Nickel-Catalyzed Kumada Cross-Coupling Reactions of Benzylic Sulfonamides

Kirsten A. Hewitt, Claire A. Herbert, Alissa C. Matus and Elizabeth R. Jarvo *

Department of Chemistry, University of California, Irvine, CA 92697-2025, USA; khewitt1@uci.edu (K.A.H.); caherber@uci.edu (C.A.H.); matusa@uci.edu (A.C.M.)
* Correspondence: erjarvo@uci.edu

Abstract: Herein, we report a Kumada cross-coupling reaction of benzylic sulfonamides. The scope of the transformation includes acyclic and cyclic sulfonamide precursors that cleanly produce highly substituted acyclic fragments. Preliminary data are consistent with a stereospecific mechanism that allows for a diastereoselective reaction.

Keywords: cross-coupling reactions; sulfonamides; nickel; catalysis; hydrocarbons

1. Introduction

Transition-metal catalyzed cross-coupling (XC) reactions have transformed modern synthetic organic chemistry by creating an arsenal of carbon–carbon bond forming reactions [1–6]. Nickel is a cost-effective metal that is capable of activating challenging electrophiles such as amine derivatives [7–10]. Intense research efforts have been employed in the development of nickel-catalyzed XC reactions of sluggish electrophiles [11–13]. However, the XC reaction of alkyl amine derivatives has remained a significant challenge [14–18]. Historically, in order to facilitate nickel-catalyzed reactions, activation of these carbon–nitrogen bonds has been achieved via incorporation into strained aziridine rings or transformation to ammonium salts [19].

Ring-strain-promoted XC of aziridines has been accomplished [20]. Early stoichiometric work by Hillhouse established that aziridines undergo facile oxidative addition with nickel complexes [21]. Catalytic Negishi reactions of sulfonylaziridines have subsequently been established. The Doyle laboratory reported a regioselective Negishi XC reaction of styrenyl aziridines with alkylzinc reagents with substitution at the benzylic position (Scheme 1a) [22,23]. Key to their success was the use of an electron deficient fumarate ligand. Shortly thereafter, the Doyle and Jamison groups independently described a regioselective Negishi XC reaction of alkyl aziridines with alkylzinc reagents to forge the desired carbon–carbon bond (Scheme 1b,c) [24,25]. The differing regioselectivity of these reactions can be explained by comparing the oxidative addition events of the C–N bonds.

Styrenyl aziridines preferentially undergo oxidative addition at the benzylic center to afford a η3-benzylnickel complex. In contrast, alkyl aziridines, which do not contain an aromatic ring to direct the nickel complex, preferentially undergo oxidative addition at the less hindered position [21]. These reports demonstrate the ability to activate the C–N bond in strained rings.

Development of XC reactions of acyclic benzylamine derivatives has relied upon formation of highly reactive electrophiles (i.e., charged ammonium salts) [26,27]. For example, the Watson laboratory demonstrated that benzyltrimethylammonium salts are competent electrophiles in Suzuki-Miyaura XC reactions with aryl and vinylboronic acids (Scheme 2a) [28,29]. Similarly, the Wang laboratory disclosed the XC reaction of benzyltrimethylammonium salts with organoaluminum reagents to forge the desired carbon–carbon bond (Scheme 2b) [30].
The use of Katritzky salts to activate amines has proven to be sufficient for activation of benzylic and alkyl amines for Suzuki-Miyaura and Negishi XC reactions. Previously, it has been observed that Katritzky salts participate in Sn2, radical, and Minisci-type reactions, and in recent years, many transition-metal catalyzed reactions have been developed [31–40]. The Watson laboratory hypothesized that these air and moisture stable salts would be suitable electrophiles in a XC reaction [41]. To test their hypothesis, primary amines were converted to Katritzky salts via a condensation reaction with 2,4,6-triphenylpyrylium tetrafluoroborate and the corresponding salts were subjected to Suzuki-Miyaura XC reactions with aryl boronic acids. The desired cross-coupled products were obtained in good yields (Scheme 3a) [42]. This strategy was amenable to the coupling of primary benzylic Katritzky salts as well (Scheme 3b) [43]. Additionally, vinyl boranes and alkylborane reagents, generated in situ by hydroboration of alkenes, participated in XC with Katritzky salts (Scheme 3c) [46]. This strategy has been extended beyond Suzuki-Miyaura reactions to include Negishi XC reactions with alkylzinc reagents (Scheme 3e) [46].

These methods establish strain- and charge-based strategies to activate amines for use as the electrophilic partner in XC reactions; however, the requirement for aziridines or functionalization as highly reactive ammonium salts remains a major limitation in broad application of these methods. In this manuscript, we report the first nickel-catalyzed Kumada XC reaction of simple benzylic sulfonamides with methylmagnesium iodide (Scheme 4). Previously, the Jarvo laboratory disclosed the Kumada XC reaction of benzylic ethers which proceeded in excellent yields, and enantio- and diastereoselectivity [12,47,48]. Building on this work, we aimed to develop an analogous reaction that employed benzylic sulfonamides. Ethers and sulfonamides have similar leaving group abilities, as the conjugate bases have similar pK_a’s, and we hypothesized sulfonamides would behave similarly to ethers in a XC reaction [49,50]. In addition, these moieties are appealing because they are common functional groups in synthesis. Furthermore, we demonstrate that sulfonamides undergo stereospecific XC reactions, in contrast to the stereoablative reactivity typically observed with styrenyl aziridines and Katritzky salts [22,36–40,51–54]. This stereospecific

Scheme 1. Cross-Coupling (XC) Reactions of Aziridines.

Scheme 2. XC Reactions of Trimethylammonium salts. Nap = Naphthyl.
manifold allows for rapid diastereoselective construction of acyclic fragments bearing 1,3-substitution [55,56].

![Scheme 3. XC Reactions of Katritzky Salts.](image)

These methods establish strain- and charge-based strategies to activate amines for manifold allows for rapid diastereoselective construction of acyclic fragments bearing 1,3-substitution [55,56].

![Scheme 3. XC Reactions of Katritzky Salts.](image)

This Work

![Scheme 4. Kumada XC Reactions of Benzylic Sulfonamides.](image)

2. Results and Discussion

We began our investigation into the Kumada XC reaction with benzylic sulfonamide 1, which was synthesized in three steps from the commercially available aldehyde (See Experimental Section for substrate synthesis). Previously, Kumada XC reactions of benzylic ethers employed Ni(cod)₂ and racemic BINAP as the optimal reaction conditions [12,47,48]. Under these conditions, we were excited to observe 25% yield of the desired cross-coupled product 2 (Table 1, entry 1). Increasing the catalyst loading to 15 mol % improved the yield of the reaction (entry 2). However, it also increased the yield of the undesired styrene product 3 arising from β-hydride elimination. In an effort to improve the ratio between desired product 2 and styrene product 3, we investigated a series of bidentate phosphine, NHC, and pyridine ligands. DPEPhos improved the yield of 2 and decreased the amount of styrene 3 (entry 3). However, all other ligands evaluated did not improve the yield of 2 (entries 4–7).
Table 1. Optimization of Kumada XC Reaction of Benzylic Sulfonamides.

| Entry | Nickel Catalyst | Ligand       | Yield 2 (%) | Yield 3 (%) | RSM 1 (%) |
|-------|-----------------|--------------|-------------|-------------|-----------|
| 1     | Ni(cod)₂        | rac-BINAP    | 25          | 10          | 19        |
| 2     | Ni(cod)₂        | rac-BINAP    | 34          | 30          | 7         |
| 3     | Ni(cod)₂        | DPEPhos      | 42          | 20          | 0         |
| 4     | Ni(cod)₂        | XantPhos     | 0           | <5          | 37        |
| 5     | Ni(cod)₂        | dppe         | 0           | <5          | 65        |
| 6     | Ni(cod)₂        | SiMes-BF₄    | 12          | 0           | 86        |
| 7     | Ni(cod)₂        | BPhen        | 0           | 0           | 61        |
| 8     | (R-BINAP)NiCl₂  | –            | 54          | 40          | 0         |

1 Yield determined by ³¹H NMR based on comparison to PhTMS as internal standard. 2 5 mol % Ni(cod)₂.

We next investigated an alternative precatalyst. Previously, the Jarvo laboratory reported the cross-electrophile coupling (XEC) reaction of benzylic and allylic sulfonamides which employed a BINAP-ligated nickel (II) precatalyst [50,57,58]. Utilizing these conditions, with 15 mol % of catalyst, we were delighted to observe the desired product in 54% yield and 40% yield of styrene 3 (entry 8). We elected to proceed with the nickel (II) precatalyst as it provided the desired product in the highest yield.

With optimized conditions in hand, we evaluated the scope of the Kumada XC reaction (Scheme 5). Naphthyl substrates were well tolerated under the standard reaction conditions and product 4 was observed in 84% yield. Notably, products such as 5 and 6 with branching at the β-position provided good yields of cross-coupled products with lesser amounts of styrenes formed from β-hydride elimination (20–30%) when compared to product 2. We hypothesized that this increase in steric bulk destabilized the conformation necessary for β-hydride elimination to proceed.

Scheme 5. Scope of the Kumada XC Reaction of Acyclic Sulfonamides. ¹ Yield determined by ³¹H NMR based on comparison to PhTMS as internal standard. ² Isolated yield.

We also sought to evaluate a series of arylpiperidines, with the expectation that a stereospecific XC reaction at the benzylic position would provide synthetic access to highly substituted acyclic fragments. Furthermore, products would bear a pendant sulfonamide moiety, available for subsequent functionalization [50]. Rapid synthesis of the requisite cyclic sulfonamides was achieved by hetero Diels-Alder (HDA) cycloadditions or azapring reactions [59–61]. For substrates with alkyl substituents in the 4-position, [4+2] HDA reactions provided the requisite starting materials (Scheme 6a). For substrates
bearing ether groups in the 4-position, an aza-Prins reaction provided the requisite 2-aryl-4-hydroxypiperidine that could be subsequently methylated or benzylated. (Scheme 6b).

a. Hetero Diels-Alder Reaction

\[
\text{NTs} + \text{FeCl}_3 (5 \text{ mol %}) \rightarrow \text{TsN} + \text{Pd/C} \rightarrow \text{TsN} > 6:1 \text{ dr} \quad R^1 = \text{Ph or Me}
\]

b. Aza-Prins Reaction

With rapid and diastereoselective access to the desired piperidines, we examined these cyclic substrates in ring-opening Kumada XC reactions (Scheme 7). Phenyl and methyl substituents (products 7 and 8) were well tolerated and minimal amounts (<5%) of β-hydride elimination were observed. Methylated and benzylated ethers were well tolerated and provided the desired products in good yields (9, 10, and 11) [62]. It is important to note that the diastereomeric ratio observed in the products is consistent with the diastereomeric ratio of the starting material (See Materials and Methods Section). Therefore, preliminary data support a stereospecific Kumada XC reaction.

![Scheme 6. Arylpiperidine Synthesis via (a) Hetero Diels-Alder (HDA) Reaction and (b) Aza-Prins Reaction.](image)

Scheme 7. Scope of the Kumada XC Reaction of Cyclic Sulfonamides. 1 Isolated yield. 2 R = OBn in starting material and provided the free alcohol in product. 3 Yield determined by \(^1\)H NMR based on comparison to PhTMS as internal standard.

To further develop the potential scope of this reaction, we sought to establish a ring-opening of a sulfonyl piperidine with an aryl Grignard reagent (Scheme 8). Such transformations would provide synthetic access to diarylalkanes bearing pendant sulfonamides, including rapid assembly of stereochemically-rich analogs of ATPase inhibitor 14 [63–67]. We have previously observed that in Kumada XC reactions of benzylic ethers employing aryl Grignard reagents, the optimal nickel catalyst is ligated by dppe [68]. We were pleased to see that this trend applied to benzylic sulfonamides: employing the commercially available precatalyst, (dppe)NiCl₂, the XC reaction proceeded smoothly to provide the desired product 13 in 58% isolated yield [69].
We propose the following catalytic cycle for the Kumada XC reaction based on related mechanisms for the Kumada XC reaction of benzylic ethers and the XEC reaction of benzylic sulfonamides (Scheme 9) [50,70]. First, reduction of the nickel(II) precatalyst with the Grignard reagent provides the active Ni(0) catalyst 15. Next, oxidative addition of the benzylic sulfonamide affords the Ni(II) intermediate 16. Based on the calculated reaction coordinate diagram and transition state energies for related transformations, we hypothesize that rate-determining oxidative addition occurs with inversion of the benzylic carbon [12,47,48,70]. This step is facilitated by Lewis acidic magnesium salts that activate the sulfonamide moiety. Transmetallation with the Grignard reagent provides alkynickel complex 17. Subsequent reductive elimination, which occurs with retention at the benzylic center, affords the desired product and turns over the catalyst. Alternatively, intermediate 16 can undergo β-hydride elimination to afford the observed styrene by-product.

Scheme 9. Proposed Mechanism of Kumada XC Reaction. Speciation of magnesium complexes are omitted for clarity.

3. Materials and Methods
3.1. General Procedures
All reactions were carried out under an atmosphere of N₂, or Ar when noted. All glassware was oven- or flame-dried prior to use. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and toluene (PhMe) were degassed with Ar and then passed through two 4 × 36 inch columns of anhydrous neutral A-2 alumina (8 × 14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 12 h) to remove H₂O [71]. All other solvents utilized were purchased anhydrous commercially, or purified as described. ¹H NMR spectra were recorded on Bruker DRX-400 (400 MHz ¹H, 100 MHz ¹³C, 376.5 MHz ¹⁹F), GN-500 (500 MHz ¹H, 125.4 MHz ¹³C), or CRYO-500 (500 MHz ¹H, 125.8 MHz ¹³C) spectrometers. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (TMS, δ 0.00). Data are reported as follows: chemical shift...
(multiplicity [singlet (s), broad singlet (br s), doublet (d), doublet of doublet (dd), doublet of doublet of doublets (ddd), doublet of doublet of doublet of doublets (dddd), doublet of triplet (dt), doublet of doublet of triplet (ddt), doublet of triplet of doublet of triplet (ddd), triplet (t), broad triplet (br t), triplet of doublet of doublet (tdd), triplet of triplet (tt), quartet (q), quartet of doublet (qd), quartet of doublet of doublets (qdd), quintet (quint), apparent quintet (appar quint), sextet, apparent sextet (appar sextet), multiplet (m)]. coupling constants [Hz], integration). Carbon chemical shifts are reported in ppm (δ) relative to TMS with the respective solvent resonance as the internal standard (CDCl₃, δ 77.16 ppm). Unless otherwise indicated, NMR data were collected at 25 °C. Infrared (IR) spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer with an iD5 ATR tip (neat) and are reported in terms of frequency of absorption (cm⁻¹). Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F₂₅₄ precoated plates (0.25 mm thickness). Visualization was accomplished by irradiation with a UV lamp and/or staining with KMnO₄ or CAM. Flash chromatography was performed using SiliaFlash F60 (40–63 µm, 60 Å) from SiliCycle. Automated chromatography was carried out on a Teledyne Isco CombiFlash Rf Plus. Melting points (m.p.) were obtained using a Mel-Temp melting point apparatus and are uncorrected. High resolution mass spectrometry was performed by the University of California, Irvine Mass Spectrometry Center. See the ¹H, ¹³C, COSY and NOE NMR detailed data in the Supplementary Materials.

Bis(1,5-cyclooctadiene)nickel was purchased from Strem, stored in a glove box freezer (−20 °C) under an atmosphere of N₂ and used as received. All ligands were purchased from Strem or Sigma Aldrich and were stored in a glovebox and used as received. The methylmagnesium iodide was titrated with iodine prior to use [72]. All other chemicals were purchased commercially and used as received, unless otherwise noted.

3.2. Experimental

3.2.1. General Kumada Cross-Coupling Reaction Procedures

Method A: Kumada Cross-Coupling Reaction

In a glovebox, a flame-dried 7 mL vial equipped with a stir bar was charged with sulfonamide substrate (1.0 equiv), nickel precatalyst (15 mol %) and PhMe (0.10–0.20 M in substrate). The Grignard reagent (2.0 equiv) was then added dropwise via a syringe. After 24 h, the reaction was removed from the glovebox, quenched with methanol, filtered through a plug of silica gel eluting with 100% Et₂O and concentrated in vacuo. Phenyltrimethylsilane (PhTMS; 8.6 µL, 0.050 mmol) was added and the yield was determined by ¹H NMR based on comparison to PhTMS as internal standard before purification by column chromatography.

For reactions in which 1.0 equiv of MgI₂ is added, the vial is wrapped in aluminum foil for the duration of the reaction due to the light sensitivity of MgI₂.

(1) Preparation of Grignard Reagent Under a N₂ atmosphere, a three-necked flask equipped with a stir bar, reflux condenser, and Schlenk filtration apparatus was charged with magnesium turnings (1.1 g, 45 mmol). The flask and magnesium turnings were then flame-dried under vacuum and the flask was back-filled with N₂. Anhydrous Et₂O (7.0 mL) and a crystal of iodine (ca. 2.0 mg) were added to the flask. Freshly distilled iodomethane (1.9 mL, 31 mmol) or 4-iodoanisole as a solution in Et₂O (4.7 g, 20. mmol, 6.7 M in Et₂O) was slowly added over 30 min to maintain a gentle reflux. The mixture was stirred for 2 h at room temperature then filtered through the fritted Schlenk filter into a Schlenk flask under N₂ atmosphere. The magnesium turnings were washed with Et₂O (2 × 1.0 mL) then the Schlenk flask was sealed, removed, and placed under an N₂ atmosphere. The resulting methylmagnesium iodide was typically between 2.4 and 3.0 M as titrated by Knochel’s method [72] and could be stored, sealed under N₂ atmosphere or in a glovebox, for up to 4 weeks.

(2) Preparation of (R-BINAP)NiCl₂ This method was adapted from a procedure reported by Jamison [57]. To a flame-dried 50 mL round bottom flask equipped with a stir bar was added NiCl₂·6H₂O (0.24 g, 1.0 mmol, 1.0 equiv). The flask was placed
under vacuum and flame-dried until nearly all of the nickel compound had turned from emerald green to yellow-orange. Some of the green hexahydrate is necessary for the reaction to proceed. The flask was allowed to cool to room temperature then (R-BINAP) (0.62 g, 1.0 mmol, 1.0 equiv) was added. The flask was then equipped with a reflux condenser and was evacuated and backfilled with N₂. Then the solids were dissolved in MeCN (20 mL, 0.05 M) and the reaction mixture was allowed to reflux for 24 h. Upon completion, the reaction was cooled to room temperature and the black crystalline precipitate was filtered under vacuum to yield a fine black powder (0.53 g, 0.71 mmol, 71% yield).

3.2.2. Characterization Data for Kumada Cross-Coupled Products

2-(4-Phenylbutan-2-yl)benzo[b]thiophene (2) was prepared according to Method A. The following amounts of reagents were used: sulfonamide 1 (87 mg, 0.20 mmol, 1.0 equiv), (R-BINAP)NiCl₂ (23 mg, 30. μmol, 15 mol %), PhMe (1.0 mL, 0.20 M), and methylmagnesium iodide (0.16 mL, 0.40 mmol, 2.0 equiv, 2.5 M in Et₂O). Before purification, a ¹H NMR yield of 54% was obtained containing 40% styrene 3 based on comparison to PhTMS as an internal standard. The residue was purified by flash chromatography (0–5% EtOAc/hexanes) to yield a mixture of the title compound and styrene 3. To separate the major product and the styrene, an Upjohn dihydroxylation was performed [60,61]. The following amounts of reagents were used: substrate (30 mg, 0.12 mmol, 1.0 equiv), OsO₄ (7.6 μL, 1.2 μmol, 1.0 mol %, 4% solution in H₂O), N-methylmorpholine N-oxide (NMO) (16 mg, 0.13 mmol, 1.1 equiv), acetone (0.25 mL) and H₂O (0.05 mL). The residue was purified by flash column chromatography to afford the title compound as a colorless oil. (13 mg, 48 µmol, 24% yield over two steps) with a small amount of styrene 3 based on comparison to PhTMS as an internal standard. The residue was purified by flash chromatography (0–5% EtOAc/hexanes) to yield the title compound as yellow oil (10. mg, 36 µmol, 46% yield) containing styrene 3.

2-(5-Phenylpentan-2-yl)naphthalene (4) was prepared according to Method A. The following amounts of reagents were used: sulfonamide 19 (22 mg, 50. μmol, 1.0 equiv), (R-BINAP)NiCl₂ (5.6 mg, 7.5. μmol, 15 mol %), PhMe (0.25 mL, 0.20 M), and methylmagnesium iodide (40. μL, 0.10 mmol, 2.0 equiv, 2.8 M in Et₂O). Before purification, a ¹H NMR yield of 84% was obtained containing 13% styrene 18 based on comparison to PhTMS as an internal standard. The residue was purified by flash chromatography (100% hexanes) to yield the title compound as yellow oil (10. mg, 36 µmol, 74% yield) containing styrene 18 (1.3 mg, 5.0 µmol, 10%) and CH₃Cl₂ (0.8 mg, 9.4 µmol, 19%). TLC Rₗ = 0.8 (5% EtOAc/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.81–7.74 (m, 3H), 7.60–7.55 (s, 1H), 7.42 (dddd, J = 16.3, 8.2, 6.8, 1.4 Hz), 7.33 (dd, J = 8.4, 1.8 Hz, 1H), 7.23 (dd, J = 7.3, 3H, 2H), 7.17–7.09 (m, 3H), 2.88 (sextet, J = 7.0 Hz, 1H), 2.64–2.53 (m, 2H), 1.79–1.55 (m, 4H), 1.31 (d, J = 6.9 Hz, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 145.2, 142.7, 133.8, 132.3, 128.5 (2C), 128.4 (2C), 128.0, 127.7, 127.7, 125.9, 125.9, 125.8, 125.3, 125.2, 40.2, 38.0, 36.1, 29.7, 22.5; HRMS (TOF MS Cl+) m/z: [M + Na]⁺ calcd. for C₂₁H₁₈SNa 289.1027, found 289.1024.
2-(1-Cyclohexylpropan-2-yl)benzothiophene (5) was prepared according to Method A. The following amounts of reagents were used: sulfonamide 21 (43 mg, 0.10 mmol, 1.0 equiv), (R-BINAP)NiCl2 (11 mg, 15 µmol, 15 mol %), PhMe (0.50 mL, 0.20 M), and methylmagnesium iodide (70 µL, 0.20 mmol, 2.0 equiv, 2.8 M in Et2O). The residue was purified by flash column chromatography (0–15% Et2O/pentanes) to afford the title compound as a clear, colorless oil (12 mg, 46 µmol, 46% yield) containing styrene 20 (7.3 mg, 30. µmol, 30%) and minimal amounts of solvent. TLC Rf = 0.7 (100% pentanes); 1H NMR: (600 MHz, CDCl3) δ 7.68 (d, J = 6.7 Hz, 1H), 7.74 (d, J = 6.9 Hz, 3H), 1.32–1.23 (m, 2H), 1.19–1.11 (m, 2H), 0.96–0.85 (m, 2H).13C NMR (150.9 MHz, CDCl3) δ 153.6, 140.2, 138.9, 124.1, 123.4, 122.9, 122.4, 119.0, 66.0, 46.7, 35.2, 33.7, 33.3, 26.8, 26.4, 23.8, 15.4; HRMS (TOF MS CI+) m/z [M]+ calcd. for C17H22S 258.1442, found 258.1453.

2-(1-Cyclohexylpropan-2-yl)naphthalene (6) was prepared according to Method A. The following amounts of reagents were used: sulfonamide 23 (44 mg, 0.10 mmol, 1.0 equiv), (R-BINAP)NiCl2 (11 mg, 15 µmol, 15 mol %), PhMe (0.50 mL, 0.20 M), and methylmagnesium iodide (70 µL, 0.20 mmol, 2.0 equiv, 2.9 M in Et2O). Before purification, a 1H NMR yield of 69% was obtained with 22% styrene 22 based on comparison to PhTMS as an internal standard. The residue was purified by flash column chromatography (0–20% EtOAc/hexanes) to afford the title compound as a colorless oil (14 mg, 54 µmol, 54% yield) with a small amount of styrene 22 (3.7 mg, 15 µmol, 15% yield). TLC Rf = 0.7 (100% hexanes); 1H NMR (500 MHz, CDCl3) δ 7.85–7.73 (m, 3H), 7.60 (s, 1H), 7.47–7.38 (m, 2H), 7.35 (dd, J = 8.4, 1.8 Hz, 1H), 2.99 (sextet, J = 6.8 Hz, 1H), 1.81 (d, J = 13.0 Hz, 1H), 1.63 (tdd, J = 14.2, 8.1, 5.0 Hz, 5H), 1.50–1.41 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.19–1.06 (m, 4H), 0.95–0.83 (m, 2H); 13C NMR (125.8 MHz, CDCl3) δ 145.8, 133.8, 132.3, 128.0, 127.72, 127.68, 126.0, 125.9, 125.2, 125.1, 46.3, 37.0, 35.3, 33.9, 33.5, 26.9, 26.4, 23.1; HRMS (TOF MS CI+) m/z: [M]+ calcd. for C19H24S 300.1574, found 300.1568.

3.2.3. Characterization Data for Ring Opening Kumada Cross-Coupled Products

N-(5-(benzo[b]thiophen-2-yl)-3-phenylhexyl)-4-methylbenzenesulfonamide (7) was prepared according to Method A. The following amounts of reagents were used: piperidine 24 (38 mg, 80 µmol, 1.0 equiv), (R-BINAP)NiCl2 (9.0 mg, 12 µmol, 15 mol %), methylmagnesium iodide (60. µL, 0.16 mmol, 2.0 equiv, 2.6 M in Et2O), and PhMe (0.5 mL). Before purification, a 1H NMR yield of 64% was obtained. The residue was purified by column chromatography (0–20% EtOAc/hexanes) to afford the title compound as pale yellow oil (23 mg, 49 µmol, 62% yield). The ratio of diastereomers was determined by integration of the resonances attributed to amine hydrogen in the 1H NMR spectrum. The relative configuration of 7 was assigned based on analogy to a compound that has been previously reported [12,47,48]. TLC Rf = 0.8 (20% EtOAc/hexanes); 1H NMR (400 MHz, CDCl3) δ 7.74 (d, J = 7.9 Hz, 1H),
8.05 Hz, 2H), 5.19 (t, J = 6.9 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H). The relative configuration of the major diastereomer was assigned based on analogy to ring opened compound 7. For clarity, the 1H NMR and 13C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.7 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS E+) m/z [M+Na] calcd. for C27H29NO2S2Na 486.1537, found 486.1524.

Major Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.81–7.76 (m, 3H), 7.69 (d, J = 8.3 Hz, 2H), 7.6 (s, 1H), 7.47–7.40 (m, 2H), 7.31–7.26 (m, 3H), 4.29 (t, J = 5.9 Hz, 1H), 3.03–2.82 (m, 3H), 2.41 (s, 3H), 1.49 (t, J = 6.2 Hz, 1H), 1.43–1.46 (m, 1H), 1.30–1.25 (m, 3H), 1.25 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.5 Hz, 3H); 13C NMR (125.8, CDCl3) δ 145.1, 148.4, 133.7, 132.2, 129.7 (2C), 128.1, 127.6, 127.6, 127.1 (2C), 126.0, 125.6, 125.2, 125.0, 45.6, 41.1, 37.2, 36.5, 28.1, 29.1, 22.1, 21.5, 19.6.

Minor Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.81–7.76 (m, 3H), 7.69 (d, J = 8.3 Hz, 2H), 7.63 (s, 1H), 7.47–7.40 (m, 2H), 7.31–7.26 (m, 3H), 4.39 (t, J = 5.5 Hz, 1H), 3.03–2.82 (m, 3H), 2.41 (s, 3H), 1.49 (t, J = 6.2 Hz, 1H), 1.43–1.46 (m, 1H), 1.30–1.25 (m, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.7 Hz, 3H); 13C NMR (125.8, CDCl3) δ 145.1, 148.4, 133.7, 132.2, 129.7 (2C), 128.1, 127.6, 127.6, 127.1 (2C), 126.0, 125.7, 125.2, 125.0, 45.6, 41.5, 37.2, 36.5, 29.7, 29.1, 22.1, 21.5, 19.6.

N-(3-hydroxy-5-(naphthalen-2-yl)hexyl)-4-methylbenzenesulfonamide (9) was prepared according to Method A. The following amounts of reagents were used: piperidine 26 (93 mg, 0.20 mmol, 1.0 equiv), (R-BINAP)NiCl2 (23 mg, 30. µmol, 15 mol%), methylmagnesium iodide (0.14 mL, 0.40 mmol, 2.0 equiv, 2.9 M in Et2O), and PhMe (2.0 mL). The residue was purified by flash column chromatography (0–15% EtOAc/hexanes) to afford the title compound as a colorless oil (42 mg, 0.11 mmol, 53% yield, 5:1 dr). The ratio of diastereomers was determined by integration of the resonances attributed to amine hydrogen in the 1H NMR spectrum. The relative configuration of the major 9 was assigned based on analogy to ring opened compound 7. For clarity, the 1H NMR and 13C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.5 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS E+) m/z [M + Na] calcd. for C23H27NO2SNa, 420.1609; found, 420.1604.
Molecules 2021, 26, x FOR PEER REVIEW 11 of 25

Major Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.79–7.75 (m, 3H), 7.69 (d, $J = 8.15$ Hz, 2H), 7.59 (s, 1H), 7.43 (appar quint, $J = 7.44$ Hz, 2H), 7.31 (d, $J = 8.82$ Hz, 1H), 7.23 (d, $J = 8.17$ Hz, 2H), 5.27 (t, $J = 5.55$ Hz, 1H), 3.74–3.70 (m, 1H), 3.12–3.06 (m, 1H), 3.01–2.93 (m, 2H), 2.37 (s, 3H), 1.89 (br s, 1H), 1.86–1.80 (m, 1H), 1.72–1.62 (m, 2H), 1.53–1.46 (m, 1H), 1.28 (d, $J = 7.23$ Hz, 3H). $^{13}$C NMR (125.8, CDCl$_3$) $\delta$ 144.4, 143.3, 136.9, 133.7, 132.3, 129.7 (2C), 128.4, 127.7, 127.6, 127.1 (2C), 126.1, 125.5, 124.4, 125.0, 69.2, 45.9, 40.8, 37.0, 36.0, 22.2, 21.5.

Minor Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.79–7.75 (m, 3H), 7.65 (d, $J = 8.14$ Hz, 2H), 7.59 (s, 1H), 7.43 (appar quint, $J = 7.44$ Hz, 2H), 7.29 (d, $J = 8.91$ Hz, 1H), 7.19 (d, $J = 8.05$ Hz, 2H), 5.19 (t, $J = 5.57$ Hz, 1H), 3.43–3.39 (m, 1H), 3.12–3.06 (m, 1H), 2.91–2.82 (m, 2H), 2.35 (s, 3H), 1.86–1.80 (m, 1H), 1.76 (br s, 1H), 1.72–1.62 (m, 2H), 1.53–1.46 (m, 1H), 1.29 (d, $J = 6.40$ Hz, 3H). $^{13}$C NMR (125.8, CDCl$_3$) $\delta$ 143.7, 143.3, 136.8, 133.7, 132.3, 129.7 (2C), 128.4, 127.7, 127.6, 127.1 (2C), 126.1, 125.5, 124.4, 125.0, 68.7, 45.6, 40.8, 36.45, 36.42 23.2, 21.5.

N-(3-methoxy-5-(naphthalen-2-yl)hexyl)-4-methylbenzenesulfonamide (10) was prepared according to Method A. The following amounts of reagents were used: piperidine 12 (58 mg, 0.15 mmol, 1.0 equiv), (R-BINAP)NiCl$_2$ (15 mg, 20. $\mu$mol, 15 mol %), methylmagnesium iodide (0.11 mL, 0.30 mmol, 2.0 equiv, 2.8 M in Et$_2$O), and PhMe (1.5 mL). The residue was purified by flash column chromatography (0–25% EtOAc/hexanes) to afford the title compound as a colorless oil (32 mg, 80. $\mu$mol, 52% yield, 51:1 dr). The ratio of diastereomers was determined by integration of the resonances attributed to amine hydrogen in the $^1$H NMR spectrum. The relative configuration of the major 10 was assigned based on analogy to ring opened compound 7. For clarity, the $^1$H NMR and $^{13}$C NMR data of the major and minor diastereomers have been tabulated individually.

TLC $R_f = 0.4$ (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS E+) $m/z$ [M + Na] calcd. for C$_{22}$H$_{29}$NO$_3$SNa, 424.1766; found, 434.1775.

Major Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81–7.76 (m, 3H), 7.68 (d, $J = 8.37$ Hz, 2H), 7.55 (s, 1H), 7.47–7.40 (m, 2H), 7.29 (dd, $J = 8.48$, 1.70 Hz, 1H), 7.26–7.24 (m, 1H), 7.21 (d, $J = 7.97$ Hz, 1H), 5.11 (t, $J = 5.53$ Hz, 1H), 3.15 (s, 3H), 3.08–2.91 (m, 3H), 2.86 (appar sextet, $J = 7.37$ Hz, 1H), 2.34 (s, 3H), 1.96 (dddd, $J = 14.3, 8.50, 5.78$ Hz, 1H), 1.82–1.76 (m, 1H), 1.58–1.50 (m, 2H), 1.28 (d, $J = 6.98$ Hz, 3H). $^{13}$C NMR (125.8, CDCl$_3$) $\delta$ 144.1, 143.2, 136.8, 133.6, 132.3, 129.7 (2C), 128.3, 127.7, 127.6, 127.1 (2C), 126.1, 125.4, 125.24, 125.17 78.4, 56.3, 40.9, 40.5, 36.3, 32.0, 22.9, 21.5.

Minor Diastereomer: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81–7.76 (m, 3H), 7.70 (d, $J = 8.60$ Hz, 2H), 7.55 (s, 1H), 7.47–7.40 (m, 2H), 7.29 (dd, $J = 8.48$, 1.70 Hz, 1H), 7.26–7.24 (m, 1H), 7.21 (d, $J = 7.97$ Hz, 1H), 5.03 (t, $J = 5.52$ Hz, 1H), 3.20 (s, 3H), 3.08–2.91 (m, 3H), 2.86 (appar sextet, $J = 7.37$ Hz, 1H), 2.38 (s, 3H), 1.96 (dddd, $J = 14.3, 8.50, 5.78$ Hz, 1H), 1.71–1.66 (m, 1H), 1.47–1.40 (m, 2H), 1.27 (d, $J = 7.32$ Hz, 3H). $^{13}$C NMR (125.8, CDCl$_3$) $\delta$ 144.2, 143.2, 136.9, 133.6, 132.3, 129.7 (2C), 128.3, 127.7, 127.6, 127.1 (2C), 126.1, 125.52, 125.46 125.4, 78.4, 56.3, 40.9, 40.5, 36.3, 32.0, 22.9, 21.5.

N-(3-methoxy-5-(naphthalen-2-yl)hexyl)-4-methylbenzenesulfonamide (10) was prepared according to Method A. The following amounts of reagents were used: piperidine 12 (58 mg, 0.15 mmol, 1.0 equiv), (R-BINAP)NiCl$_2$ (15 mg, 20. $\mu$mol, 15 mol %), methylmagnesium iodide (0.11 mL, 0.30 mmol, 2.0 equiv, 2.8 M in Et$_2$O), and PhMe (1.5 mL). The residue was...
purified by flash column chromatography (0–15% EtOAc/hexanes) to afford a mixture of the title compound and styrene. To separate the major product and the styrene, a dihydroxylation was performed. The following amounts of reagents were used: AD-mix-β (52 mg, 1.4 g/mmol), t-BuOH (1.0 mL), and H₂O (1.0 mL). The residue was purified by flash column chromatography to afford the title compound as a colorless oil. (7.0 mg, 15 µmol, 8.6% yield over two steps, 5:1 dr). The ratio of diastereomers was determined by integration of the resonances attributed to amine hydrogen in the ¹H NMR spectrum. The relative configuration of the major 11 was assigned based on analogy to ring opened compound 7. When the reaction was performed with 2.0 equivalents of methylmagnesium iodide, a ¹H NMR yield of 41% was obtained based on comparison to PhTMS as an internal standard before purification. For clarity, the ¹H NMR and ¹³C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf 0.5 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS E+) m/z [M + Na] calcd. for C_{28}H_{31}NO_{4}SNa, 500.1872; found, 500.1861.

**Major Diastereomer:** ¹H NMR (500 MHz, CDCl₃) δ 7.64 (d, J = 7.9 Hz, 2H), 7.48 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.9 Hz, 1H), 7.27–7.16 (m, 8H), 6.33 (s, 1H), 4.79 (t, J = 6.0 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 4.31 (d, J = 11.4 Hz, 1H), 3.49–3.42 (m, 1H), 3.09–2.95 (m, 3H), 2.38 (s, 3H), 2.12 (appar quint, J = 6.9 Hz, 1H), 1.87–1.81 (m, 1H), 1.65–1.54 (m, 3H), 1.29 (d, J = 6.9 Hz, 3H) ¹³C NMR (125.8, CDCl₃) δ 162.6, 154.5, 143.3, 137.9, 136.9, 129.4 (2C), 128.7 (2C), 128.3 (2C), 127.9, 127.1 (2C), 123.4, 122.6, 120.5, 110.9, 101.1, 75.0, 70.7, 40.2, 39.1, 32.9, 30.5, 29.7, 21.5, 19.7.

**Minor Diastereomer:** ¹H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 7.7 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.27–7.16 (m, 8H), 6.25 (s, 1H), 4.79 (t, J = 6.0 Hz, 1H), 4.40 (s, 2H), 3.53–3.48 (m, 1H), 3.09–2.95 (m, 3H), 2.73 (appar quint, J = 6.5 Hz, 1H), 2.40 (s, 3H), 1.80–1.77 (m, 1H), 1.65–1.60 (m, 3H), 0.88 (d, J = 7.0 Hz, 3H); ¹³C NMR (125.8, CDCl₃) δ 162.6, 154.5, 143.3, 137.9, 136.9, 129.4 (2C), 128.7 (2C), 128.3 (2C), 127.9, 127.1 (2C), 123.4, 122.6, 120.5, 110.9, 101.4, 75.6, 71.4, 39.9, 39.1, 32.8, 30.5, 29.7, 21.5, 20.2.

**N-3-methoxy-5-(4-methoxyphenyl)-5-(naphthalen-2-yl)pentyl)-4-methylbenzenesulfonamide (13)** was prepared according to Method A. The following amounts of reagents were used: piperidine 12 (37 mg, 90 µmol, 1.0 equiv), Ni(dppe)Cl₂ (7.0 mg, 10. µmol, 15 mol %), (4-methoxyphenyl)magnesium iodide (0.11 mL, 0.18 mmol, 2.0 equiv, 1.7 M in Et₂O), and PhMe (0.90 mL). Before purification, a ¹H NMR yield of 56% was obtained based on comparison to PhTMS as an internal standard. The residue was purified by flash column chromatography (0–20% EtOAc/hexanes) to afford the title compound as a yellow oil (26 mg, 50. µmol, 8.5% yield, 3:1 dr). The ratio of diastereomers was determined by integration of the resonances attributed to methyl hydrogens of the tosyl group in the ¹H NMR spectrum. The relative configuration of the major 13 was assigned based on analogy to ring opened compound 7. For clarity, the ¹H NMR and ¹³C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf 0.3 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS E+) m/z [M + H] calcd. for C_{30}H_{34}NO_{4}S, 504.2209; found, 504.2206.

**Major Diastereomer:** ¹H NMR (500 MHz, CDCl₃) δ 7.76 (d, J = 7.3 Hz, 2H), 7.70–7.69 (m, 3H), 7.61 (s, 1H), 7.43 (dt, J = 20.4, 7.3 Hz, 2H), 7.29–7.19 (m, 3H), 7.13 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.09–5.5 (m, 1H), 4.12 (t, J = 7.8 Hz, 1H), 3.76 (s, 3H), 3.20 (s, 3H), 3.13–3.09 (m, 1H), 3.05–2.97 (m, 2H), 2.30 (s, 3H), 2.25 (appar sext, J = 7.3 Hz, 1H), 2.02–1.97 (m, 1H), 1.85–1.80 (m, 1H), 1.58–1.52 (m, 1H); ¹³C NMR (125.8, CDCl₃) δ 158.2,
143.4, 142.4, 136.8, 135.2, 133.6, 129.7 (2C), 129.0 (2C), 128.8, 128.3, 127.8, 127.7, 127.2 (2C), 126.5, 126.2, 125.6, 125.5, 114.1 (2C), 78.0, 56.7, 55.3, 46.5, 40.3, 39.1, 31.8, 21.5.

**Minor Diastereomer:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (d, $J = 7.3$ Hz, 2H), 7.73–7.70 (m, 3H), 7.63 (s, 1H), 7.43 (dt, $J = 20.4, 7.3$ Hz, 2H), 7.29–7.19 (m, 3H), 7.14 (d, $J = 7.7$ Hz, 2H), 6.81 (d, $J = 8.8$ Hz, 2H), 5.09–5.5 (m, 1H), 4.12 (t, $J = 7.8$ Hz, 1H), 3.76 (s, 3H), 3.19 (s, 3H), 3.13–3.09 (m, 1H), 3.05–2.97 (m, 2H), 2.35 (s, 3H), 2.25 (appar sext, $J = 7.3$ Hz, 1H), 2.06–2.03 (m, 1H), 1.76–1.78 (m, 1H), 1.58–1.52 (m, 1H); $^{13}$C NMR (125.8, CDCl$_3$) $\delta$ 158.2, 143.4, 142.0, 136.9, 136.5, 133.6, 129.7 (2C), 129.0 (2C), 128.8, 128.4, 127.8, 127.7, 127.2 (2C), 126.5, 126.2, 125.9, 125.6, 114.1 (2C), 78.0, 56.7, 55.3, 46.5, 40.3, 39.1, 31.9, 21.6.

3.2.4. General Procedures for Synthesis of Starting Materials

**Method B: Condensation Reaction**

This method was adapted from a procedure reported by Ruano et al. [73]. A flame-dried two-neck flask equipped with a stir bar, condenser, septum and N$_2$ inlet was charged with aldehyde (1.0 equiv), and p-toluenesulfonylamine (1.0 equiv) and CH$_2$Cl$_2$ (330 mL). Then Ti(OEt)$_4$ (2.0 equiv) was added dropwise. The deep orange solution was brought to reflux (~45 °C) and allowed to stir for 48 h. The solution was cooled to room temperature and was quenched with H$_2$O. The mixture was vacuum filtered and the filtrate was concentrated in vacuo.

**Method C: Methylation of Sulfonamide with Methyl Iodide**

This method was adapted from a procedure reported by Jarvo [12,47,48]. To a suspension of NaH (1.3 equiv) in THF (0.10 M) was added a solution of sulfonamide (1.0 equiv) in THF (0.15 M) at 0 °C. The mixture was warmed to rt and allowed to stir for 1 h before the addition of iodomethane (1.1 equiv). The reaction was allowed to stir overnight at rt. The excess NaH was quenched with sat. NH$_4$Cl and the solution was extracted with EtOAc (×3). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, concentrated in vacuo, and purified by flash column chromatography.

**Method D: Fe-Catalyzed Formal [4+2] Cycloaddition**

This method was adapted from a procedure reported by Matsubara [59]. To a flame-dried round-bottom flask equipped with a stir bar was added imine (1.0 equiv), FeCl$_3$ (5.0 mol%), and PhMe (0.1 M). Once the solution was homogenous, diene (2.0 equiv) was added. The reaction mixture was allowed to stir at rt overnight. After completion, the reaction mixture was filtered through a short pad of silica, washed with excess ethyl acetate, and concentrated in vacuo.

**Method E: Pd/C Reduction of Alkenes**
A flame-dried round-bottom flask with stir bar was charged with palladium on carbon (1.0 mg/3.5 mmol of substrate), flushed with N₂, and capped with septum. Slowly, DCM was added, until Pd/C was fully submerged. Then MeOH (0.2 M in substrate), and alkene (1.0 equiv) were added. Vacuum was pulled on the flask until the solvent began to bubble, at which point the flask was backfilled with N₂ (x3). An H₂ balloon was added and the reaction mixture was allowed to stir vigorously until complete by ¹H NMR. The balloon was then removed, and the flask was purged with N₂ for 30 min. The septum was removed, and the reaction mixture was filtered through Celite using MeOH (100 mL). The collected solvent was then concentrated in vacuo.

**Method F: TFA Mediated Aza-Prins Cyclization**

![Diagram of reaction](image)

This method was adapted from a procedure reported by Sabitha [60,61]. To a flame-dried pressure tube equipped with a stir bar was added aldehyde (1.0 equiv), homoallylic sulfonamide 33 (1.1 equiv), and CH₂Cl₂ (0.10 M). Then trifluoroacetic acid (10.0 equiv) was added slowly via syringe. The solution was warmed to 60 °C and allowed to stir for 72 h. The solution was then cooled to rt and quenched with saturated aq. NaHCO₃. Then the pH was adjusted to >7 by the addition of Et₃N. The solution was transferred to a separatory funnel, and the aqueous layer was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo.

**Method G: Alkylation of Secondary Alcohol**

This method was adapted from a procedure reported by Yang [74]. In a glovebox, to a flame-dried round-bottom flask equipped with a stir bar was added aldehyde (1.0 equiv), homoallylic sulfonamide 33 (1.1 equiv), and CH₂Cl₂ (0.10 M). Then trifluoroacetic acid (10.0 equiv) was added slowly via syringe. The solution was warmed to 60 °C and allowed to stir for 72 h. The solution was then cooled to rt and quenched with saturated aq. NaHCO₃. Then the pH was adjusted to >7 by the addition of Et₃N. The solution was transferred to a separatory funnel, and the aqueous layer was extracted with CH₂Cl₂ (x3). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo.

3.2.5. Synthesis and Characterization Data of Sulfonamide Starting Materials

**N-(benzo[b]thiophen-2-ylmethylene)-4-methylbenzenesulfonamide (28)** was prepared according to Method B. The following amounts of reagents were used: benzo[b]thiophene-2-carbaldehyde (3.2 g, 20. mmol, 1.0 equiv), p-toluenesulfonamide (3.1 g, 20. mmol,
(benzo[b]thiophen-2-yl)-3-phenylpropyl)-4-methylbenzenesulfonamide (680 mg, 1.6 mmol, 1.0 equiv), NaH (36 mg, 1.5 mmol, 1.3 equiv), methyl iodide (80.0 mL, 4.0 mmol, 2.0 equiv), and CH2Cl2 (33 mL). The residue was purified by flash column chromatography (5–25% EtOAc/hexanes) to yield the title compound as a yellow oil (0.52 g, 1.2 mmol, 68% yield). Analytical data are consistent with literature values. [75] 1H NMR (400 MHz, CDCl3) δ 7.98–7.86 (m, 5H), 7.67–7.55 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H). 

4-Methyl-N-(naphthalen-2-ylmethylene)benzenesulfonamide (29) was prepared according to Method B. The following amounts of reagents were used: 2-naphthaldehyde (0.31 g, 2.0 mmol, 1.0 equiv), NaH (36 mg, 1.5 mmol, 1.3 equiv), methyl iodide (80.0 mL, 4.0 mmol, 2.0 equiv), and CH2Cl2 (33 mL). The residue was purified by flash column chromatography (5–25% EtOAc/hexanes) to yield the title compound as a yellow oil (0.52 g, 1.2 mmol, 68% yield). Analytical data are consistent with literature values. [75] 1H NMR (400 MHz, CDCl3) δ 9.18 (s, 1H), 8.34 (s, 1H), 8.04 (dd, J = 8.6, 1.7 Hz, 1H), 7.98–7.86 (m, 5H), 7.67–7.55 (m, 2H), 7.36 (d, J = 8.0 Hz, 2H), 2.44 (s, 3H).

N-(1-(benzo[b]thiophen-2-yl)-3-phenylpropyl)-N,4-dimethylbenzenesulfonamide (1) was prepared according to Method C. The following amounts of reagents were used: N-(1-(benzo[b]thiophen-2-yl)-3-phenylpropyl)-4-methylbenzenesulfonamide (680 mg, 1.6 mmol, 1.0 equiv), NaH (50. mg, 2.1 mmol, 1.3 equiv), methyl iodide (0.11 mL, 1.8 mmol, 1.1 equiv) and THF (30 mL). The residue was purified by flash column chromatography (5–25% EtOAc/hexanes) to yield the title compound as a yellow oil (0.52 g, 1.2 mmol, 68% yield) TLC Rf = 0.8 (25% EtOAc/hexanes); 1H NMR (500 MHz, CDCl3) δ 7.73 (d, J = 7.9 Hz, 1H), 7.70–7.62 (m, 3H), 7.40–7.27 (m, 4H), 7.27–7.19 (m, 3H), 7.16 (d, J = 7.7 Hz, 2H), 7.06 (s, 1H), 5.42 (s, J = 7.5 Hz, 1H), 2.77 (s, 3H), 2.69 (qdd, J = 14.1, 10.4, 5.9 Hz, 2H), 2.40 (s, 3H), 2.30 (dddd, J = 13.7, 10.3, 7.2, 5.4 Hz, 1H), 2.08 (dddd, J = 13.9, 10.5, 7.8, 6.3 Hz, 1H), 13C NMR (125.7 MHz, CDCl3) δ 143.31, 143.30, 141.0, 139.6, 139.2, 137.0, 137.2, 137.6 (2C), 128.6 (2C), 128.5 (2C), 127.3 (2C), 126.3, 124.5, 124.4, 123.6, 122.9, 122.3, 56.5, 34.6, 33.0, 29.0, 21.6; HRMS (TOF MS ES+) m/z: [M + Na]+ calcd. for C28H29NO2S 466.1817, found 466.1816.

N,4-dimethyl-N-(1-(naphthalen-2-yl)-4-phenylbutyl)benzenesulfonamide (19) was prepared according to Method C. The following amounts of reagents were used: 4-methyl-N-(1-(naphthalen-2-yl)-4-phenylbutyl)benzenesulfonamide (0.50 g, 1.2 mmol, 1.0 equiv), NaH (36 mg, 1.5 mmol, 1.3 equiv), methyl iodide (80. μL, 1.3 mmol, 1.1 equiv) and THF (23 mL). The residue was purified by flash column chromatography (0–25% EtOAc/hexanes) to yield the title compound as a pale yellow solid (0.42 g, 0.95 mmol, 82% yield). TLC Rf = 0.3 (25% EtOAc/hexanes); 1H NMR (500 MHz, CDCl3) δ 7.85 (td, J = 8.1, 7.1, 4.1 Hz, 2H), 7.80 (d, J = 8.5 Hz, 1H), 7.75 (dt, J = 6.1, 3.7 Hz, 1H), 7.72 (d, J = 8.1 Hz, 2H), 7.58–7.50 (m, 3H), 7.46–7.39 (m, 1H), 7.36–7.31 (m, 2H), 7.26 (t, J = 7.8 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 7.06 (s, 1H), 5.42 (s, J = 7.5 Hz, 1H), 2.77 (s, 3H), 2.69 (qdd, J = 14.1, 10.4, 5.9 Hz, 2H), 2.40 (s, 3H), 2.30 (dddd, J = 13.7, 10.3, 7.2, 5.4 Hz, 1H), 2.08 (dddd, J = 13.9, 10.5, 7.8, 6.3 Hz, 1H), 13C NMR (125.7 MHz, CDCl3) δ 143.31, 143.30, 141.0, 139.6, 139.2, 137.0, 137.2, 137.6 (2C), 128.6 (2C), 128.5 (2C), 127.3 (2C), 126.3, 124.5, 124.4, 123.6, 122.9, 122.3, 56.5, 34.6, 33.0, 29.0, 21.6; HRMS (TOF MS ES+) m/z: [M + Na]+ calcd. for C28H29NO2S 466.1817, found 466.1816.
7.46–7.39 (m, 1H), 7.36–7.31 (m, 2H), 7.26 (t, J = 8.3 Hz, 2H), 7.20 (d, J = 7.3 Hz, 2H), 5.34 (t, J = 7.7 Hz, 1H), 2.72 (td, J = 7.5, 2.3 Hz, 2H), 2.68 (s, 3H), 2.44 (s, 3H), 2.16–2.06 (m, 1H), 1.88 (ddd, J = 15.6, 14.0, 7.6 Hz, 1H), 1.70 (quint, J = 9.0 Hz, 2H); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 143.1, 141.9, 135.9, 133.1, 132.9, 129.9, 129.6 (2C), 128.53 (2C), 128.3, 128.1, 127.7, 127.6, 127.3 (2C), 126.7, 126.4, 126.3, 126.0, 60.0, 35.5, 30.0, 28.9, 28.3, 21.6; HRMS (TOF MS ES+) \(m/z\) [M + Na]+ calcd. for C\(_{24}\)H\(_{30}\)NO\(_2\)SNa 450.1537, found 450.1530.

\[\text{N-(1-benzo[b]thiophen-2-yl)-2-cyclohexylethyl)-N,4-dimethylbenzenesulfonamide (21)}\]

was prepared according to Method C. The following amounts of reagents were used: N-(1-benzo[b]thiophen-2-yl)-2-cyclohexylethyl)-4-methylbenzenesulfonamide (170 mg, 0.41 mmol, 1.0 equiv), NaH (31 mg, 0.53 mmol, 1.3 equiv), methyl iodide (30. \(\mu\)L, 0.45 mmol, 1.1 equiv), and THF (8.2 mL). The residue was purified by flash column chromatography (20% EtOAc/hexanes) to afford the title compound as a yellow oil (180 mg, 0.43 mmol, 86% yield). TLC \(R_f = 0.8\) (25% EtOAc/hexanes); \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.0 Hz, 2H), 5.45 (br t, \(J = 8.0\) Hz, 2H), 2.96 (ddt, \(J = 18.7, 2.8\) Hz, 1H), 2.16–2.08 (m, 2H), 1.78–1.72 (m, 2H), 1.72–1.60 (m, 5H), 1.33–1.23 (m, 1H), 1.20–1.10 (m, 3H), 1.04–0.83 (m, 1H). \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta\) 144.1, 143.0, 139.1, 139.1, 137.0, 129.4 (2C), 127.2 (2C), 124.2, 123.3, 122.3, 122.5, 122.1, 53.9, 40.3, 34.0, 33.4, 33.0, 28.7, 26.3, 26.0, 25.9, 21.4; HRMS (TOF MS ES+) \(m/z\) [M + Na]+ calcd. for C\(_{24}\)H\(_{30}\)NO\(_2\)SNa 450.1537, found 450.1530.

\[\text{N-(2-cyclohexyl-1(napthalen-2-yl)ethyl)-N,4-dimethylbenzenesulfonamide (23)}\]

was prepared according to Method C. The following amounts of reagents were used: N-(2-cyclohexyl-1(napthalen-2-yl)ethyl)-4-methylbenzenesulfonamide (190 mg, 0.46 mmol, 1.0 equiv), NaH (17 mg, 0.70 mmol, 1.5 equiv), methyl iodide (30. \(\mu\)L, 0.60 mmol, 1.1 equiv), and THF (11 mL). The residue was purified by flash column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a yellow oil (170 mg, 0.40 mmol, 98% yield). TLC \(R_f = 0.40\) (10% EtOAc/hexanes); \(^{1}H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.73 (d, \(J = 7.8\) Hz, 1H), 7.70 (d, \(J = 8.3\) Hz, 2H), 7.66 (d, \(J = 7.2\) Hz, 1H), 7.30 (ddt, \(J = 16.4, 7.2, 1.3\) Hz, 2H), 7.24 (d, \(J = 8.0\) Hz, 2H), 7.05 (s, 1H), 5.50 (t, \(J = 7.6\) Hz, 1H), 2.71 (s, 3H), 2.39 (s, 3H), 1.92–1.78 (m, 2H), 1.76–1.59 (m, 5H), 1.33–1.23 (m, 1H), 1.20–1.10 (m, 3H), 1.04–0.83 (m, 1H). \(^{13}\)C NMR (126.8 MHz, CDCl\(_3\)) \(\delta\) 144.1, 143.0, 139.4, 139.1, 137.0, 129.4 (2C), 127.2 (2C), 124.2, 123.3, 122.3, 122.5, 122.1, 53.9, 40.3, 34.0, 33.4, 33.0, 28.7, 26.3, 26.0, 25.9, 21.4; HRMS (TOF MS ES+) \(m/z\) [M + Na]+ calcd. for C\(_{24}\)H\(_{28}\)NO\(_2\)SNa 450.1537, found 450.1530.

\[\text{2-(Benzo[b]thiophen-2-yl)-4-phenyl-1-tosyl-1,2,3,6-tetrahydropyridine (30)}\]

was prepared according to Method D. The following amounts of reagents were used: imine 28 (240 mg, 0.75 mmol, 1.0 equiv), buta-1,3-dien-2-yldibenzene (190 mg, 1.5 mmol, 2.0 equiv) [76], FeCl\(_3\) (6.0 mg, 40. \(\mu\)mol, 5.0 mol %), and PhMe (10 mL). The residue was purified by column...
chromatography (0–10% EtOAc/hexanes) to afford the title compound as a yellow oil (154 mg, 0.34 mmol, 46% yield). TLC Rf = 0.5 (20% EtOAc/hexanes); 1H NMR (500 MHz, CDCl3) δ 7.71 (d, J = 8.1 Hz, 2H), 7.68 (d, J = 7.8 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.36–7.22 (m, 8H), 7.18 (d, J = 8.0 Hz, 2H), 7.10 (s, 1H), 5.95 (s, 1H), 5.80 (d, J = 6.1 Hz, 1H), 4.35 (dt, J = 18.6, 3.5 Hz, 1H), 3.84 (dq, J = 18.7, 2.8 Hz, 1H), 2.96 (ddt, J = 16.3, 6.4, 3.2 Hz, 1H), 2.87 (d, J = 17.2 Hz, 1H), 2.33 (s, 3H); 13C NMR (126 MHz, CDCl3) δ 144.9, 144.6, 143.6, 140.0, 139.9, 129.9 (2C), 129.2, 128.8 (2C), 128.4, 127.4 (2C), 126.8 (2C), 124.5, 124.3, 123.5, 122.3, 122.3, 53.9, 42.2, 37.1, 36.7, 31.7, 21.7.

2-(Benzo[b]thiophen-2-yl)-4-phenyl-1-tosylpiperidine (24) was prepared according to Method E. The following amounts of reagents were used: substrate 30 (100 mg, 0.22 mmol, 1.0 equiv), Pd/C (20 mg), DCM (2.0 mL) and MeOH (5.0 mL). The residue was purified by flash column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a pale yellow oil (24 mg, 53% yield). TLC Rf = 0.5 (20% EtOAc/hexanes); 1H NMR (500 MHz, CDCl3) δ 7.81 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 7.9 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.40–7.26 (m, 6H), 7.23–7.18 (m, 1H), 7.13 (d, J = 1.5 Hz, 1H), 7.06 (d, J = 7.4 Hz, 2H), 5.70 (d, J = 5.2 Hz, 1H), 4.03 (d, J = 14.0 Hz, 1H), 3.34 (dd, J = 14.1, 12.7, 3.0 Hz, 1H), 2.93 (tt, J = 12.6, 3.6 Hz, 1H), 2.43 (s, 3H), 2.33 (d, J = 13.0 Hz, 1H), 2.01 (td, J = 13.5, 5.5 Hz, 1H), 1.68 (d, J = 12.5 Hz, 1H), 1.61 (td, J = 12.7, 4.4 Hz, 1H); 13C NMR (151 MHz, CDCl3) δ 144.8, 144.5, 139.9, 139.8, 129.8 (2C), 129.1, 128.7 (2C), 128.3, 127.3 (2C), 126.7 (2C), 124.4, 124.2, 123.4, 122.2, 122.2, 76.8, 53.8, 42.1, 36.9, 36.6, 31.6, 21.6; HRMS (TOF MS ES+) m/z [M+Na] calcd. for C42H30NO2S2Na 470.1228, found 470.1228.

4-Methyl-2-(naphthalen-2-yl)-1-tosyl-1,2,3,6-tetrahydropyridine (31) was prepared according to Method D. The following amounts of reagents were used: imine 28 (0.31 g, 1.0 mmol, 1.0 equiv), isoprene (1.5 mL, 15 mmol, 15 equiv), FeCl3 (16 mg, 0.10 mmol, 10 mol %), and PhMe (10 mL, 0.10 M). The residue was purified by flash column chromatography (0–5% EtOAc/hexanes) to afford the title compound as a yellow oil (150 mg, 0.40 mmol, 40% yield). TLC Rf = 0.5 (20% EtOAc/hexanes); 1H NMR (500 MHz, CDCl3) δ 7.78–7.71 (m, 3H), 7.69 (d, J = 8.5 Hz, 2H), 7.56 (s, 1H), 7.48–7.40 (m, 3H), 7.20 (d, J = 8.1 Hz, 2H), 5.43 (d, J = 3.5 Hz, 1H), 5.29 (s, 1H), 4.11 (d, J = 18.0 Hz, 1H), 3.35 (d, J = 18.1 Hz, 1H), 2.40–2.30 (m, 2H), 2.35 (s, 3H), 1.68 (s, 3H).
4-Methyl-2-(naphthalen-2-yl)-1-tosylpiperidine (25) was prepared according to Method E. The following amounts of reagents were used: substrate 31 (53 mg, 0.14 mmol, 1.0 equiv), Pd/C (27 mg), DCM (1.0 mL) and MeOH (1.0 mL). The residue was purified by flash column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a pale yellow oil (9.6 mg, 25 µmol, 18% yield; 6:1 dr cis:trans). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the 1H NMR spectrum. The relative configuration was assigned based on NOE analysis. For clarity, the 1H NMR and 13C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.5 (10% EtOAc/hexanes); HRMS (TOF MS ES+) m/z [M + H] calcd. for C23H20NO5S2 380.1684, found 380.1689.

Major Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.80–7.76 (m, 4H), 7.73–7.71 (m, 1H), 7.63 (s, 1H), 7.46–7.44 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 5.48 (d, J = 4.5 Hz, 1H), 3.96 (d, J = 14.4 Hz, 1H), 3.06 (ddd, J = 14.0, 13.2, 3.1 Hz, 1H), 2.69 (d, J = 25.9 Hz, 1H), 2.42 (s, 3H), 2.30 (d, J = 13.3 Hz, 1H), 1.43–1.36 (m, 2H), 0.98 (ddd, J = 24.5, 12.4, 4.5 Hz, 1H), 0.82 (d, J = 6.5 Hz, 3H); 13C NMR (151 MHz, CDCl3) δ 143.1, 138.8, 136.7, 133.3, 132.3, 129.7 (2C), 128.4, 128.0, 127.5, 127.1 (2C), 126.1, 125.9, 125.8, 125.1, 55.6, 42.0, 36.0, 33.0, 25.3, 22.2, 21.5.

Minor Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.80–7.76 (m, 4H), 7.73–7.71 (m, 1H), 7.63 (s, 1H), 7.46–7.44 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 5.25 (d, J = 4.9 Hz, 1H), 3.88 (d, J = 10.6 Hz, 1H), 3.04–2.98 (m, 1H), 2.42 (s, 3H), 2.38 (d, J = 3.86 Hz, 1H), 2.14 (d, J = 13.7 Hz, 1H), 1.43–1.36 (m, 2H), 0.79 (d, J = 6.5 Hz, 3H), 0.75 (d, J = 6.4 Hz, 1H); 13C NMR (151 MHz, CDCl3) δ 143.1, 138.8, 136.7, 133.3, 132.3, 129.6 (2C), 129.3, 128.0, 127.6, 127.1 (2C), 126.1, 125.9, 125.8, 124.0, 55.2, 41.8, 36.0, 33.1, 25.2, 23.3, 21.5.

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{(but-3-en-1-yl)}-4\text{-methylbenzenesulfonamide (34)} & \quad \text{K}_2\text{CO}_3 (1.2 \text{ equiv}) \\
\text{MeCN, 60 °C, 48 h} & \quad \text{N} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

2-(Naphthalen-2-yl)-1-tosylpiperidin-4-ol (35) was prepared according to Method F. The following amounts of reagents were used: 2-napthaldehyde (0.94 g, 6.0 mmol, 1.0 equiv), homoallylic sulfonamide 35 (1.1 mL, 6.0 mmol, 1.0 equiv), TFA (4.6 mL, 60. mmol, 10 equiv), and CH₂Cl₂ (60 mL, 0.10 M). The residue was purified by flash column chromatography (0–30% EtOAc/hexanes) to afford the title compound as an orange solid (0.72 g, 1.8 mmol, 31% yield, 5:1 dr trans:cis). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the 1H NMR spectrum. The relative configuration of the major 34 was assigned based on analogy to compound 24. For clarity, the 1H NMR data of the major and minor diastereomers have been tabulated individually.
TLC Rf = 0.1 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS ES+) m/z [M + H] calcd. for C_{22}H_{34}NO_{3}S 382.1477, found 382.1483.

**Major Diastereomer:** 1H NMR (500 MHz, CDCl₃) δ 7.79–7.77 (m, 4H), 7.68 (s, 1H), 7.49–7.41 (m, 4H), 7.29 (d, J = 8.1 Hz, 2H), 5.54 (d, J = 4.5 Hz, 1H), 3.99 (d, J = 15.0 Hz, 1H), 3.74 (tt, J = 10.9, 7.9 Hz, 1H), 3.03 (td, J = 15.3, 2.7 Hz, 1H), 2.63 (dt, J = 13.3, 2.0 Hz 1H), 2.43 (s, 3H), 1.70 (br s, 1H), 1.58 (ddd J = 13.6, 11.3, 5.5 Hz, 1H), 1.26–1.18 (m, 2H). 13C NMR (151 MHz, CDCl₃) δ 143.5, 138.3, 135.9, 133.3, 132.5, 130.0 (2C), 128.7, 128.0, 127.5, 127.0 (2C), 126.3, 126.2, 125.5, 124.7, 64.7, 55.8, 40.7, 36.2, 33.8, 21.6.

**Minor Diastereomer:** 1H NMR (500 MHz, CDCl₃) δ 7.74–7.70 (m, 4H), 7.63 (s, 1H), 7.60 (d, J = 8.3 Hz, 2H), 7.49–7.41 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 5.10 (t, J = 5.1 Hz, 1H), 3.99 (d, J = 15.0 Hz, 1H), 3.67 (tt, J = 13.4, 4.6 Hz, 1H), 3.03 (td, J = 15.3, 2.7 Hz, 1H), 2.63 (dt, J = 13.3, 2.0 Hz 1H), 2.36 (s, 3H), 1.81–1.73 (m, 1H), 1.67 (br s, 1H), 1.26–1.18 (m, 2H). 13C NMR (151 MHz, CDCl₃) δ 143.3, 137.7, 135.9, 133.2, 132.5, 129.6 (2C), 128.7, 128.2, 127.5, 127.2 (2C), 126.3, 126.0, 125.3, 124.8, 65.1, 55.5, 39.0, 37.0, 31.9, 21.5.

![Diagram](image_url)

4-(Benzylxy)-2-(naphthalen-2-yl)-1-tosylpiperidine (26) was prepared according to Method G. The following amounts of reagents were used: alcohol 35 (0.25 g, 0.66 mmol, 1.0 equiv), NaH (63 mg, 2.6 mmol, 4.0 equiv), benzyl bromide (90.9 µL, 0.73 mmol, 1.1 equiv), and THF (2.3 mL, 0.2 M). The residue was purified by column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a white solid (140 mg, 0.30 mmol, 56% yield, 5:1 dr trans:cis). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the 1H NMR spectrum. The relative configuration was assigned based on nOe analysis. For clarity, the 1H NMR and 13C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.8 (20% EtOAc/hexanes; stained with CAM); HRMS (TOF MS ES+) m/z [M + Na] calcd. for C_{35}H_{35}NO_{3}SNa 494.1766, found 494.1758.

**Major Diastereomer:** 1H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 8.1 Hz, 4H), 7.70 (d, 1H), 7.61 (s, 1H), 7.48–7.45 (m, 3H), 7.32–7.26 (m, 7H), 5.55 (d, J = 3.8 Hz, 1H), 4.50 (d, J = 11.9 Hz, 1H), 4.43 (d, J = 11.9 Hz, 1H), 4.02 (d, J = 14.7 Hz, 1H), 3.52 (tt, J = 10.8 Hz, 1H), 3.04 (td, J = 14.5, 2.5 Hz, 1H), 2.68 (d, J = 13.6 Hz, 1H), 2.43 (s, 1H), 1.80 (d, J = 11.5 Hz, 1H), 1.62 (ddd, J = 17.7, 11.9, 6.1 Hz, 1H), 1.31–1.34 (m, 1H); 13C NMR (151 MHz, CDCl₃) δ 143.4, 138.3, 136.0, 133.2, 132.5, 130.0 (2C), 129.5, 128.6, 128.5 (2C), 128.0, 127.8, 127.7 (2C), 127.5, 127.0 (2C), 126.2, 126.1, 125.5, 124.8, 71.3, 70.2, 55.8, 40.8, 33.4, 30.8, 21.6.

**Minor Diastereomer:** 1H NMR (500 MHz, CDCl₃) δ 7.80 (d, J = 8.1 Hz, 4H), 7.70 (d, 1H), 7.59 (s, 1H), 7.48–7.45 (m, 3H), 7.32–7.26 (m, 2H), 7.15 (d, J = 8.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.96 (t, J = 7.3 Hz, 2H), 6.69 (d, J = 7.6 Hz, 1H), 5.17 (t, J = 5.1 Hz, 1H), 4.24, 4.20 (ABq, JAB = 12.3 Hz, 2H), 3.80–3.68 (m, 3H), 2.53 (dt, J = 14.4, 9.4 Hz, 1H), 2.35 (s, 3H), 2.06 (ddd, J = 14.3, 5.3, 2.9 Hz, 1H), 1.81–1.80 (m, 2H), 1.31–1.34 (m, 1H); 13C NMR (151 MHz, CDCl₃) δ 143.4, 138.4, 136.0, 133.2, 132.5, 130.0 (2C), 129.5, 128.6, 128.5 (2C), 128.0, 127.8, 127.7 (2C), 127.5, 127.19 (2C), 127.16, 125.9, 125.6, 125.2, 71.2, 69.8, 55.8, 39.3, 34.2, 30.8, 21.6.
4-Methoxy-2-(naphthalen-2-yl)-1-tosylpiperidine (12) was prepared according to Method G. The following amounts of reagents were used: alcohol 35 (110 mg, 0.30 mmol, 1.0 equiv), NaH (16 mg, 0.67 mmol, 2.2 equiv), methyl iodide (20. μL, 0.33 mmol, 1.1 equiv), and THF (1.5 mL, 0.20 M). The residue was purified by column chromatography (0–20% EtOAc/hexanes) to afford the title compound as a pale yellow solid (61 mg, 0.15 mmol, 52% yield, 5:1 dr trans:cis). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the \(^1\)H NMR spectrum. The relative configuration was assigned based on nOe analysis. For clarity, the \(^1\)H NMR and \(^{13}\)C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.6 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS ES+) m/z [M + Na] calcd. for C\(_{25}\)H\(_{25}\)NO\(_5\)Na 396.1633, found 396.1636.

**Major Diastereomer:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.83–7.76 (m, 5H), 7.72 (s, 1H), 7.54–7.51 (m, 1H), 7.48–7.46 (m, 2H), 7.29 (d, \(J = 7.9\) Hz, 2H), 5.56 (s, 1H), 4.04 (d, \(J = 14.1\) Hz, 1H), 3.29 (tt, \(J = 7.4, 3.0\) Hz, 1H), 3.25 (s, 3H), 3.09 (t, \(J = 13.1\) Hz, 1H), 2.68 (d, \(J = 13.2\) Hz, 1H), 2.42 (s, 3H), 1.80 (d, \(J = 11.5\) Hz, 1H), 1.53 (td, \(J = 12.2\) Hz, 1H), 1.16 (qd, \(J = 11.6, 5.8\) Hz, 1H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 143.4, 138.4, 136.1, 133.4, 132.5, 130.0 (2C), 126.7, 128.1, 127.6, 127.0 (2C), 126.3, 126.1, 125.5, 124.7, 73.2, 55.8, 55.5, 40.8, 33.2, 30.2, 21.6.

**Minor Diastereomer:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.83–7.76 (m, 5H), 7.72 (s, 1H), 7.54–7.51 (m, 1H), 7.48–7.46 (m, 2H), 7.29 (d, \(J = 7.9\) Hz, 2H), 4.99 (t, \(J = 5.38\) Hz, 1H), 3.77–3.71 (m, 1H), 3.60 (dt, \(J = 13.6, 4.6\) Hz, 1H), 3.42 (br s, 1H), 3.03 (s, 3H), 2.37–2.29 (m, 1H), 2.33 (s, 3H), 2.02 (d, \(J = 15.2\) Hz, 1H), 1.86–1.82 (m, 1H), 1.72–1.68 (m, 1H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\) 143.0, 138.3, 137.4, 133.1, 132.5, 129.4 (2C), 126.7, 128.0, 127.5, 127.2 (2C), 125.8, 125.7, 125.5, 125.2, 73.5, 56.4, 55.5, 40.0, 34.1, 29.6, 21.5.

\[ \text{2-(Naphthalen-2-yl)-1-tosylpiperidin-4-ol (36) was prepared according to Method F. The following amounts of reagents were used: 2-benzofurancarboxaldehyde (0.60 mL, 5.0 mmol, 1.0 equiv), homoallylic sulfonamide 34 (0.91 mL, 5.0 mmol, 1.0 equiv), TFA (3.8 mL, 50. mmol, 10 equiv), CH\(_2\)Cl\(_2\) (50 mL, 0.10 M). The residue was purified by flash column chromatography (0–50% EtOAc/hexanes) to afford the title compound as an orange solid (0.42 g, 1.1 mmol, 22% yield, 5:1 dr trans:cis). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the \(^1\)H NMR spectrum. The relative configuration was assigned based on analogy to compound 26. For clarity, the \(^1\)H NMR data of the major and minor diastereomers have been tabulated individually.} \]

TLC Rf = 0.1 (30% EtOAc/hexanes, stained with CAM).

**Major Diastereomer:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 (d, \(J = 8.29\) Hz, 2H), 7.46 (dd, \(J = 6.75, 2.12\) Hz, 1H), 7.21–7.18 (m, 3H), 7.15 (d, \(J = 8.61\) Hz, 2H), 6.49 (t, \(J = 2.0\) Hz, 1H), 5.51 (d, \(J = 5.48\) Hz, 1H), 3.97–3.90 (m, 2H), 3.23 (td, \(J = 13.5, 2.7\) Hz, 1H), 2.51–2.45 (m, 1H), 2.33 (s, 3H), 1.94–1.88 (m, 1H), 1.75 (ddd, \(J = 13.0, 11.6, 5.9\) Hz, 1H), 1.53 (d, \(J = 5.0\) Hz, 1H), 1.44 (ddd, \(J = 24.1, 12.8, 4.5\) Hz, 1H).

**Minor Diastereomer:** \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.65 (d, \(J = 8.29\) Hz, 2H), 7.46 (dd, \(J = 6.75, 2.12\) Hz, 1H), 7.21–7.18 (m, 3H), 7.15 (d, \(J = 8.61\) Hz, 2H), 6.51 (t, \(J = 1.1\) Hz, 1H).
Molecules 2021, 26, x FOR PEER REVIEW 21 of 25

Minor Diastereomer: (ddd, J = 14.4, 6.7, 3.3 Hz, 1H), 1.94–1.88 (m, 1H), 1.53 (d, J = 5.0 Hz, 1H), 1.44 (ddd, J = 24.1, 12.8, 4.5 Hz, 1H).

2-(benzofuran-2-yl)-4-(benzoxyl)-1-tosylpiperidine (27) was prepared according to method G. The following amounts of reagents were used: alcohol 36 (0.15 g, 0.40 mmol, 1.0 equiv), NaH (46 mg, 1.9 mmol, 4.7 equiv), benzyl bromide (52 µL, 0.44 mmol, 1.1 equiv), and THF (3.0 mL, 0.2 M). The residue was purified by column chromatography (0–10% EtOAc/hexanes) to afford the title compound as a yellow solid (87 mg, 0.19 mmol, 47% yield, 5:1 dr trans:cis). The dr was determined based on the integration of the resonances attributed to the benzylic hydrogens in the 1H NMR spectrum. The relative configuration was assigned based on nOe analysis. For clarity, the 1H NMR and 13C NMR data of the major and minor diastereomers have been tabulated individually.

TLC Rf = 0.8 (30% EtOAc/hexanes, stained with CAM); HRMS (TOF MS ES+) m/z [M + Na] calcd. for C27H27NO6SNa 484.1559, found 484.1542.

Major Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.65 (d, J = 8.3 Hz, 2H), 7.45, (d, J = 8.3 Hz, 1H), 7.30–7.17 (m, 8H), 7.15 (d, J = 8.2 Hz, 2H), 6.44 (s, 1H), 5.52 (d, J = 5.3 Hz, 1H), 4.49 (s, 2H), 3.94 (d, J = 13.7 Hz, 1H), 3.66 (tt, J = 11.2, 4.0 Hz, 1H), 3.20 (td, J = 7.6, 4.8 Hz, 1H); 7.68 (d, J = 8.3 Hz, 2H), 7.45 (d, J = 8.3 Hz, 1H), 7.30–7.17 (m, 8H), 7.15 (d, J = 8.2 Hz, 2H), 6.44 (s, 1H), 5.52 (d, J = 5.3 Hz, 1H), 4.49 (s, 2H), 3.94 (d, J = 13.7 Hz, 1H), 3.66 (tt, J = 11.2, 4.0 Hz, 1H), 3.20 (td, J = 7.6, 4.8 Hz, 1H); 13C NMR (151 MHz, CDCl3) δ 155.3, 154.7, 143.3, 138.2, 137.2, 129.5 (2C), 128.5 (2C), 128.1, 128.0, 127.8, 127.1, 126.9, 126.4, 124.1, 122.9, 120.9, 111.1, 104.8, 71.8, 70.2, 51.7, 41.4, 34.2, 31.3, 21.5.

Minor Diastereomer: 1H NMR (500 MHz, CDCl3) δ 7.68 (d, J = 8.3 Hz, 2H), 7.35, (d, J = 4.4 Hz, 1H), 7.30–7.17 (m, 8H), 7.07 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.6, 2H), 6.79 (d, J = 7.6 Hz, 2H), 6.42 (s, 1H), 5.36 (d, J = 6.4 Hz, 1H), 4.28 (s, 2H), 3.76–3.73 (m, 2H), 3.66 (tt, J = 11.2, 4.0 Hz, 1H), 2.70 (d, J = 14.1 Hz, 1H), 2.32 (s, 3H), 1.97 (d, J = 12.3 Hz, 1H), 1.83 (d, J = 13.8 Hz, 1H), 1.72–1.68 (m, 1H); 13C NMR (151 MHz, CDCl3) δ 155.3, 154.7, 143.3, 138.2, 137.2, 129.5 (2C), 128.5 (2C), 128.1, 128.0, 127.8, 127.1, 126.9, 126.4, 124.1, 122.9, 120.9, 111.1, 104.8, 71.8, 70.2, 51.7, 41.4, 34.2, 31.3, 21.5.

4. Conclusions

In conclusion, we have developed a Kumada XC reaction of benzylic sulfonamides with Grignard reagents including methylmagnesium iodide and arylmagnesium iodide. This reaction utilizes readily available starting materials that are not activated prior to the XC reaction. We have demonstrated that increasing the steric bulk adjacent to the reactive center destabilizes the conformation necessary for β-hydride elimination to occur. A stereospecific ring opening Kumada XC reaction has been established to synthesize highly substituted acyclic fragments. This work provides a basis for the XC reaction of simple benzylic sulfonamides.

Supplementary Materials: The following are available online, 1H, 13C, COSY and NOE NMR data are available online.

Author Contributions: K.A.H., C.A.H. and A.C.M. performed the experiments and analyzed the NMR data. K.A.H. wrote the first draft of the paper. E.R.J. conceived, wrote and finalized the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the National Science Foundation (NSF CHE-1900340).
Institutional Review Board Statement: Not application.

Informed Consent Statement: Not application.

Data Availability Statement: Data sharing not applicable.

Acknowledgments: We gratefully acknowledge Felix Grun and the UC Irvine Mass Spectrometry Facility for mass spectrometry data.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

References and Note

1. De Meijere, A.; Diederich, F. (Eds.) Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004.

2. Hartwig, J.F. Organotransition Metal Chemistry: From Bonding to Catalysis; University Science Books: Sausalito, CA, USA, 2010.

3. Jana, R.; Pathak, T.P.; Sigman, M.S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling Reactions Using Alkyl-Organometallics as Reaction Partners. Chem. Rev. 2011, 111, 1417–1492. [CrossRef] [PubMed]

4. Cherney, A.H.; Kadunce, N.T.; Reisman, S.E. Enantioselective and Enantiospecific Transition-Metal-Catalyzed Cross-Coupling Reactions of Organometallic Reagents to Construct C–C bonds. Chem. Rev. 2015, 115, 9587–9652. [CrossRef] [PubMed]

5. Choi, J.; Fu, G.C. Transition Metal-Catalyzed Alkyl-Alkyl Bond Formation: Another Dimension in Cross-Coupling Chemistry. Acc. Chem. Res. 2015, 48, 2344–2353. [CrossRef] [PubMed]

6. Ogoshi, S. (Ed.) Nickel Catalysis in Organic Synthesis; Methods and Reactions; Wiley: Hoboken, NJ, USA, 2020.

7. Tasker, S.Z.; Standley, E.A.; Jamison, T.F. Recent Advances in Homogeneous Nickel Catalysis. Acc. Chem. Res. 2015, 48, 2344–2353. [CrossRef] [PubMed]

8. Pound, S.M.; Watson, M.P. Asymmetric Synthesis via Stereospecific C–N and C–O Bond Activation of Alkyl Amine and Alcohol Derivatives. Chem. Commun. 2018, 54, 12286–12301. [CrossRef] [PubMed]

9. Rosen, B.M.; Quasdorf, K.W.; Wilson, D.A.; Hansen, E.C. Recent Advances in Nonprecious Metal Catalysis. Chem. Rev. 2011, 111, 1346–1416. [CrossRef]

10. Tollefson, E.J.; Hanna, L.E.; Jarvo, E.R. Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Benzyl Ethers and Esters. Org. Process. Res. Dev. 2019, 23, 115, 1245–1260. [CrossRef] [PubMed]

11. Wang, W.; Su, Y.; Li, L.; Huang, H. Transition-Metal Catalysts: C–N Bond Activation. Chem. Soc. Rev. 2016, 45, 1257–1272. [CrossRef]

12. Pound, S.M.; Watson, M.P. Asymmetric Synthesis via Stereospecific C–N and C–O Bond Activation of Alkyl Amine and Alcohol Derivatives. Chem. Commun. 2018, 54, 12286–12301. [CrossRef] [PubMed]

13. Dander, J.E.; Garg, N.K. Breaking Amides using Nickel Catalysis. Acc. Chem. Res. 2017, 50, 1413–1423. [CrossRef] [PubMed]

14. Li, G.; Ma, S.; Szostak, M. Amide Bond Activation: The Power of Resonance. Trends Chem. 2020, 2, 914–928. [CrossRef] [PubMed]

15. Lin, B.L.; Clough, C.R.; Hillhouse, G.L. Interactions of Aziridines with Nickel Complexes: Oxidative-Addition and Reductive-Elimination Reactions that Break and Make C–N Bonds. J. Am. Chem. Soc. 2002, 124, 2890–2891. [CrossRef] [PubMed]

16. Huang, C.-Y.; Doyle, A.G. The Chemistry of Transition Metals with Three-Membered Ring Heterocycles. Chem. Rev. 2014, 114, 8153–8198. [CrossRef]

17. Lin, B.L.; Clough, C.R.; Hillhouse, G.L. Interactions of Aziridines with Nickel Complexes: Oxidative-Addition and Reductive-Elimination Reactions that Break and Make C–N Bonds. J. Am. Chem. Soc. 2002, 124, 2890–2891. [CrossRef] [PubMed]

18. Huang, C.-Y.; Doyle, A.G. Nickel-Catalyzed Negishi Alkylation of Styrenyl Aziridines. J. Am. Chem. Soc. 2012, 134, 9541–9544. [CrossRef]

19. Huang, C.-Y.; Doyle, A.G. Electron-Deficient Olefin Ligands Enable Generation of Quaternary Carbons by Ni-Catalyzed Cross Coupling. J. Am. Chem. Soc. 2015, 137, 5638–5641. [CrossRef]

20. Nielsen, D.K.; Huang, C.-Y.; Doyle, A.G. Directed Nickel-Catalyzed Negishi Cross Coupling of Alkyl Aziridines. J. Am. Chem. Soc. 2013, 135, 13605–13609. [CrossRef]

21. Jensen, K.L.; Standley, E.A.; Jamison, T.F. Highly Regioselective Nickel-Catalyzed Cross-Coupling of N-Tosylaziridines and Alkylzinc Reagents. J. Am. Chem. Soc. 2014, 136, 11145–11152. [CrossRef] [PubMed]

22. Wenkert, E.; Han, A.-L.; Jenny, C.-J. Nickel-Induced Conversion of Carbon-Nitrogen into Carbon-Carbon Bonds. One-Step Transformations of Aryl, Quaternary Ammonium Salts into Alkylarenes and Biaryls. J. Chem. Soc. Chem. Commun. 1988, 975–976. [CrossRef]
27. Blakey, S.B.; MacMillan, D.W.C. The First Suzuki Cross-Couplings of Aryltrimethylammonium Salts. *J. Am. Chem. Soc.* **2003**, *125*, 6046–6047. [CrossRef] [PubMed]

28. Maity, P.; Shacklady-McAtee, D.M.; Yap, G.P.A.; Siriani, E.R.; Watson, M.P. Nickel-Catalyzed Cross-Couplings of Benzylic Ammonium Salts and Boronic Acids: Stereospecific Formation of Diarylethanes via C–N Bond Activation. *J. Am. Chem. Soc.* **2013**, *135*, 280–285. [CrossRef] [PubMed]

29. Shacklady-McAtee, D.M.; Roberts, K.M.; Basch, C.H.; Song, Y.-G.; Watson, M.P. A General, Simple Catalyst for Enantiospecific Cross Couplings of Benzylic Ammonium Triflates and Boronic Acids: No Phosphine Ligand Required. *Tetrahedron* **2014**, *70*, 4257–4263. [CrossRef]

30. He, F.; Wang, Z.-X. Nickel-Catalyzed Cross-Coupling of Aryl or -2-Menaphthyl Quaternary Ammonium Triflates with Organoa-luminum Reagents. *Tetrahedron 2017*, 73, 4450–4457. [CrossRef]

31. Bapat, J.B.; Blade, R.J.; Boulton, A.J.; Epsztajn, J.; Katritzky, A.R.; Lewis, J.; Molina-Buenia, P.; Nie, P.-L.; Ramsden, C.A. Pyridines as Leaving Groups in Synthetic Transformations: Nucleophilic Displacements of Amino Groups, and Novel Preparations of Nitriles and Isoyanate. *Tetrahedron Lett.* **1976**, *17*, 2691–2694. [CrossRef]

32. Katritzky, A.R.; De Ville, G.; Patel, R.C. Carbon-Alkylation of Simple Nitronate Anions by N-Substituted Pyridiniums. *Tetrahedron* **1981**, *37*, 25–30. [CrossRef]

33. Katritzky, A.R.; Marson, C.M. Pyrylium Mediated Transformations of Primary Amino Groups into Other Functional Groups. New Synthetic Methods (41). *Angew. Chem. Int. Ed.* **1984**, *23*, 420–429. [CrossRef]

34. Said, S.A.; Fiksdaih, A. Stereoselective Transformation of Amines via Chiral 2,4,6-Triphenylpyridinium Intermediates. *Tetrahedron Asymmetry* **2001**, *12*, 1947–1951. [CrossRef]

35. Klauk, F.; James, M.J.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem. Int. Ed.* **2017**, *56*, 12336–12339. [CrossRef] [PubMed]

36. He, F.-S.; Ye, S.; Wu, J. Recent Advances in Pyridinium Salts as Radical Reservoirs in Organic Synthesis. *ACS Catal.* **2019**, *9*, 8943–8960. [CrossRef]

37. Pang, Y.; Moser, D.; Cornella, J. Pyrylium Salts: Selective Reagents for the Activation of Primary Amino Groups in Organic Synthesis. *Synthesis 2020*, 52, 489–503.

38. Rössler, S.L.; Jelier, B.J.; Magnier, E.; Dagoussset, G.; Carreira, E.M.; Togni, A. Pyridinium Salts as Redox-Active Functional Group Transfer Reagents. *Angew. Chem. Int. Ed.* **2021**, *60*, 9264–9280. [CrossRef] [PubMed]

39. Li, Y.-N.; Xiao, F.; Guo, Y.; Zeng, Y.-F. Recent Developments in Deaminative Functionalization of Alkyl Amines. *Eur. J. Org. Chem.* **2021**, 2021, 1215–1228. [CrossRef]

40. Kong, D.; Moon, P.J.; Lundgren, R.J. Radical Coupling from Alkyl Amines. *Nat. Catal.* **2019**, *2*, 473–476. [CrossRef]

41. Basch, C.H.; Liao, J.; Xu, J.; Plane, J.J.; Watson, M.P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316. [CrossRef] [PubMed]

42. Hoerner, M.E.; Baker, K.M.; Basch, C.H.; Bampo, E.M.; Watson, M.P. Deaminative Amination of Aromatic Acid-Derived Pyridinium Salts. *Org. Lett.* **2019**, *21*, 7356–7360. [CrossRef]

43. Liao, J.; Guan, W.; Bosco, B.P.; Tucker, J.W.; Tomlin, J.W.; Garnsey, M.R.; Watson, M.P. Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C–N Bond Activation. *Org. Lett.* **2018**, *20*, 3030–3033. [CrossRef]

44. Baker, K.M.; Baca, D.L.; Plunkett, S.; Daneker, M.E.; Watson, M.P. Engaging Alkenes and Alkynes in Deaminative Alkyl–Alkyl and Alkyl–Vinyl Cross-Couplings of Alkylpyridinium Salts. *Org. Lett.* **2019**, *21*, 9738–9741. [CrossRef]

45. Guan, W.; Liao, J.; Watson, M.P. Vinylation of Benzylic Amines via C–N Bond Functionalization of Benzylic Pyridinium Salts. *Synthesis 2018*, 50, 3231–3237.

46. Plunkett, S.; Basch, C.H.; Santana, S.O.; Watson, M.P. Harnessing Alkylpyridinium Salts as Electrophiles in Deaminative Alkyl-Alkyl Cross-Couplings. *J. Am. Chem. Soc.* **2019**, *141*, 2251–2262. [CrossRef]

47. Taylor, B.L.H.; Swift, E.C.; Waetzig, J.D.; Jarvo, E.R. Stereospecific Nickel-Catalyzed Cross-Coupling Reactions of Alkyl Ethers: Enantioselective Synthesis of Diarylethanes. *J. Am. Chem. Soc.* **2011**, *133*, 389–391. [CrossRef] [PubMed]

48. Tollefson, E.J.; Dawson, D.D.; Osborn, K.A.; Jarvo, E.R. Stereospecific Cross-Coupling Reactions of Aryl-Substituted Tetrahydrofurans, Tetrahydropryans, and Lactones. *J. Am. Chem. Soc.* **2014**, *136*, 14951–14958. [CrossRef]

49. Marshall, D.R.; Thomas, P.J.; Stirling, C.J.M. Leaving Group Ability in Base-Promoted Alkene-Forming 1,2-Eliminations. *J. Chem. Soc. Chem. Commun.* **1975**, *23*, 940–941. [CrossRef]

50. Lucas, E.L.; Hewitt, K.A.; Chen, P.-P.; Castro, A.J.; Hong, X.; Jarvo, E.R. Engaging Sulfonamides: Intramolecular Cross-Electrophile Coupling Reaction of Sulfonylamides with Alkyl Chlorides. *J. Org. Chem.* **2020**, *85*, 1775–1793. [CrossRef] [PubMed]

51. Steinman, T.J.; Liu, J.; Mengiste, A.; Doyle, A.G. Synthesis of β-Phenylthiylmines via Ni/Photoredox Cross-Electrophile Coupling of Aliphatic Aziridines and Aryl Iodides. *J. Am. Chem. Soc.* **2020**, *142*, 7598–7605. [CrossRef]

52. Tsyrlinukov, S.; Cai, Q.; Twitty, J.C.; Xu, J.; Atifi, A.; Bercher, O.P.; Yap, G.P.A.; Rosenthal, J.; Watson, M.P.; Kozlowski, M.C. Dissection of Alkylpyridinium Structures to Understand Deamination Reactions. *ACS Catal.* **2021**, *11*, 8456–8466. [CrossRef]

53. Xu, J.; Bercher, O.P.; Talley, M.R.; Watson, M.P. Nickel-Catalyzed, Stereospecific C–C and C–B Cross-Couplings via C–N and C–O Bond Activation. *ACS Catal.* **2021**, *11*, 1604–1612. [CrossRef]

54. Moragas, T.; Gaydou, M.; Martin, R. Nickel-Catalyzed Carboxylation of Benzylic C–N Bonds with CO2. *Angew. Chem. Int. Ed.* **2016**, *55*, 5053–5057. [CrossRef]
