ChemInform Abstract: Pd/Cu-Catalyzed C-H Arylation of 1,3,4-Thiadiazoles with (Hetero)aryl Iodides, Bromides, and Triflates.

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · SEPTEMBER 2012

Impact Factor: 4.72 · DOI: 10.1021/jo301401q · Source: PubMed

3 AUTHORS, INCLUDING:

Dipak D. Vachhani
University of Leuven
31 PUBLICATIONS **367** CITATIONS

SEE PROFILE

JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

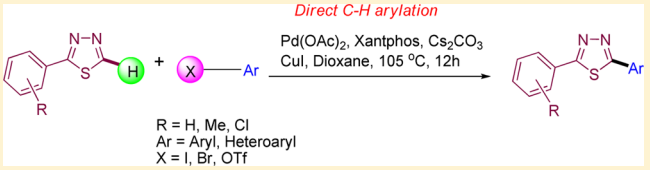
Pd/Cu-Catalyzed C−H Arylation of 1,3,4-Thiadiazoles with (Hetero)aryl Iodides, Bromides, and Triflates

Dipak D. Vachhani,[†] Abhishek Sharma,[†,‡] and Erik Van der Eycken*[,†]

[†]Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001, Leuven, Belgium

Supporting Information

ABSTRACT: The direct C−H arylation of 1,3,4-thiadiazoles with a wide range of (hetero)aryl iodides, bromides, and triflates is described using a Pd/Cu-catalyzed protocol. The methodology is compatible with substrates possessing electron-donating or electron-withdrawing substituents and also tolerates sterically hindered aryl halides. The utility of the developed protocol is demonstrated by a one-pot C−H arylation-Suzuki coupling sequence.

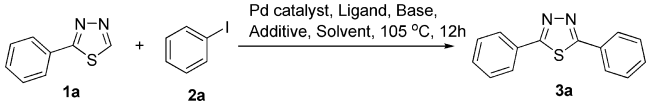


1,3,4-Thiadiazoles represent an important class of five-membered heterocycles possessing diverse biological properties[1] including adenosine[1a]/histamine[1b] receptor antagonists, antidiabetic,[1c] antidepressant[1d] and anticancer[1e] activities. Moreover, they have also found applications in material science[2] and for the synthesis of heterocycles fused[3] with peptides. Thus it would be highly desirable if direct functionalization strategies could be developed for this heteroarene, thereby enabling the late stage decoration of the thiadiazole core.

In recent years, transition-metal-catalyzed direct C−H arylation has emerged as a promising stratgey for the construction of biaryl units.[4] In this context, a diverse range of N- and/or O-containing heteroarenes has been arylated using aryl halides/pseudohalides.[4c,d,5] However, the scope of C−H arylation of various heterocyclic systems still needs to be evaluated. In particular, S-containing heterocycles pose a significant challenge due to the poisoning effect of sulfur,[6] although thiazoles, thiophenes have been found to undergo direct C−H arylations.[7] To the best of our knowledge, a direct arylation of 1,3,4-thiadiazoles with aryl halides has not been reported until date. We describe herein, a Pd/Cu-catalyzed direct C−H arylation of various 1,3,4-thiadiazoles using a wide range of aryl iodides/bromides as well as triflates.

In continuation of our longstanding interest in the synthesis and diversification of novel heterocycles bearing biaryl units,[8] we initiated our studies with the direct C−H arylation of 2-phenyl-1,3,4-thiadiazole (**1a**, 0.5 mmol) with phenyl iodide (**2a**, 2 equiv) under concerted metalation-deprotonation (CMD) conditions[7d,9] using $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Cs_2CO_3 (2 equiv) and pivalic acid (30 mol %) as additive in DMA. However, after heating the above reaction mixture at 105 °C for 12 h, the desired product **3a** could only be obtained in 15% yield (Table 1, entry 1). Replacement of DMA with dioxane enhanced the yield to 30% (Table 1, entry 2) while DME as solvent led to a lower yield (Table 1, entry 3). Further, the use of K_2CO_3 as base provided **3a** in only trace amounts (Table 1, entry 4). Screening of various other ligands and Pd-catalysts (Table 1, entries 5−8) failed to further improve the reaction. Interestingly, replacement of pivalic acid by CuI (10 mol %) as additive substantially enhanced the yield of **3a** (84%, Table 1, entry 9). The use of PPh_3 in place of Xantphos under these new conditions decreased the reaction performance (54% yield, Table 1, entry 10). Further, the replacement of conventional heating with microwave irradiation resulted in

Table 1. Optimization of the Direct Arylation of 2-Phenyl-1,3,4-thiadiazole[a]



1a 2a 3a

entry	solvent	base	Pd/Ligand	additive	yield[b] (%)
1	DMA	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	Pivalic acid	15
2	Dioxane	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	Pivalic acid	30
3	DME	Cs2CO3	$Pd(OAc)_2/PPh_3$	Pivalic acid	28
4	Dioxane	K_2CO_3	$Pd(OAc)_2/PPh_3$	Pivalic acid	traces
5	Dioxane	Cs_2CO_3	$Pd(OAc)_2$/dppp	Pivalic acid	27
6	Dioxane	Cs_2CO_3	$Pd(OAc)_2$/Xantphos	Pivalic acid	30
7	Dioxane	Cs_2CO_3	$Pd(OAc)_2$/CyJohnphos	Pivalic acid	traces
8	Dioxane	Cs_2CO_3	$Pd(PPh_3)Cl_2$	Pivalic acid	7
9	Dioxane	Cs_2CO_3	$Pd(OAc)_2$ /Xantphos	CuI	84 (73)[c]
10	Dioxane	Cs_2CO_3	$Pd(OAc)_2/PPh_3$	CuI	54
11	Dioxane	Cs_2CO_3	$Pd(OAc)_2$ /Xantphos	CuI	27[d]
12	Dioxane	Cs_2CO_3		CuI	nd[e]

[a]General Conditions: **1a** (0.5 mmol), Pd-catalyst (5 mol %), ligand (10 mol %), base (2 equiv), additive: pivalic acid (30 mol %), CuI (10 mol %), solvent (2 mL), **2a** (2 equiv), 105 °C, 12 h. [b]Yield of isolated product. [c]Yield of the reaction under focused microwave irradiation (105 °C, 100 W), 50 min. [d]$Pd(OAc)_2$ (2 mol %), Xantphos (4 mol %) and CuI (4 mol %) were used. [e]Not detected.

Received: July 5, 2012
Published: September 7, 2012

   dx.doi.org/10.1021/jo301401q | J. Org. Chem. 2012, 77, 8768−8774

reduced reaction time (50 min) but afforded comparatively lower yield of **3a** (73%, Table 1, entry 9). On the other hand, direct arylation of **1a** did not proceed in the absence of Pd using CuI as the sole catalyst (Table 1, entry 12).

Having established the optimum conditions, the substrate scope was next examined. The protocol was found to be broadly applicable for C−H arylation of thiadiazoles bearing electron donating or withdrawing substituents on phenyl ring (Table 2).

The arylation could be accomplished efficiently using aryl iodides/bromides as well as triflates. Moreover, the sterically hindered *o*-tolyl bromide (2e) or *o*-phenyl bromobenzene (2p) were tolerated (Table 2, entries 5, 14, 20) while the aryl halide possessing bulkier 2,6-diisopropyl substitution was not compatible (Table 2, entry 21). On the other hand, no reaction was observed using aryl halides bearing highly polar substituents like nitro (Table 2, entry 4) or carboxylic acid (Table 2, entry 17) presumably due to catalyst inactivation.[10] Importantly, the use of heteroaryl halides comprising thiophene, pyridine or even indole moieties (Table 2, entries 7, 9, 10 and 13) was found to be feasible, thereby enabling a facile diversification into biologically important biheterocyclic frameworks.[11]

Encouraged by the good tolerance for the above conditions of the 4-chloro-phenyl substituent (Table 2, entries 2, 12−14 and 19), we became interested to introduce further diversity employing this moiety. A one-pot C−H arylation-Suzuki coupling sequence was envisaged, wherein after the initial formation of **3b**, *p*-tolylboronic acid **4**, (1.5 equiv), $Pd(OAc)_2$ (5 mol %), SPhos (10 mol %), K_3PO_4 (2 equiv) THF/water (3:1) (2 mL) were added and the mixture was heated at 105 °C for 8 h. To our great satisfaction, this one-pot approach successfully afforded the corresponding **5a** in 58% overall yield (Table 3, entry 1).[12] Analogously, the **5b** could be synthesized in 70% overall yield (Table 3, entry 2).

On the basis of experimental observations as as well as some earlier reports,[13] a plausible mechanism of this Pd/Cu-catalyzed direct arylation of thiadiazoles might involve a base assisted cupration of the thiadiazole to give the aryl-Cu species **I** (Scheme 1).[13] Subsequently, **I** undergoes transmetalation with an aryl-Pd complex (**II** formed by the oxidative addition of Pd^0 to aryl halide) to give intermediate **III** which undergoes reductive elimination to furnish the product with concomitant release of both the Pd and Cu catalyst.

In conclusion, we have elaborated a hitherto unknown direct C−H arylation of substituted 1,3,4-thiadiazoles using a Pd/Cu-catalyzed protocol. This is applicable for the facile coupling of 2-substituted 1,3,4-thiadiazoles with a wide range of aryl halides/triflates bearing electron donating/withdrawing groups or ortho substituents. Moreover, heteroaryl halides bearing thiophene, pyridine and indole moieties could also be successfully employed. Interestingly, a one-pot direct arylation−Suzuki coupling sequence was found to be feasible, thereby furnishing a convenient access to polyarylated thiadiazoles.

EXPERIMENTAL SECTION

Materials. The various 1,3,4-thiadiazoles were synthesized according to a known literature procedure.[14] The aryl halides, reagents and catalysts were obtained from commercial sources and used as such. For thin layer chromatography, analytical TLC plates (70−230 mesh silica gel) were used. Column chromatography was performed using silica gel (60−120 mesh size). Anhydrous solvents were purchased from commercial sources and stored over molecular sieves. The chromatographic solvents used for isolation/purification of compounds were distilled prior to use. The chromatographic solvents are mentioned as volume:volume ratios. Reactions were typically run in oven-dried screw-cap vial under inert atmosphere.

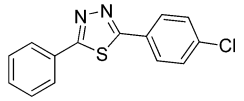
Apparatus. NMR spectra were recorded at 300 MHz (^{1}H) and 75.5 MHz (^{13}C). The ^{1}H and ^{13}C chemical shifts are reported in parts per million relative to tetramethylsilane using the residual solvent signal as the internal reference. The following abbreviation were used to designate chemical shift multiplicities: s = singlet, bs = broad singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet. The ^{13}C NMR spectra are proton decoupled. High-resolution mass spectra were recorded by using double-focusing magnetic sector analyzer and at an ion source temperature 150−250 °C as required. High resolution EI-mass spectra were performed with a resolution of 10 000.

Microwave Irradiation Experiment. All microwave irradiation experiments were carried out in a dedicated CEM-Discover monomode microwave apparatus, operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 300 W with utilization of the standard absorbance level of 300 W maximum power. The reactions were carried out in 10-mL glass tubes, sealed with Teflon septum and placed in the microwave cavity. Initially, microwave irradiation of required watts was used and the temperature is being ramped from room temperature to the desired temperature. Once this was reached the reaction mixture was held at this temperature for the required time. The reaction mixture was continuously stirred during the reaction. The temperature was measured with an IR sensor on the outer surface of the process vial. After the irradiation period, gas jet cooling cooled the reaction vessel rapidly to ambient temperature.

General Procedure for Arylation of 1,3,4-Thiadiazole. *Synthesis of 2,5-Diphenyl-1,3,4-thiadiazole (Table 2, **3a**).* **1a** (81 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Xantphos (28.9 mg, 0.05 mmol), Cs_2CO_3 (326 mg, 1.0 mmol) and CuI (9.5 mg, 0.05 mmol) were taken in a 10 mL oven-dried screw-cap vial and **2a** (204 mg, 1 mmol), 1,4-Dioxane (1.5 mL) were added to it. The reaction tube was evacuated-backfilled with argon (5 cycles), sealed and subsequently heated at 105 °C for 12 h. After completion of the reaction (confirmed by mass and TLC analysis), poured in to water (50 mL) and extracted by ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (using 5−10% EtOAc in heptane as eluant) to afford **3a** as a white solid (100 mg, 84% yield), mp 131−133 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−7.96 (m, 4H), 7.55−7.44 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.1, 131.0, 130.1, 129.1, 127.9. HRMS (EI): calcd for $C_{14}H_{10}N_2S$ 238.0565, found 238.0553

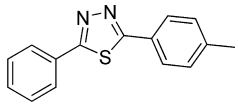
The above procedure was also used for heteroarylation of various other 1,3,4-thiadiazoles (Table 2, **3b**−**r**).

*2-(4-Chlorophenyl)-5-phenyl-1,3,4-thiadiazole (Table 2, **3b**).*



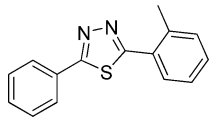
White solid, mp 179−181 °C, 81 mg, yield 60%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06−7.88 (m, 4H), 7.58−7.39 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 166.8, 137.2, 131.2, 129.9, 129.4, 129.2, 129.1, 129.0, 128.6, 127.9. HRMS (EI): calcd for $C_{14}H_9ClN_2S$ 272.0175, found 272.0168

*2-Phenyl-5-p-tolyl-1,3,4-thiadiazole (Table 2, **3c**).*



White solid, mp 123−124 °C, 99 mg, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07−7.97 (m, 2H), 7.91 (d, J = 7.74 Hz, 2H), 7.53−7.46 (m, 3H), 7.30 (d, J = 7.53 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 167.7, 141.5, 131.5, 130.2, 129.8, 129.1, 127.9, 127.89, 127.84, 127.4, 21.5 . HRMS (EI): calcd for $C_{15}H_{12}N_2S$: 252.0721, found: 252.0719

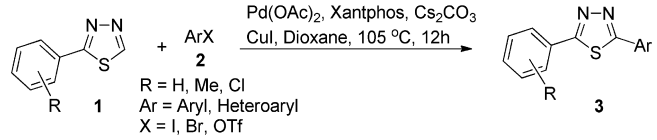
*2-Phenyl-5-o-tolyl-1,3,4-thiadiazole (Table 2, **3e**).*



Creamish white solid, mp 55−57 °C, 96 mg, yield 76%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08−7.98 (m, 2H), 7.74 (d, J = 7.53 Hz, 1H), 7.55−7.47 (m, 3H), 7.44−7.28 (m, 3H), 2.65 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$):

dx.doi.org/10.1021/jo301401q | J. Org. Chem. 2012, 77, 8768−8774

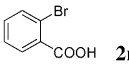
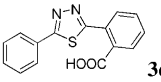
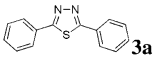
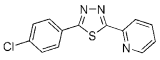
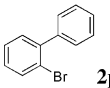
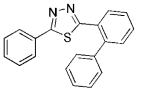
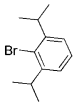
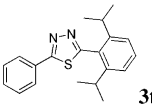
Table 2. Substrate Scope of the Pd/Cu-catalyzed Direct Arylation of 1,3,4-Thiadiazoles[a]



entry	substrate (**1**)	Ar-X (**2**)	product (**3**)	yield[b] (%)
1	**1a**	**2a**	**3a**	84
2	**1a**	**2b**	**3b**	60
3	**1a**	**2c**	**3c**	79
4	**1a**	**2d**	**3d**	traces
5	**1a**	**2e**	**3e**	76
6	**1a**	**2f**	**3f**	81
7	**1a**	**2g**	**3g**	79
8	**1b**	**2c**	**3h**	74
9	**1b**	**2h**	**3i**	38
10	**1b**	**2i**	**3j**	51
11	**1c**	**2c**	**3k**	71
12	**1b**	**2j**	**3l**	69
13	**1c**	**2g**	**3m**	78
14	**1c**	**2e**	**3n**	74
15	**1a**	**2k**	**3o**	49
16	**1a**	**2l**	**3p**	79

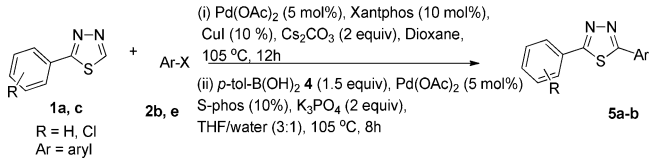
dx.doi.org/10.1021/jo301401q | J. Org. Chem. 2012, 77, 8768−8774

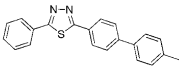
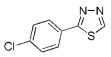
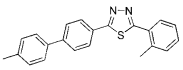
Table 2. continued

entry	substrate (**1**)	Ar-X (**2**)	product (**3**)	yield[b] (%)
17	**1a**	 **2m**	 **3q**	nd[c]
18	**1a**	 **2n**	 **3a**	72
19	**1c**	 **2o**	 **3r**	39
20	**1a**	 **2p**	 **3s**	24
21	**1a**	 **2q**	 **3t**	nd[c]

[a]Conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), Cs_2CO_3 (2 equiv), CuI (10 mol %), **2** (2 equiv) in dioxane (1.5 mL), 105 °C, 12 h. [b]Yield of isolated product. [c]Not detected.

Table 3. One-pot Sequential C−H Arylation-Suzuki Coupling of 1,3,4-Thiadiazoles[a]

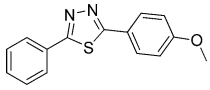


entry	substrate (**1**)	Ar-X (**2**)	product (**5**)	yield[b] (%)
1	 **1a**	 **2b**	 **5a**	58
2	 **1c**	 **2e**	 **5b**	70

[a]Conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (10 mol %), Cs_2CO_3 (2 equiv), CuI (10 mol %), **2** (1.5 equiv) in dioxane (1.5 mL), 105 °C, 12 h; then *p*-tolylboronic acid (1.5 equiv), K_3PO_4 (2 equiv), $Pd(OAc)_2$ (5 mol %), S-phos (10 mol %), THF/water (3:1) (2 mL), 105 °C, 8 h. [b]Yield of isolated product.

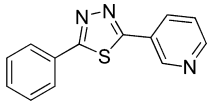
δ 168.6, 167.4, 137.3, 131.6, 131.1, 130.7, 130.4, 130.1, 129.2, 127.9, 126.3, 21.7. HRMS (EI): calcd for $C_{15}H_{12}N_2S$ 252.0721, found 252.0731.

*2-(4-Methoxyphenyl)-5-phenyl-1,3,4-thiadiazole (Table 2, **3f**).*



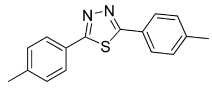
White solid, mp 136−137 °C, 108 mg, yield 81%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05−7.98 (m, 2H), 7.96 (d, *J* = 8.46 Hz, 2H), 7.57−7.43 (m, 3H), 7.01 (d, *J* = 8.46 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 167.3, 161.9, 130.9, 130.2, 129.4, 129.1, 127.8, 122.8, 114.5, 55.4. HRMS (EI): calcd for $C_{15}H_{12}N_2OS$ 268.0670, found 268.0653

*2-Phenyl-5-(pyridine-3-yl)-1,3,4-thiadiazole (Table 2, **3g**).*



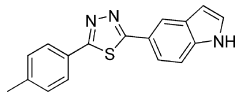
White solid, mp 147−149 °C, 94 mg, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.75 (d, *J* = 3.96 Hz, 1H), 8.38 (d, *J* = 7.89 Hz, 1H), 8.10−7.95 (m, 2H), 7.60−7.40 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 164.7, 151.8, 148.8, 134.7, 131.4, 129.7, 129.2, 128.0, 126.5, 123.9. HRMS (EI): calcd for $C_{13}H_9N_3S$ 239.0517, found 239.0503

*2,5-dip-Tolyl-1,3,4-thiadiazole (Table 2, **3h**).*



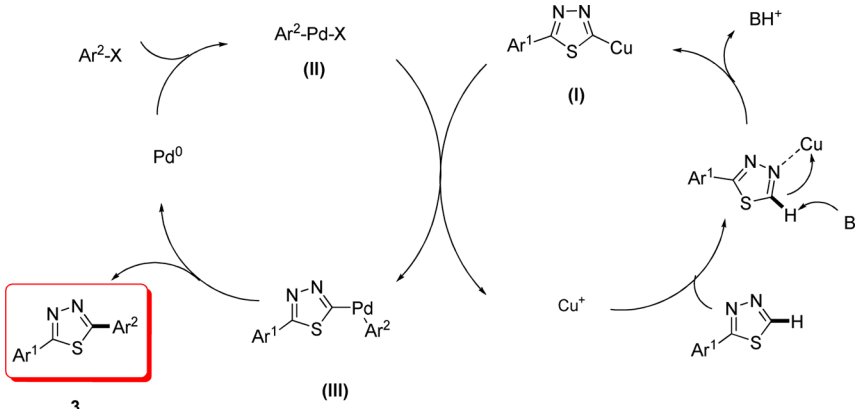
White solid, mp 146−148 °C, 98 mg, yield 74%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.10 Hz, 4H), 7.29 (d, *J* = 7.92 Hz, 4H), 2.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 141.4, 129.8, 127.7, 21.5. HRMS (EI): calcd for $C_{16}H_{14}N_2S$ 266.0878, found 266.0858

*2-(1H-Indol-5-yl)-5-p-tolyl-1,3,4-thiadiazole (Table 2, **3i**).*



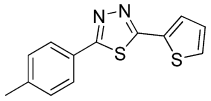
dx.doi.org/10.1021/jo301401q | J. Org. Chem. 2012, 77, 8768−8774

Scheme 1. Plausible Mechanism for the Pd/Cu-catalyzed Direct C−H Arylation of 1,3,4-Thiadiazoles



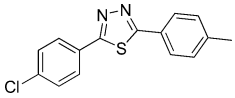
Pale-brown solid, mp 263−266 °C, 55 mg, yield 38%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 11.49 (s, 1H), 8.22 (s, 1H), 7.90 (d, J = 7.53 Hz, 2H), 7.78 (d, J = 8.64 Hz, 1H), 7.57 (d, J = 8.28 Hz, 1H), 7.49 (bs, 1H), 7.39 (d, J = 7.92 Hz, 2H), 6.61 (bs, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.1, 166.4, 141.1, 137.4, 129.9, 127.9, 127.4, 127.3, 127.0, 120.6, 120.5, 120.4, 112.3, 102.2, 20.9. HRMS (EI): calcd for $C_{17}H_{13}N_3S$ 291.0830, found 291.0833

2-(Thiophen-2-yl)-5-p-tolyl-1,3,4-thiadiazole (Table 2, ***3j****).*



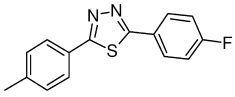
Pale-yellow solid, mp 125−127 °C, 66 mg, yield 51%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.10 Hz, 2H), 7.58 (d, J = 3.57 Hz, 1H), 7.49 (d, J = 4.89 Hz, 1H), 7.29 (d, J = 8.07 Hz, 2H), 7.13 (dd, J = 4.71, 3.93 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 161.4, 141.6, 132.5, 129.8, 129.4, 129.1, 127.9, 127.8, 127.2, 21.5. HRMS (EI): calcd for $C_{13}H_{10}N_2S_2$ 258.0285, found 258.0295

2-(4-Chlorophenyl)-5-p-tolyl-1,3,4-thiadiazole (Table 2, ***3k****).*



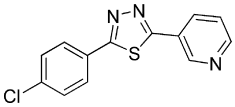
White solid, mp 184−186 °C, 102 mg, yield 71%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.46 Hz, 2H), 7.90 (d, J = 8.10 Hz, 2H), 7.47 (d, J = 8.46 Hz, 2H), 7.30 (d, J = 8.10 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.5, 166.4, 141.7, 137.0, 129.9, 129.4, 129.0, 128.7, 127.8, 127.2, 21.5. HRMS (EI): calcd for $C_{15}H_{11}ClN_2S$ 286.0331, found 286.0331

2-(4-Fluorophenyl)-5- p-tolyl-1,3,4-thiadiazole (Table 2, ***3l****).*



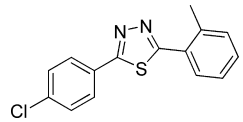
White solid, mp 177−178 °C, 77 mg, yield 57%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (dd, J = 8.37, 5.28 Hz, 2H), 7.89 (d, J = 7.92 Hz, 2H), 7.30 (d, J = 7.92 Hz, 2H), 7.19 (t, J = 8.46 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.3, 166.4, 166.0, 162.6, 141.6, 129.9, 129.88, 129.80, 127.8, 127.3, 126.6, 126.5, 116.5, 116.2, 21.5. HRMS (EI): calcd for $C_{15}H_{11}FN_2S$ 270.0627, found 270.0629.

*2-(4-Chlorophenyl)-5-(pyridin-3-yl)-1,3,4-thiadiazole (*lTable 2, ***3m****).*



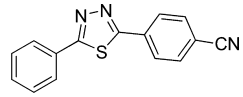
White solid, mp 179−181 °C, 106 mg, yield 78%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.18 (s, 1H), 8.75 (bs,1H), 8.37 (d, J = 7.89 Hz, 1H), 7.98 (d, J = 8.10 Hz, 2H), 7.55−7.42 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 164.9, 152.0, 148.8, 137.6, 134.7, 129.5, 129.1, 128.2, 126.3, 124.0, . HRMS (EI): calcd for $C_{13}H_8ClN_3S$ 273.0127, found 273.0132

2-(4-Chlorophenyl)-5-o-tolyl-1,3,4-thiadiazole (Table 2, ***3n****).*



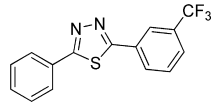
White solid, mp 134−135 °C, 106 mg, yield 74%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 8.46 Hz, 2H), 7.73 (d, J = 7.53 Hz, 1H), 7.49 (d, J = 8.49 Hz, 2H), 7.44−7.28 (m, 3H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 167.3, 137.3, 137.1, 131.6, 130.7, 130.5, 129.4, 129.1, 129.0, 128.6, 126.3, 21.6. HRMS (EI): calcd for $C_{15}H_{11}ClN_2S$ 286.0331, found 286.0353

4-(5-Phenyl-1,3,4-thiadiazol-2-yl)benzonitrile (Table 2, ***3o****).*



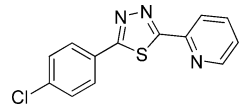
White solid, mp 210−211 °C, 64 mg, yield 49%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 8.28 Hz, 2H), 8.07−7.96 (m, 2H), 7.79 (d, J = 8.49 Hz, 2H), 7.59−7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 165.9, 134.1, 132.9, 131.6, 129.6, 129.3, 128.3, 128.1, 127.9, 118.0, 114.4. HRMS (EI): calcd for $C_{15}H_9N_3S$ 263.0517, found 263.0523

2-Phenyl-5-(3-(trifluoromethyl)phenyl)-1,3,4-thiadiazole (Table 2, ***3p****).*



White solid, mp 125−127 °C, 121 mg, yield 79%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.22 (d, J = 7.92 Hz, 1H), 8.08−7.94 (m, 2H), 7.77 (d, J = 7.92 Hz, 1H), 7.65 (t, J = 7.71 Hz, 1H), 7.58−7.41 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.8, 166.4, 132.0, 131.5, 131.4, 131.1, 130.9, 129.8, 129.83, 129.29, 129.19, 128.0, 127.9, 127.6, 127.5, 125.4, 124.7, 124.70, 124.6, 124.5, 121.8. HRMS (EI): calcd for $C_{15}H_9F_3N_2S$ 306.0439, found 306.0412.

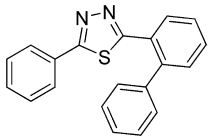
2-(4-Chlorophenyl)-5-(pyridin-2-yl)-1,3,4-thiadiazole (Table 2, ***3r****).*



White solid, mp 203−205 °C, 53 mg, yield 39%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (d, J = 4.53 Hz, 1H), 8.39 (d, J = 7.89 Hz, 1H), 7.99 (d, J = 8.46 Hz, 2H), 7.88 (t, J = 7.35 Hz, 1H), 7.49 (d, J = 8.49 Hz, 2H), 7.41 (t, J = 5.28 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 168.7, 149.8, 149.0, 137.3, 137.2, 129.4, 129.1, 128.7, 125.4, 121.0. HRMS (EI): calcd for $C_{13}H_8ClN_3S$ 273.0127, found 273.0119

dx.doi.org/10.1021/jo301401q | J. Org. Chem. 2012, 77, 8768−8774

*2-(Biphenyl-2-yl)-5-phenyl-1,3,4-thiadiazole (Table 2, **3s**).*



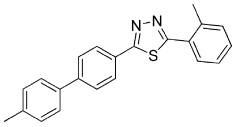
Colorless viscous liquid, 37 mg, yield 24%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19−8.11 (m, 1H), 7.85−7.75 (m, 2H), 7.58−7.47 (m, 3H), 7.44−7.35 (m, 7H), 7.33−7.27 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 166.8, 141.9, 139.7, 130.8, 130.3, 130.1, 130.0, 129.8, 129.0, 128.6, 128.2, 127.9, 127.7. HRMS (EI): calcd for $C_{20}H_{14}N_2S$ 314.0878, found 314.0880

General Procedure for One-pot Sequential C−H Arylation-Suzuki Coupling of 1,3,4-Thiadiazole. *Synthesis of 2-(4′-methylbiphenyl-4-yl)-5-phenyl-1,3,4-thiadiazole (Table 3, **5a**).* **1a** (81 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), Xantphos (28.9 mg, 0.05 mmol), Cs_2CO_3 (326 mg, 1.0 mmol) and CuI (9.5 mg, 0.05 mmol) were taken in a 10 mL oven-dried screw-cap vial and **2b** (178 mg, 0.75 mmol), 1,4-Dioxane (1.5 mL) were added to it. The reaction tube was evacuated-backfilled with argon (5 cycles), sealed and subsequently heated at 105 °C for 12 h. After completion of the reaction (confirmed by mass and TLC analysis), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), S-phos (20.5 mg, 0.05 mmol), K_3PO_4 (212.2 mg, 1 mmol), *p*-tolylboronic acid **4** (102 mg, 0.75 mmol), and THF:water (3:1) 2 mL was added and heated at 105 °C for 8 h. Subsequently, the reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (using 5−10% EtOAc in heptane as eluant) to afford **5a** as a white solid (95 mg, 58% yield),

White solid, mp 178−180 °C, 95 mg, yield 58%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 8.28 Hz, 2H), 8.05−7.97 (m, 2H), 7.71 (d, J = 8.10 Hz, 2H), 7.55 (d, J = 7.92 Hz, 2H), 7.53−7.45 (m, 3H), 7.29 (d, J = 7.89 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.98, 167.94, 143.8, 138.0, 136.9, 131.1, 130.2, 129.7, 129.2, 128.7, 128.3, 127.9, 127.5, 126.9, 21.1. HRMS (EI): calcd for $C_{21}H_{16}N_2S$ 328.1034, found 328.1037

The above procedure was also used for synthesis of **5b** (Table 3).

*2-(4′-methylbiphenyl-4-yl)-5-o-tolyl-1,3,4-thiadiazole (Table 3, **5b**).*



White solid, mp 156−158 °C, 120 mg, yield 70%, ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 8.10 Hz, 2H), 7.80−7.66 (m, 3H), 7.56 (d, J = 7.92 Hz, 2H), 7.45−7.31 (m, 3H), 7.29 (d, J = 7.71 Hz, 2H), 2.66 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.4, 167.2, 143.7, 138.0, 137.3, 136.9, 131.6, 130.7, 130.3, 129.6, 129.2, 128.6, 128.3, 127.5, 126.9, 126.2, 21.7, 21.1. HRMS (EI): calcd for $C_{22}H_{18}N_2S$ 342.1191, found 342.1203

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*erik.vandereycken@chem.kuleuven.be

Present Address

‡Department of Chemistry, University of Illinois at Urbana−Champaign, Urbana, Illinois, 61801, United States

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the FWO [Fund for Scientific Research - Flanders (Belgium)] and the Research Fund of the University of Leuven (KU Leuven) for financial support. D.D.V. is grateful to EMECW13 (Erasmus Mundus External Cooperation Window Lot 13) for obtaining a doctoral scholarship. A.S. is thankful to the FWO for obtaining a Visiting Postdoctoral Fellowship.

■ REFERENCES

(1) (a) Koezen, J. E. M.; Timmerman, H.; Vollinga, R. C.; Kunzel, J. F. V. D.; Groote, M. D.; Visser, S.; Ijzerman, A. P. *J. Med. Chem.* **2001**, *44*, 749. (b) Rao, A. U.; Shao, N.; Aslanian, R. G.; Chan, T. Y.; Degrado, S. J.; Wang, L.; McKittrick, B.; Senior, M.; West, R. E.; Williams, S. M.; Wu, R.-L.; Hwa, J.; Patel, B.; Zheng, S.; Sondey, C.; Palani, A. *ACS Med. Chem. Lett.* **2012**, 3 (3), 198−202. (c) Lee, J.; Han Lee, S.; Jeong Seo, H.; Jung Son, E.; Lee, S. H.; Jung, M. E.; Lee, M. W.; Han, H. K.; Kim, J.; Kang, J.; Lee, J. *Bioorg. Med. Chem.* **2010**, *18*, 2178. (d) Clerici, F.; Pocar, D. *J. Med. Chem.* **2001**, *44*, 931. (e) Wei, M. X.; Feng, L.; Qiang, Li, X.; Zhang Zhou, X.; Shao, Z. H. *Eur. J. Med. Chem.* **2009**, *44*, 3340.

(2) (a) Ying, L.; Hsu, B. B.; Zhan, H.; Welch, G. C.; Zalar, P.; Perez, L. A.; Kramer, E. J.; Nguyen, T. Q.; Heeger, A. J.; Wong, W. Y.; Bazan, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 18538. (b) Yi, H.; Faifi, S. A.; Iraqi, A.; Watters, D. C.; Kingsley, J.; Lidzey, D. G. *J. Mater. Chem.* **2011**, *21*, 13649.

(3) Katrizky, A. R.; Nachef, C. E.; Bajaj, K.; Kubik, J.; Haase, D. N. *J. Org. Chem.* **2010**, *75*, 6009.

(4) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (c) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 3850.

(5) Selected examples: (a) Kawano, T.; Yoshizumi, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 3072. (b) Strotman, N. A.; Chobanian, H. R.; Guo, Y.; He, J.; Wilson, J. E. *Org. Lett.* **2010**, *12*, 3578. (c) Roy, D.; Mom, A.; Beauperin, M.; Doucet, H.; Hierso, J.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 6459. (d) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926.

(6) (a) Bryan, S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *121*, 7198. (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.

(7) (a) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996. (b) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (c) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296. (d) Liegault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (e) Yang, F.; Xu, Z.; Wang, Z.; Yu, Z.; Wang, R. *Chem.—Eur. J.* **2011**, *17*, 6321.

(8) (a) Beryozkina, T.; Appukkuttan, P.; Mont, N.; Van der Eycken, E. *Org. Lett.* **2006**, *8*, 487. (b) Appukkuttan, P.; Dehaen, W.; Van der Eycken, E. *Chem.—Eur. J.* **2007**, *13*, 6452. (c) Mont, N.; Mehta, V. P.; Appukkuttan, P.; Beryozkina, T.; Toppet, S.; Van Hecke, K.; Meervelt, L. V.; Voet, A.; De Maeyer, M.; Van der Eycken, E. *J. Org. Chem.* **2008**, *73*, 7509. (d) Sharma, A.; Vachhani, D.; Van der Eycken, E. *Org. Lett.* **2012**, *14*, 1854.

(9) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Gorelsky, S. I.; Lapointe, D; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658.

(10) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

(11) (a) Steel, P. J. *Adv. Heterocycl. Chem.* **1996**, *67*, 1−117. and references therein (b) Zhao, D.; You, J.; Hu, C. *Chem.—Eur. J.* **2011**, *17*, 5466.

(12) A similar reaction but without using $Pd(OAc)_2$ in the second step led to a considerably lower yield (10%) of **5a**.
(13) (a) Huang, J.; Chan, J.; Chen, Y.; Borths, C. J.; Baucom, K. D.; Larsen, R. D. *J. Am. Chem. Soc.* **2010**, *132*, 3674. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379.
(14) Gierczyk, B.; Zalas, M. *Org. Prep. Proc. Int.* **2005**, *37*, 213−222.

dx.doi.org/10.1021/jo301401q | *J. Org. Chem.* 2012, 77, 8768−8774