DOI: 10.1002/adsc.201600090

Advanced Synthesis & Catalysis

# Palladium-Catalyzed α-Arylation of Methyl Sulfonamides with Aryl Chlorides

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Received: January 21, 2016; Revised: April 11, 2016; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201600090.

**Abstract:** A palladium-catalyzed α-arylation of sulfonamides with aryl chlorides is presented. A Buchwald-type pre-catalyst formed with Kwong's indole-based ligand enabled this transformation to be compatible with a large variety of methyl sulfonamides and aryl chlorides in good to excellent yields. Importantly, under the optimized reaction conditions, only mono-arylated products were observed. This method has been applied to the efficient synthesis of sumatriptan, which is used to treat migraines.

**Keywords:** aryl chlorides; arylation; palladium-catalyzed reaction; sulfonamides; sumatriptan

## Introduction

Sulfonamides are widely occurring in synthetic intermediates and bioactive compounds.[1] They are also important structural motifs in drugs such as Almotriptan,[2] Avitriptan[3] and Sumatriptan[4] (Figure 1). Previous methods to access sulfonamides range from simple N–S bond formation,[5] to tandem reactions that also include S=O,[6] C–S,[7] and C–N bond-forming reactions.[8] Although α-arylation of unfunctionalized methyl sulfonamides with aryl halides to form C–C bonds is an attractive route to these important compounds, such transformations have met with limited success.

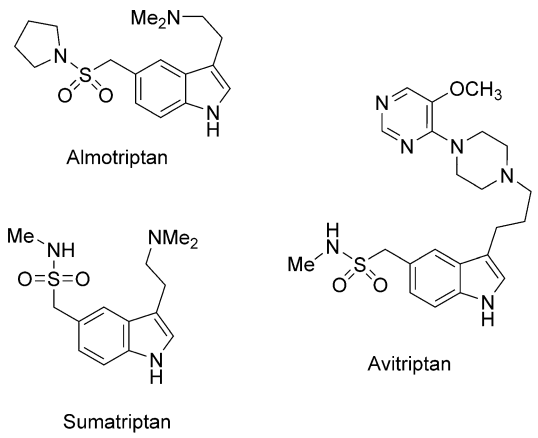
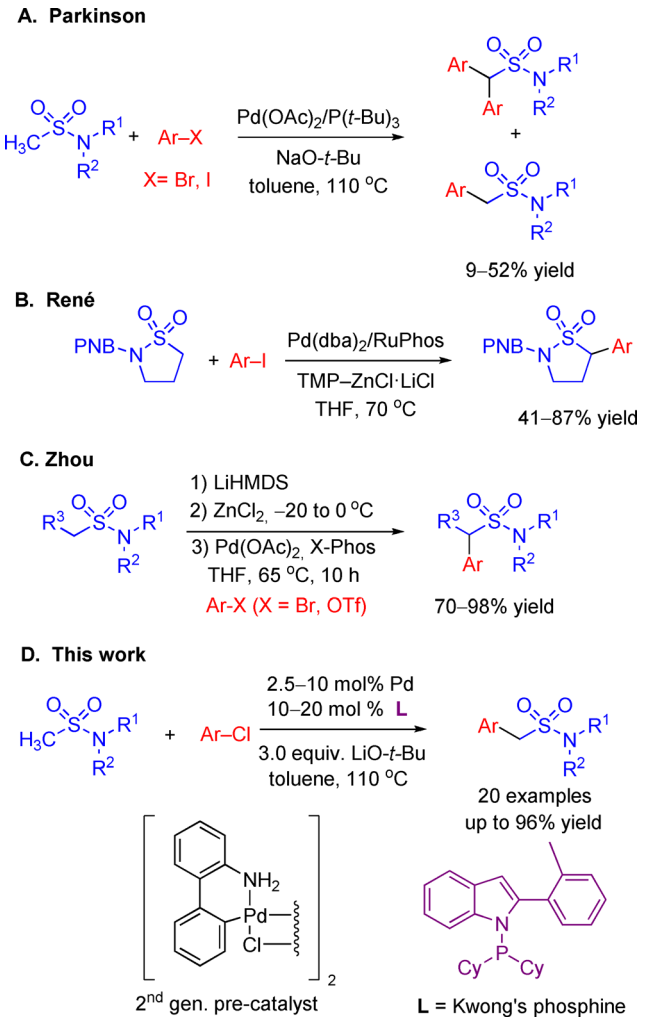



**Figure 1.** Sulfonamide motifs in drugs.

A viable approach to the α-arylation of sulfonamides is that used in the arylation of ketones and esters.[9] Due to the synthetic utility of α-arylated carbonyl compounds, the arylation of these substrates has been investigated by numerous research groups.

Despite similarities between α-arylation of ketones and α-arylation of sulfonamides, the p$K_a$ values of the α-hydrogens of sulfonamides, such as $CH_3SO_2NR_2$, are estimated to be in the range of 32–35.[10,11] This high p$K_a$ value is approaching those of the α-hydrogens of acetamides, $CH_3CONR_2$, which have proved to be very challenging substrates in arylation reactions.[10]

Early studies on the α-arylation of methyl sulfonamides by the Parkinson group[11] (Scheme 1, A) employed $Pd(OAc)_2$/P(*t*-Bu)$_3$, NaO-*t*-Bu, and aryl bromides and gave moderate yields (average yield with Ph-Br of 44%). The dominant by-products in these reactions were derived from deprotonation of the more acidic monoarylation product and subsequent arylation to provide diarylated products. Recently, René and co-workers explored the arylation of cyclic sulfonamides (*sultams*).[12] They noted that the arylation did not provide any product in the presence of $LiN(SiMe_3)_2$, $KN(SiMe_3)_2$, NaO-*t*-Bu, or TMP-




**Scheme 1.** Palladium-catalyzed α-arylation of sulfonamides.

MgCl·LiCl bases. Arylation of sultams was observed with TMP-ZnCl·LiCl, aryl iodides, and 10 mol% of a Pd(RuPhos)-based catalyst (Scheme 1, B). One example with chlorobenzene was presented in this study that gave 39% yield. The results from these two groups suggest that the direct C–H arylation of sulfonamides is a challenging reaction.

The Zhou group also reported difficulties in the direct C–H functionalization of sulfonamides.[13] They found that the reaction of 1-(methylsulfonyl)piperidine, bromobenzene, and $LiN(SiMe_3)_2$ in the presence of a palladium catalyst failed to give coupling product. Switching to a Negishi coupling with intermediate transmetallation to zinc, they discovered that the combination of 1.25 equiv. $LiN(SiMe_3)_2$ and 1.5 equiv. of $ZnCl_2$ with methyl sulfonamides and a Pd(X-Phos)-based catalyst resulted in cross-coupling to furnish the arylation product in good to excellent yields (Scheme 1, C).[14] Although the transmetallation to zinc facilitated the coupling process, introduction of the zinc salts increases the cost and lowers the overall atom economy.

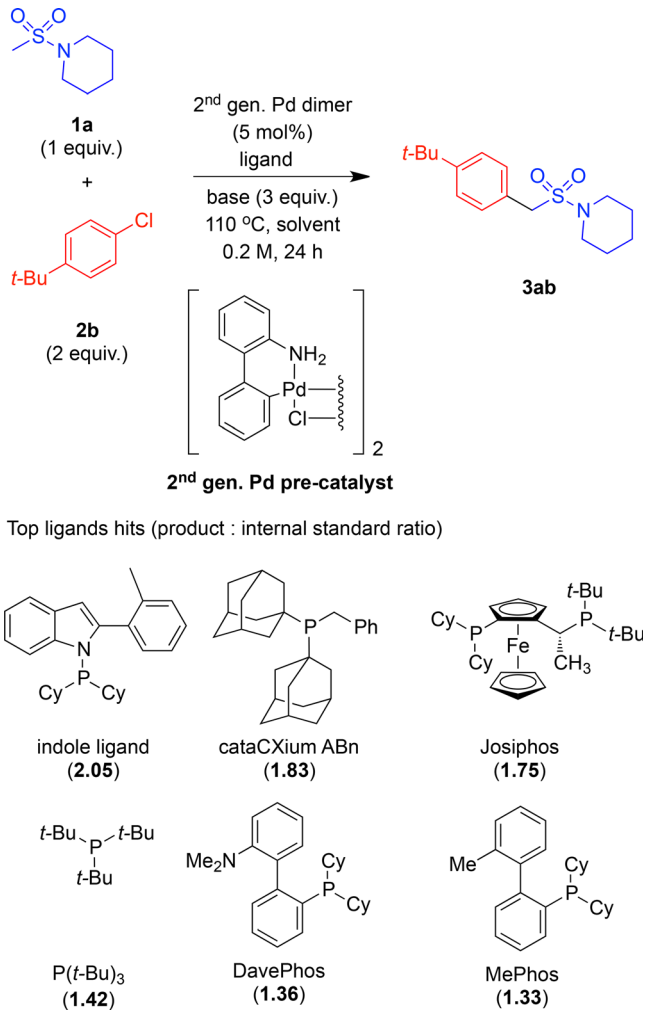
Despite these efforts, a general direct intermolecular C–H α-arylation of methyl sulfonamides with more economical and abundant *aryl chlorides* is scarcely reported. Herein, we report the first chemoselective mono-arylation of methyl sulfonamides with aryl chlorides (Scheme 1, D). A Buchwald-type pre-catalyst[15] formed with Kwong's indole-based ligand[16] and alkoxide base led to formation of mono-arylation products, with no diarylation observed. This method has been applied to the efficient synthesis of the marketed medication sumatriptan.

## Results and Discussion

Two important variables in the development of arylation of weakly acidic C($sp^3$)–H's are (i) identification of a suitable ligand and (ii) choice of a palladium precursor that will efficiently generate the catalyst. Based on our previous experience in the palladium-catalyzed α-arylation of sulfoxides,[17] sulfones,[18] and amides,[19] we initiated studies of the coupling between 1-(methylsulfonyl)piperidine **1a** and aryl chlorides employing Buchwald's palladium pre-catalysts (see Table 1 for structures).

Using microscale (10 umol) high throughput experimentation (HTE) techniques[20] we examined the coupling between 1-(methylsulfonyl)piperidine **1a** and 4-*tert*-butyl-1-chlorobenzene **2b** by screening ligands (Scheme 2) known to perform well in many coupling reactions. A total of 37 electronically diverse mono- and bidentate phosphines were examined using Buchwald's 2nd generation palladium dimer, LiO-*t*-Bu as base, toluene as solvent at 110 °C for 24 h (see the Supporting Information for details). In the ligand screen, the reaction using Kwong's indole-based ligand exhibited the highest assay yield based on the product/internal standard ratio (2.05) (determined by integration of the product against the biphenyl internal standard by HPLC (UV/vis, see the Supporting Information for details). Other ligands that showed good HPLC assay yields were cataCXium ABn (1.83), JosiPhos (1.75), P(*t*-Bu)$_3$ (1.42), DavePhos (1.36), MePhos (1.33).

With the best ligand hit, we next conducted a second microscale screen (0.01 mmol) focusing on six bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and $KN(SiMe_3)_2$] and four solvents [THF, CPME, DME, toluene] with Buchwald's 2nd and 3rd generation palladium dimers (see the Supporting Information for details). The most promising hit from this screen was LiO-*t*-Bu, Buchwald-type 2nd generation palladium dimer in toluene at 110 °C. On a laboratory scale (0.1 mmol), such conditions led to the desired arylation product in 96%

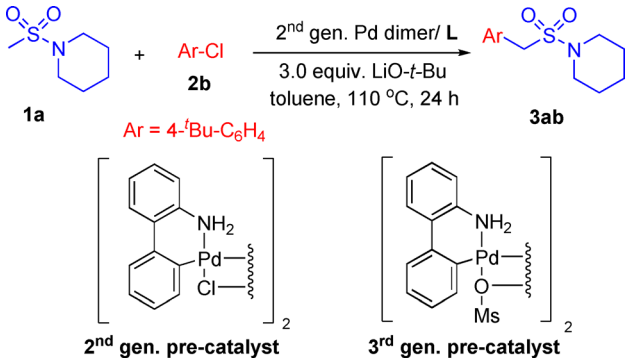



**Scheme 2.** Ligand screening.

assay yield (determined by $^1$H NMR analysis, Table 1, entry 1). Changing the concentration from 0.2 to 0.1 and 0.05 M resulted in decreased assay yields to 88% and 80%, respectively (entries 2 and 3). A significant decrease in assay yield to 66% was observed when lowering the temperature to 80 °C (entry 4). Further optimization of the catalyst loading indicated that the assay yield fell to 87% at 5 mol% Pd (entry 5) and dropped to 75% at 2.5 mol% (entry 6). Using 5.0 mol% palladium, the isolated yield was 85% (entry 5).

Starting from the optimized conditions (Table 1, entry 5), we explored the scope of the reaction (Table 2). In general, mono-arylated products were formed with very good yields. Chlorobenzene rendered product **3aa** in 80% yield. Aryl chlorides bearing electron donating 4-*t*-Bu (**2b**) and 4-methoxy (**2c**) groups provided products in excellent yields at 5 and 10 mol% Pd loading (85% and 79% yield, respectively, for **3ab** and **3ac**). 4-Fluoro-1-chlorobenzene was successfully coupled with **1a** to afford **3ad** in 69%

**Table 1.** Optimization of α-arylation of sulfonamide **1a** with Ar-Cl **2b**.[a,b]



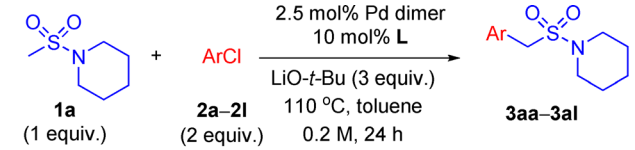

| Entry | Dimer/L [mol%] | Conc. [M] | Temp. [°C] | Assay yield [%] |
|---|---|---|---|---|
| 1 | 5/20 | 0.2 | 110 | 96 |
| 2 | 5/20 | 0.1 | 110 | 88 |
| 3 | 5/20 | 0.05 | 110 | 80 |
| 4 | 5/20 | 0.2 | 80 | 66 |
| 5 | 2.5/10 | 0.2 | 110 | 87 (85)[c] |
| 6 | 1.25/5 | 0.2 | 110 | 75 |

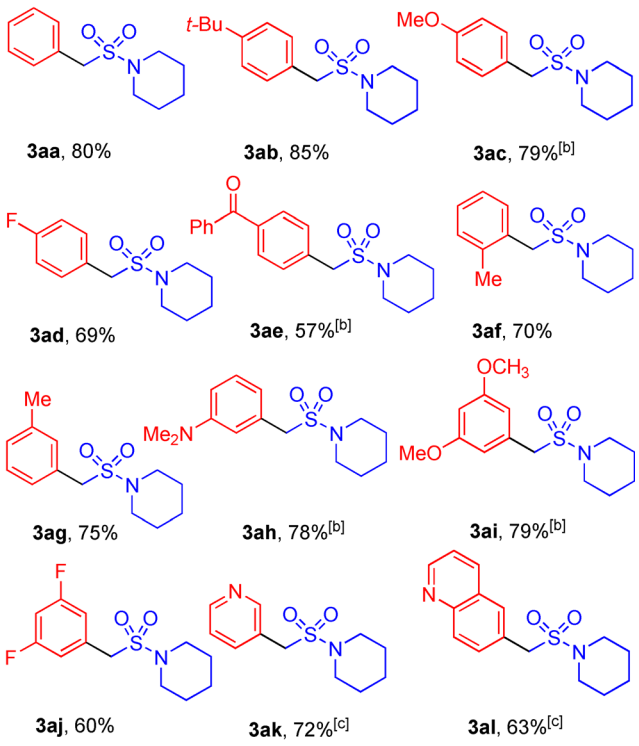
[a] Reactions conducted on a 0.1 mmol scale using 1 equiv. of **1a**, 3 equiv. of LiO-*t*-Bu, and 2 equiv. of ArCl.
[b] Yields determined by $^1$H NMR spectroscopy of the crude reaction mixtures on a 0.1 mmol scale.
[c] Isolated yield after chromatographic purification.

yield. Electron poor 4-chlorobenzophenone afforded **3ae** in 57% yield at 10 mol% Pd loading in CPME. Sterically hindered 2-chlorotoluene (**2f**) delivered desired product **3af** in 70% yield. Aryl chlorides bearing various substituents at the 3-position were good substrates. For example, 3-chlorotoluene furnished the product (**3ag**) in 75% yield, 3-chloro-*N*,*N*-dimethylaniline provided **3ah** in 78% yield (10 mol% Pd in CPME), 1-chloro-3,5-dimethoxybenzene led to **3ai** in 79% yield (10 mol% Pd in CPME), and 1-chloro-3,5-difluorobenzene resulted in formation of **3aj** in 60% yield. Heteroaryl chlorides 3-chloropyridine and 5-chloroquinoline were coupled with **1a** to afford **3ak** and **3al** in 72% and 63% yield, respectively, after extending reaction times to 48 h.

We next examined the substrate scope of sulfonamides with different substituents on the nitrogen (Table 3). Arylation of pyrrolidine-substituted sulfonamide (**1b**) was sluggish under the optimized conditions, and required increasing Pd loading from 5 to 10 mol% to afford product **3ba** in 75% yield. Morpholine substituted sulfonamide **1c** underwent coupling with chlorobenzene to give product **3ca** in 69% yield under the standard conditions. Acyclic substrates *N*,*N*-dimethyl (**1d**) and *N*,*N*-diethyl (**1e**) methyl sulfonamides coupled with chlorobenzene to form the mono-arylated products **3da** and **3ea** in 78% and 63% yield, respectively. Extending the alkyl

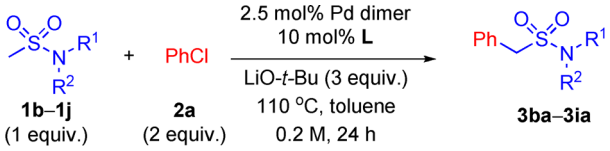
**Table 2.** Substrate scope of aryl chlorides in the α-arylation of sulfonamide **1a** with Kwong's indole-based phosphine.[a]

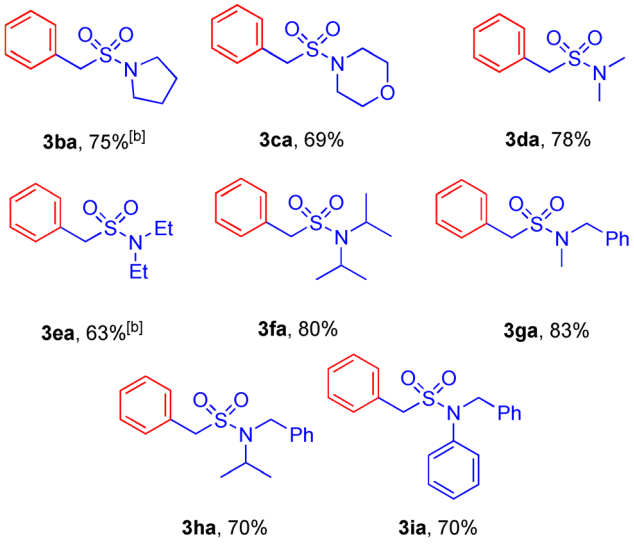


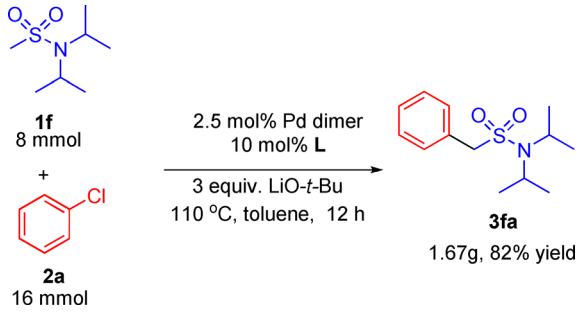

[a] Reactions conducted on a 0.2 mmol scale using 1 equiv. of **1a**, 3 equiv. of LiO-*t*-Bu, and 2 equiv. of ArCl. Isolated yields after chromatographic purification.
[b] 10 mol% Pd loading in CPME.
[c] 10 mol% Pd loading after 48 h.

**Table 3.** Substrate scope of sulfonamides in the α-arylation of aryl chloride **2a**.[a]




[a] Reactions conducted on a 0.2 mmol scale using 1 equiv. of sulfonamide, 3 equiv. of LiO-*t*-Bu, and 2 equiv. of PhCl. Isolated yield after chromatographic purification.
[b] 10 mol% Pd loading.




**Scheme 3.** Gram scale synthesis of **3fa**.

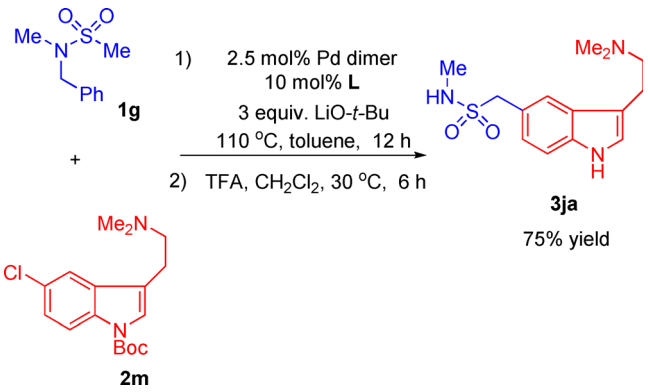
group to *N,N*-diisopropyl rendered product **3fa** in 80% yield. Furthermore, *N*-benzyl-*N*-methyl, *N*-benzyl-*N*-isopropyl, and *N*-benzyl-*N*-phenyl-substituted sulfonamides led to satisfactory yields of arylation products **3ga**, **3ha**, **3ia** in 83, 70 and 70% yield, respectively, without any arylation at the benzylic positions observed.[21]

We desired to evaluate the scalability of our method (Scheme 3). We conducted the arylation of *N,N*-diisopropylmethanesulfonamide **1f** with chlorobenzene **2a** on an 8 mmol scale with 5.0 mol% Pd loading. The product **3fa** was isolated in 82% yield (1.67 g).

We next applied our method in the synthesis of a marketed pharmaceutical. Sumatriptan is a 5-HT receptor agonist[22] used in the treatment of migraines. The synthesis of sumatriptan (**3ja**) was envisioned through the coupling of *N*-benzyl-*N*-methylmethanesulfonamide (**1g**) with *tert*-butyl 5-chloro-3-[2-(dimethylamino)ethyl]-1*H*-indole-1-carboxylate (**2m**). The coupling between **1g** and **2m** under standard conditions followed by removal of the protecting group gave rise to sumatriptan in 75% yield (Scheme 4).

## Conclusions

In summary, benzylic sulfonamides are an important class of bioactive compounds and marketed pharmaceuticals. One can envision the rapid assembly of an array of such compounds from methyl sulfonamides and commercially available aryl halides, however, an




**Scheme 4.** Synthesis of sumatriptan (**3ja**).

α-arylation of methyl sulfonamides that avoids an intermediate transmetallation step remained elusive. Herein, we advance the first general palladium-catalyzed α-arylation of sulfonamides with *aryl chlorides*. Under the optimized reaction conditions, good to excellent yields of mono-arylated methyl sulfonamides have been achieved.

A significant finding of our research efforts into the α-arylation of sulfonamides, sulfones, and sulfoxides is that Kwong's indole-based phosphine exhibits excellent selectivity with these challenging substrates. Despite the increased acidity of the products over the starting materials by at lease 5 p$K_a$ units, we observe mono-arylation with high selectivity. We hypothesize that the large size of Kwong's ligand is responsible for the remarkable selectivity for the monoarylation product in these reactions. We attribute the observed selectivity to a slow rate of transmetallation of the deprotonated benzyl sulfonamide with Pd(II) ligated to Kwong's bulky phosphine. It will be interesting to see if our hypothesis above can be supported by successful application of Kwong's ligand to other systems where diarylation is problematic.

## Experimental Section

### General Information

All reactions were carried out under an atmosphere of dry nitrogen. Anhydrous dioxane, CPME, and toluene were purchased from Sigma–Aldrich and used without further purification. THF was dried through activated alumina columns. Unless otherwise stated, all reagents were commercially available and used without further purification. Flash chromatography was performed with silica gel (300–400 mesh). The NMR spectra were obtained using a Brüker 500 MHz Fourier-transform NMR spectrometer. High-resolution mass spectrometry (HR-MS) data were obtained on a Waters LC-TOF mass spectrometer (model LCT-XE Premier) using chemical ionization (CI) or electrospray ionization (ESI) in positive or negative mode, depending on the analyte.

### General Experimental Procedure: High-Throughput Experimentation Screening for Palladium-Catalyzed α-Arylation of Methyl Sulfonamides with Aryl Chlorides

**(1) Screening of ligand:** ***Set up:*** Two 24-well plate experiments were set up inside a glovebox under a nitrogen atmosphere. A 24-well aluminum block containing 1 mL glass vials was predosed with Buchwald-type 2$^{nd}$ generation palladium dimer (0.5 μmol) and the phosphine ligands (2 μmol for monodentate ligands and 1 μmol for bidentate ligands) in THF. The solvent was removed to dryness using a GeneVac and LiO-*t*-Bu (30 μmol) in THF was added to the ligand/catalyst mixture. The solvent was removed on the GeneVac and a parylene stir bar was then added to each reaction vial. 1-(Methylsulfonyl)piperidine **1a** (10 μmol/reaction) and 4-*tert*-butyl-1-chlorobenzene **2b** (20 μmol) were then dosed together into each reaction vial as a solution in toluene (50 μL, 0.2 M). The 24-well plate was then sealed and stirred for 24 h at 110 °C.

***Work up:*** Upon opening the plate to air, 500 μL of a solution of biphenyl (used as internal standard to measure HPLC yields) in acetonitrile (0.002 mol/L) were added into each vial. The plate was covered again and the vials stirred for 10 min to ensure good homogenization. Into a separate 96-well LC block were added 700 μL of acetonitrile, followed by 25 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

**(2) Screening of Pd source, base and solvent:** ***Set up:*** Experiments were set up inside a glovebox under a nitrogen atmosphere. A 24-well aluminum block containing 1 mL glass vials was predosed with 2$^{nd}$ gen. Pd dimer (0.5 μmol) and the *N*-(dicyclohexylphosphino)-2,2′-tolylindole (2 μmol) in THF. The solvent was removed to dryness using a GeneVac and 6 different bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$ 30 μmol] in THF were added to the ligand/catalyst mixture. The solvent was removed on the GeneVac and a parylene stir bar was then added to each reaction vial. 1-(Methylsulfonyl)piperidine **1a** (10 μmol/reaction) and 4-*tert*-butyl-1-chlorobenzene **2b** (20 μmol/reaction) were then dosed together into each reaction vial as a solution in 4 different solvents (CPME, THF, DME, toluene, 50 μL, 0.2 M). The 24-well plate was then sealed and stirred for 24 h at 110 °C then cooled to room temperature.

***Work up:*** Upon opening the plate to air, 500 μL of a solution of biphenyl (used as internal standard to measure HPLC yields) in acetonitrile (0.002 mol/L) were added into each vial. The plate was covered again and the vials stirred for 10 min to ensure good homogenization. Into a separate 96-well LC block were added 700 μL of acetonitrile, followed by 25 μL of the diluted reaction mixtures. The LC block was then sealed with a silicon-rubber storage mat and mounted on an automated HPLC instrument for analysis.

### Procedures for the Pd-Catalyzed Arylation of Sulfonamides

An oven-dried microwave vial equipped with a stir bar was charged with 2$^{nd}$ generation Pd dimer (7.2 mg, 0.010 mmol) and ligand **L** (16.2 mg, 0.040 mmol) under a nitrogen atmos-

phere, followed by 1 mL dry toluene *via* syringe. After the catalyst solution had been stirred for 120 min at 25 °C, LiO-*t*-Bu (48.3 mg, 0.60 mmol, 3.0 equiv.) was added to the reaction vial and 1-(methylsulfonyl) piperidine (32.6 mg, 0.20 mmol, 1.0 equiv.) was added dropwise. The microwave vial was sealed and chlorobenzene (40.6 μL, 0.40 mmol, 2.0 equiv.) was added by syringe while under a nitrogen atmosphere. The reaction was stirred at 110 °C for the specified time then allowed to cool to room temperature. The reaction mixture was quenched with $H_2O$ (0.2 mL) and passed through a short pad of silica gel and eluted with ethyl acetate. The combined organics were dried over $Na_2SO_4$ and concentrated under vacuum. The crude residue was purified by flash column chromatography to yield the monoarylated sulfonamides derivatives **3**.

### Synthesis of Sumatriptan 3ja

The reaction was performed following the general procedure with **2m** (128.9 mg, 0.40 mmol), LiO-*t*-Bu (48.3 mg, 0.60 mmol) and **1g** (39.8 mg, 0.20 mmol). Then the crude material was reacted in $CF_3COOH$ for 12 h. After work-up following the general procedure, the product was purified by flash chromatography on silica gel (eluted with MeOH:$CH_2Cl_2$ = 2:1) to give the product **3ja** as a white solid; yield: 44.2 mg (75%). The $^1H$ and $^{13}C\{^1H\}$ NMR data for this compound match the literature data.

## Acknowledgements

*We thank the National Science Foundation (CHE-1464744) and National Institutes of Health (NIGMS 104349) for financial support. BZ thanks the Chinese Universities Scientific Fund (2015QC001) and Peking College Students Innovation Training Program (2015bj127 and 2015bj145).*

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**8** Palladium-Catalyzed α-Arylation of Methyl Sulfonamides with Aryl Chlorides

*Adv. Synth. Catal.* **2016**, *358*, 1 – 8

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