Chen, G. Benzazetidine synthesis via palladium-catalysed intramolecular C–H amination. *Nature Chem.* **2016**, *8*, 1131.

(22) Martínez, Á.M.; Rodríguez, N.; Arrayás, G. R.; Carretero, J. C. Synthesis of alkylidene pyrrolo[*3,4-b*]pyridin-7-one derivatives via Rh^{III}-catalyzed cascade oxidative alkenylation/annulation of picolinamides. *Chem. Commun.* **2014**, *50*, 6105.

(23) Buil, M. A.; Calbet, M.; Castillo, M.; Castro, J.; Esteve, C.; Ferrer, M.; Forns, P.; González, J.; López, S.; Roberts, R. S.; Sevilla, S.; Vidal, B.; Vidal, L.; Vilaseca, P. Structure-activity relationships (SAR) and structure-kinetic relationships (SKR) of sulphone-based CRTh2 antagonists. *Eur. J. Med. Chem.* **2016**, *113*, 102.

(24) Powers, D. C.; Ritter, T. Palladium (III) in synthesis and catalysis. *Top Organomet Chem.* **2011**, *503*, 129.

(25) (a) Aneja, B.; Irfan, M.; Kapil, Charu.; Jairajpuri, M. A.; Maguire, R.; Kavanagh, K.; M. Moshahid A. Rizvi, M. M. A.; Manzoor, N.; Azamb, A.; Abid, M. Effect of novel triazole–amino acid hybrids on growth and virulence of Candida species: in vitro and in vivo studies. *Org. Biomol. Chem.* **2016**, *14*, 10599. (b) Kirmse, W.; Kund, K. Carbenes and the oxygen-hydrogen bond: hydroxyalkyl-substituted arylcarbenes. *J. Org. Chem.* **1990**, *55*, 2325. (c) Schmidt, J.; Rotter, M.; Weiser, T; Wittmann, S.; Weizel, L.; Kaiser, A.;

Heering, J.; Goebel, T.; Angioni, C.; Wurglics, M.; Paulke‖, A.; Geisslinger, G.; Kahnt, A.; Steinhilber, D.; Proschak. E. A Dual Modulator of Farnesoid X Receptor and Soluble Epoxide Hydrolase to Counter Nonalcoholic Steatohepatitis. *J. Med. Chem.*, **2017**, *60*, 7703. (d) Jiang, L.; Yin, R.; Wang, X.; Dai, J.; Li, J.; Jiang T.; Yu, R. Design and synthesis of neolamellarin a derivatives targeting heat shock protein 90. *Eur. J. Med. Chem.* **2017**, *135*, 24. (e) Yang, F-L.; Zhu, X.; Rao, D-K.; Cao, X-N.; Li, K.; Xu, Y.; Hao, X-Q.; Song. M-P. Highly efficient synthesis of primary amides via aldoximes rearrangement in water under air atmosphere catalyzed by an ionic ruthenium pincer complex. *RSC Adv.* **2016**, *6*, 37093. (f) Su, B.; Deng, M.; Wang, Q. Sodium nitrite-catalyzed aerobic oxidative Csp^2-Csp^3 coupling: direct construction of the 4-Aryldihydroisoquinolinone moiety. *Adv. Synth. Catal.* **2014**, *356*, 977. (g) Komanoya, T.; Kinemura, T.; Kita, Y.; Kamata, K.; Hara; M. Electronic effect of ruthenium nanoparticles on efficient reductive amination of carbonyl compounds. *J. Am. Chem. Soc.* **2017**, *139*, 11493. (h) Miyazaki, D.; Nomura, K.; Yamashita, T.; Iwakura, I.; Ikeno, T.; Yamada, T. Enantioselective borodeuteride reduction of aldimines catalyzed by Cobalt complexes: Preparation of optically active deuterated primary amines. *Org. Lett.* **2003**, *5*, 3555. (i) Goszczycki, P.; Stadnicka, K.; Brela, M. Z.; Grolik, J.; Ostrowska, K. Synthesis, crystal structures, and optical properties of the p-p interacting pyrrolo[2,3-b]quinoxaline derivatives containing 2-thienyl substituent. *J. Mol. Struct.* **2017**, *1146*, 337. (j) Ayedi, M. A.; Bigot, Y. L.; Ammar, H.; Abid, S.; Gharbi, R. El.; Delmas, Michel. Synthesis of Primary Amines by One-Pot Reductive Amination of Aldehydes. *Synth. Commun.* **2013**, *43*, 2127. (k) Zhang, F-L.; Wang, Y-F.; Chiba, S. Orthogonal aerobic conversion of N-benzyl amidoximes to 1,2,4-oxadiazoles or quinazolinones. *Org. Biomol. Chem.* **2013**, *11*, 6003.

(26) Kuai, C.; Wang, L.; Li, B.; Yang, Z.; Cui, X. Cobalt-catalyzed selective synthesis of Isoquinolines using picolinamide as a traceless directing group. *Org. Lett.* **2017**, *19*, 2102.

(27) (a) Liu, L.; Chi, Y.; Jen,-Y. K. Copper-catalyzed additions of sulfonyl iodides to simple and cyclic alkenes. *J. Org. Chem.* **1980**, *45*, 406. (b) Liu, J.; Zhou, X.; Rao, H.; Xiao, F.; Li, C. J.; Deng, G. J. Direct synthesis of aryl ketones by palladium-catalyzed desulfinative addition of sodium sulfinates to nitriles. *Chem. Eur. J.* **2011**, *17*, 7996. (c) Meyer, A. U.; Straková, K.; Slanina, T.; König, B. Eosin Y (EY) photoredox-catalyzed sulfonylation of alkenes: scope and mechanism. *Chem. Eur. J.* **2016**, *22*, 8694. (d) Meyer, A. U.; Jäger, S.; Hari, D. P.; König, B. Visible Light-mediated metal-free synthesis of Vinyl sulfones from aryl sulfinates. *Adv. Synth. Catal.* **2015**, *357*, 2050. (e) Skillinghaug, B.; Rydfjord, J.; Odell, L. R. Synthesis of sodium aryl sulfinates from aryl bromides employing 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct (DABSO) as a bench-stable, gas-free alternative to SO_2. *Tetrahedron Lett.* **2016**, *57*, 533. (f) Ortgies, D. H.; Chen, F.; Forgione, P. Palladium and TEMPO as co-catalysts in a desulfinative homocoupling reaction. *Eur. J. Org. Chem.* **2014**, 3917. (g) Wu, W.; Yi, S.; Huang, W.; Luo, D.; Jiang, H. Ag-Catalyzed Oxidative Cyclization Reaction of 1,6-Enynes and Sodium Sulfinate: Access to Sulfonylated Benzofurans. *Org. Lett.* **2017**, *19*, 2825.