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Selective Palladium-Catalyzed Direct C–H Arylation of Unsubstituted *N*-Protected Pyrazoles

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Abstract: A highly selective C-5 arylation of *N*-dimethylaminosulfamoyl-protected pyrazole with aryl bromides is catalyzed by 2–5 mol% palladium in the presence of triphenylphosphine ligand and carboxylic acid additive. Selectivities up to 45:1 (C-5:C-4) can be achieved by running the reaction in non-polar solvents. A thorough study of scope and limitations shows good general tolerance of aryl bromide substitution. However, limitations on tolerance of *ortho*-subsitution and protic functional groups were established. Together with a telescoped deprotection step this method presents a viable alternative for the synthesis of C-3 arylated pyrazole building blocks.

Keywords: C–C coupling; C–H activation; heterocycles; homogeneous catalysis; palladium

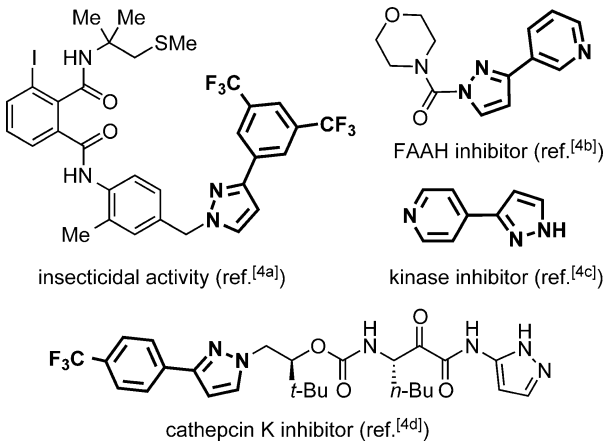
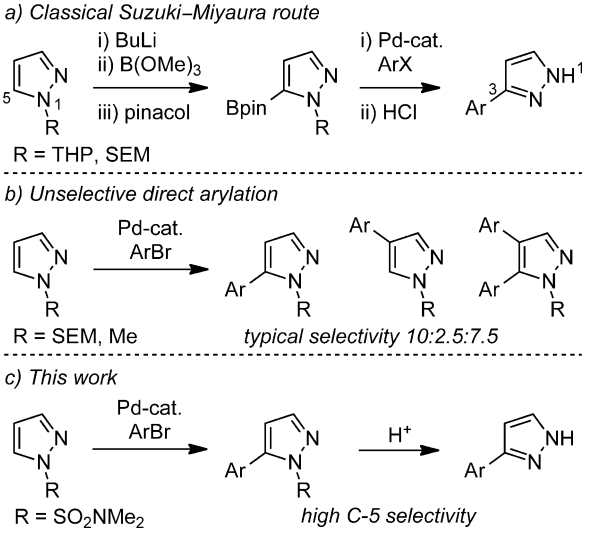


Figure 1. Examples of bioactive compounds containing the C-3 arylpyrazole unit.[4]

Pyrazole is a common structural unit in biologically active compounds. A recent database search revealed that there are over 1000 compounds containing C-3 arylpyrazole motifs that had measured biological data (Figure 1).[1] In a recent study conducted by Richie et al. at GlaxoSmithKline the pyrazole ring turned out to be among the most common heteroaryl rings in drug research molecules.[2] According to the study the pyrazole ring has a good developability score indicating that it is less likely to cause pharmacological or toxicological problems during the development phase. For these reasons, there is interest and demand for new synthesis strategies that could benefit the pharmaceutical industry in the construction of pyrazole -containing structural units.

Commonly C-3 arylated pyrazoles are built from the corresponding acetophenones by treatment with *N,N*-dimethylformamide dimethyl acetal followed by condensation with hydrazine.[3] Sometimes the required acetophenone is not commercially available and its synthesis might be laborious. In those cases C-3 arylated pyrazole building blocks are often obtained *via* directed metallation of *N*-protected pyrazole followed by transition metal-catalyzed cross-coupling reactions with aryl halides (Scheme 1).[5–7] A streamlined version of this approach, the direct catalytic C–H arylation[8,9] of the pyrazole ring, has also been studied but so far these methods suffer from poor site selectivity.[10] A common way to improve the selectivity is to introduce site-blocking groups such as alkyl and aryl groups,[10a,e,11] chlorine atoms[10b,12] or to use an intramolecular annulation strategy.[13] However, these approaches are only useful if the substituent introduced is a part of the actual target molecule. Sames and co-workers have reported a direct C–H monoarylation of an unsubstituted SEM-pyrazole [SEM = 2-(trimethylsilyl)ethoxymethyl] containing a removable *N*-protective group thus allowing the construction of monosubstituted C-3 arylated pyrazoles (Scheme 1b).[10a] Although their example was very promising, it still suffered from poor site selectivity.



Scheme 1. Comparison of known literature to this work.

Our interest was to develop a selective direct monoarylation of protected pyrazoles from the C-5 position without the need of using a laborious metallation-borylation sequence. We chose to use dimethylaminosulfamoyl-protected pyrazole as the starting point since this protective group appeared to be readily removable and its use had been previously reported in directed metallation chemistry in conjunction with alkylation,[14] halogenation[15] and Negishi coupling[6a] reactions. We selected 3-bromopyridine to be the coupling partner in our initial studies since it allows easy ^{1}H NMR analysis of crude reaction mixtures for the identification of regiochemical isomers.

The search for reactivity was started using palladium acetate in dimethylformamide (DMF) and these conditions already provided the desired mass signal in LC-MS analysis (Table 1, entry 1). Further analysis revealed the major product to be 3,3′-bipyridine **3**, a result of the reductive homocoupling reaction. The desired pyrazole coupling products (**4** and **5**) were formed in 1:3 ratio favoring the C-4 isomer. Addition of triphenylphosphine (PPh_3) slightly suppressed the formation of 3,3′-bipyridine **3** and increased the amount of C-5 isomer **4** (Table 1, entry 2). The same trend was further enhanced when pivalic acid (PivOH) was used as an additive (Table 1, entry 3). However, the key to high C-5 selectivity turned out to be the change of reaction medium to less polar and coordinating solvents such as dioxane, anisole, xylenes and toluene (Table 1, entries 4–7).

The ligand was found to have a significant effect in non-polar solvents (Table 1, entries 7–11). Varying the amount of PPh_3 to from 20 to 10 mol% led to a higher reaction rate but slightly decreased the selectivity. The absence of PPh_3 reversed the selectivity to favor C-4 isomer **5**. Other more expensive ligands such as electron-rich tricyclohexylphosphine (PCy_3) and electron-poor tris(4-fluorophenyl)phosphine [P(4-$FC_6H_4)_3$] gave no advantage over PPh_3. Although 10-15 mol% of PPh_3 seemed to be enough to ensure high C-5 selectivity, we opted to use 20 mol% to compensate for ligand oxidation due to adventitious oxygen in the solvent. Pivalic acid could be replaced with 2-ethylhexanoic acid (EHA) which gave similar selectivity and slightly higher reactivity (Table 1, entries 13–16).[16] A temperature of 130–140 °C was required for practical reaction rates and thus xylenes or anisole were found to be the solvents of choice. Unfortunately the high conversions inevitably led to formation of small amounts of doubly substituted pyrazoles **7** and **8** (Table 1, entries 14–17).

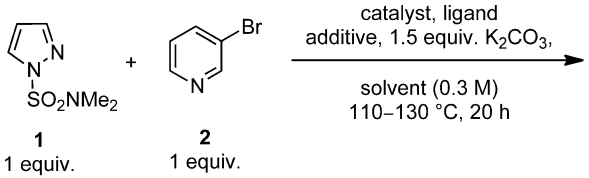
A few other palladium sources were also tested (Table 1, entries 20–25). Palladium dichloride and its PPh_3 complex gave identical results with $Pd(OAc)_2$. Palladium on activated carbon worked very selectively but with diminished reaction rate. Polymer-supported palladium sources (Pd EnCat™ 30, 40 and TPP30) also showed good selectivity but lower conversion than the non-supported catalysts.

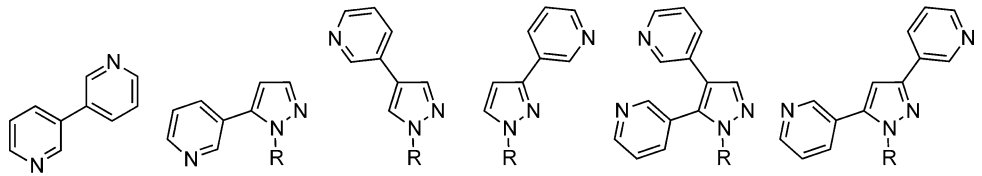
The performance of the optimized catalyst system (Table 1, entry 16) was evaluated by testing the reaction with various aryl bromides (Table 2). Moderate to good isolated yields (53–83%) were obtained with *para*- and *meta*-substituted aryl bromides containing both electron-rich and electron-poor functional groups. Steric hindrance at *ortho*-positions resulted in moderate to poor yields (32–50%), with the exception of *ortho*-fluorophenyl bromide which gave a good isolated yield (77%). More hindered systems (**35**, **38**) gave very poor reactivity even after prolongened reaction times (Figure 2). Bromopyridines and bromopyrimidines with halide at the 3- or 4-position gave moderate (61–73%) yields (Table 2). Heteroaryls with halide at the 2-position (**33**, **36**, **39**) gave no reaction or only trace of products (Figure 2). Heteroaryls (**39**, **41**) that are known to be easily C–H activated themselves gave poor yields. Direct C-5 arylation of pyrazole **1** did not tolerate free NH or OH protons.

Initial attempts to couple **1** with *p*-bromoanisole resulted in significant amounts of phenylated product **9** along with the desired product **10** (Scheme 2). This result is likely explained by the exchange of aryl groups between the phosphine and the palladium center and could be avoided by using the more electron-rich PCy_3 ligand (Table 2).[17] Similar side reactions have been previously reported for Heck reaction,[18] Stille coupling,[19] Suzuki–Miyaura coupling[20] and Buchwald–Hartwig coupling[21] and it occurs typically with electron-rich aryl bromides.

To explore the origin for the high selectivity we decided to test the outcome of the model C–H activation reaction with pyrazoles containg various N-sustituents employing different coordinating properties. For further insight, reactivity was tested in two dis-

Table 1. Palladium catalyzed direct arylation of *N*-SO_2NMe_2 pyrazole **1**.[a]

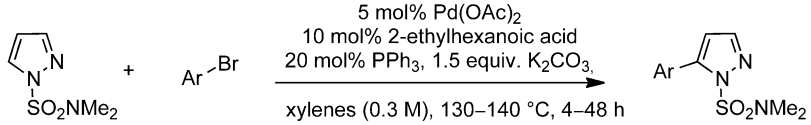


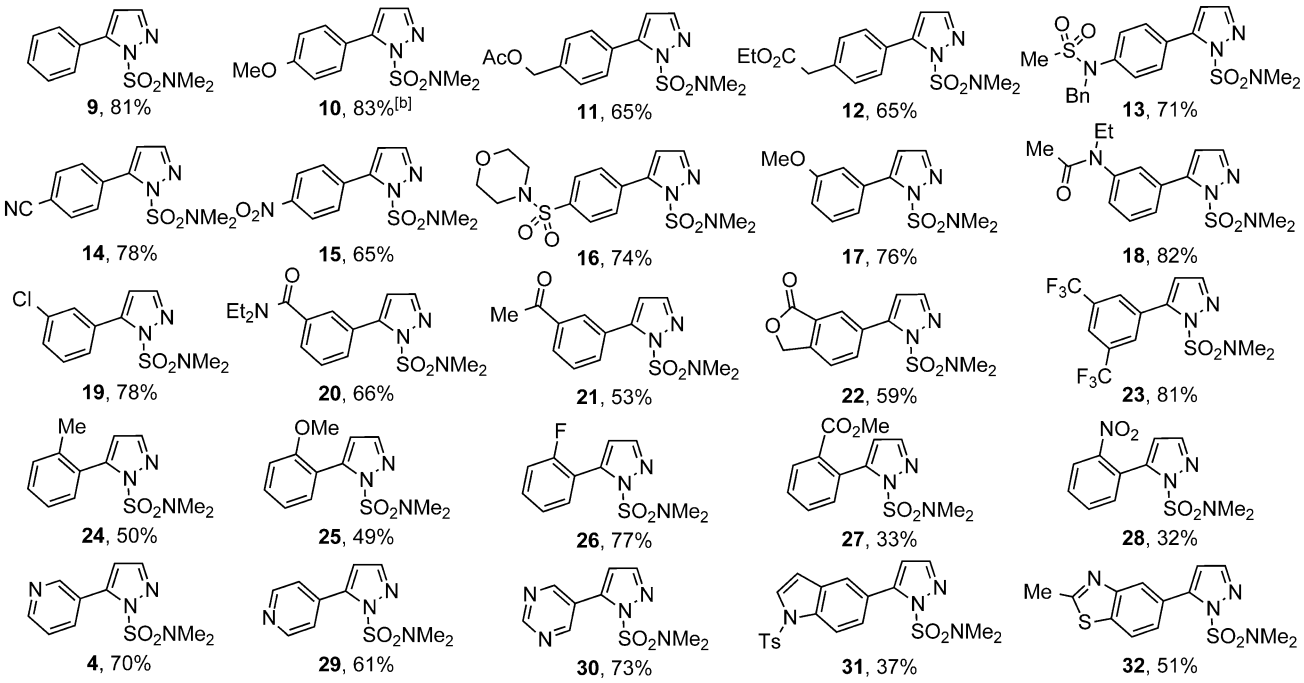


Entry	Catalyst	Ligand	Additive	Solvent	Temp. [°C]	Conv. [%][b]	3,3′-bpy	C-5	C-4	C-3	C-5, C-4	C-5, C-3
1	5% $Pd(OAc)_2$	none	none	DMF	110	45	65	9	25	0	1	0
2	5% $Pd(OAc)_2$	20% PPh_3	none	DMF	110	21	34	28	38	0	0	0
3	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	DMF	110	20	4	66	21	0	9	0
4	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	dioxane	110	18	6	90	3	0	1	0
5	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	anisole	110	13	1	99	0	0	0	0
6	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	xylenes	110	11	0	100	0	0	0	0
7	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	toluene	110	24	0	99	0	0	1	0
8	5% $Pd(OAc)_2$	10% PPh_3	30% PivOH	toluene	110	45	0	93	2	0	4	1
9	5% $Pd(OAc)_2$	none	30% PivOH	toluene	110	20	6	25	64	0	4	1
10	5% $Pd(OAc)_2$	20% PCy_3	30% PivOH	toluene	110	6	0	100	0	0	0	0
11	5% $Pd(OAc)_2$	20% $P(4\text{-F-}C_6H_4)_3$	30% PivOH	toluene	110	19	0	100	0	0	0	0
12	5% $Pd(OAc)_2$	20% PPh_3	30% EHA[c]	toluene	110	16	0	100	0	0	0	0
13	5% $Pd(OAc)_2$	20% PPh_3	30% PivOH	xylenes	130	65	0	95	1	0	2	2
14	5% $Pd(OAc)_2$	20% PPh_3	30% EHA[c]	xylenes	130	100	0	91	2	0	4	3
15	5% $Pd(OAc)_2$	20% PPh_3	20% EHA[c]	xylenes	130	94	0	93	0	0	4	3
16	**5% $Pd(OAc)_2$**	**20% PPh_3**	**10% EHA[c]**	**xylenes**	**130**	**100**	**0**	**91**	**2**	**0**	**4**	**3**
17	5% $Pd(OAc)_2$	20% PPh_3	10% EHA[c]	anisole	130	100	0	92	2	0	3	3
18	5% $Pd(OAc)_2$	20% PPh_3	10% EHA[c]	DMF	130	100	33	21	33	0	13	0
19	5% $Pd(OAc)_2$	15% PPh_3	10% EHA[c]	xylenes	130	100	0	92	0	0	4	4
20	5% $PdCl_2$	20% PPh_3	10% EHA[c]	xylenes	130	100	0	91	2	0	4	3
21	5% $PdCl_2(PPh_3)_2$	10% PPh_3	10% EHA[c]	xylenes	130	100	0	91	2	0	4	3
22	5% Pd/C 10 wt%	15% PPh_3	10% EHA[c]	xylenes	130	24	0	100	0	0	0	0
23	5% Pd EnCat 30	15% PPh_3	10% EHA[c]	xylenes	130	47	0	94	3	0	1	2
24	5% Pd EnCat 40	15% PPh_3	10% EHA[c]	xylenes	130	9	0	90	10	0	0	0
25	5% Pd EnCat TPP30	none	10% EHA[c]	xylenes	130	11	0	100	0	0	0	0

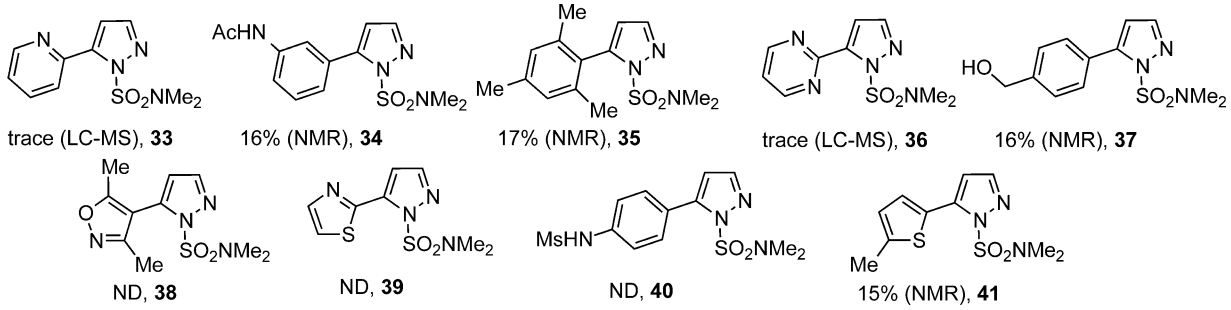
[a] Relative product ratios were determined with UV factor corrected HPLC analysis of the reaction mixtures.
[b] HPLC analysis on the conversion of 3-bromopyridine using mesitylene as an internal standard.
[c] EHA = 2-ethylhexanoic acid.

Table 2. Substrate scope in the direct C-H arylation of *N*-SO_2NMe_2 pyrazole **1**.[a]





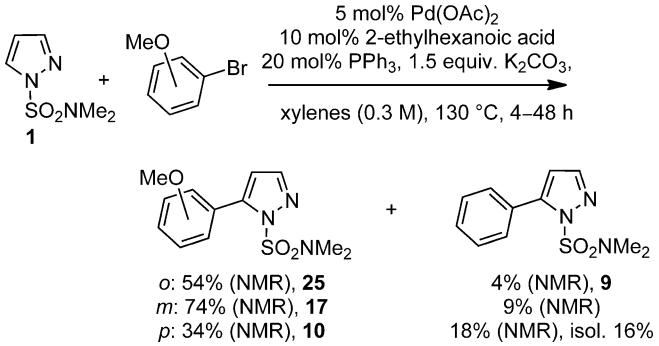
[a] Isolated yields.
[b] PCy_3 was used instead of PPh_3.



ND = not detected with LC-MS.

Figure 2. Limitations in the direct C–H arylation of **1**.

tinctly different conditions. In Method A, which was identical to our conditions, ligand additive was used in a non-polar aprotic solvent whereas in method B a coordinative polar aprotic solvent (DMA = *N,N*-dimethylacetamide) was used in the absence of a ligand.[10d] Our method performed as expected and gave full conversion and high C-5 selectivity (Table 3, entry 1). Method B reversed the selectivity to favor C-4 isomer **5** and increased the amount of homocoupling product 3,3′-bpy **3** (Table 3, entry 2). This trend was already observed during the optimization studies (Table 1, entries 1–3). Pyrazoles with potentially coordinating protecting groups, tosyl (Ts), dimethylaminocarbonyl, *tert*-butyloxycarbonyl (Boc) and tetrahydropyranyl (THP) were poor substrates for the direct C–H arylation reaction (Table 3, entries 3–8). Among them THP-protected pyrazole **60** was the only one to react in a measurable extent. Notably, *N*-benzyl- and *N*-methylpyrazoles (**66** and **72**) gave mainly C-5 isomers (**67**, **73**) along with the C-3 products (**69**, **75**) in



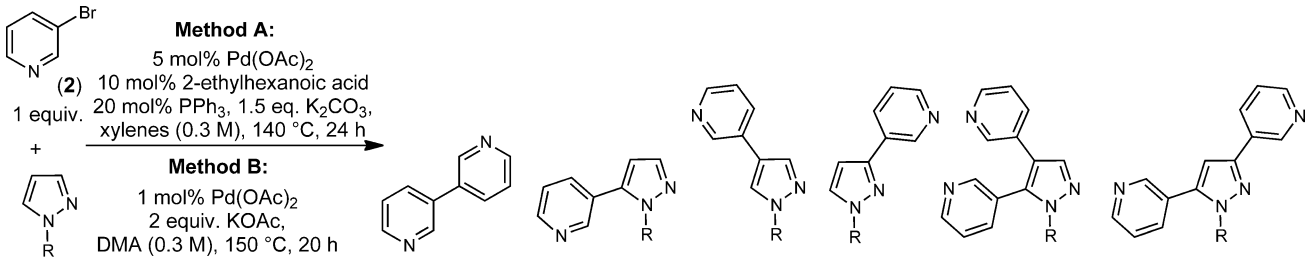
Scheme 2. Unexpected aryl transfer from PPh_3.

our conditions (Table 3, entries 9 and 11). Method B, for example, gave mainly C-5 and C-4 products with the same pyrazoles (Table 3, entries 10 and 12). Based on these results, we suggest that coordinating *N*-protective groups (THP, SO_2NMe_2) enhance C-5 selectivity in poorly coordinative solvents.[22] However, electronic effects of the protecting group influence the reactivity and site selectivity (Table 3, entries 1 and 9). Likely both of these effects have a role in the total outcome of the direct C–H arylation reaction.

Finally, we demonstrated the efficiency of this direct C–H arylation of pyrazoles using an arylation–deprotection sequence (Table 4). Reactions were carried out on the 10-mmol scale and moderate yields (61–73%) were obtained over two steps. The atom economy of this new methodology is significantly better than that in the Suzuki–Miyaura route which requires the use of pyrophoric organometallic reagents and borate esters which eventually generate boron-containing aqueous waste.

In summary, unsubstituted SO_2NMe_2-protected pyrazole can be directly C–H arylated at the C-5 position with high selectivity. The outcome of the reaction is influenced by the phosphine ligand, acid additive and solvent selection. The reaction works with electron-rich and electron-poor aryl bromides that have substituents in *para*- or *meta*-position and tolerates various functional groups. Sterically hindered aryl bro-

Table 3. Analysis of the product ratios in the direct C–H activation of *N*-protected pyrazoles.[a]

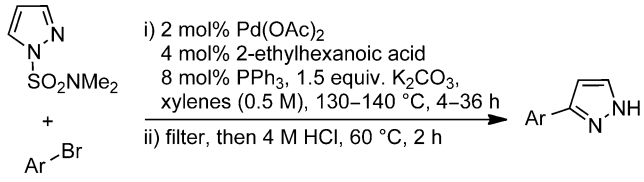


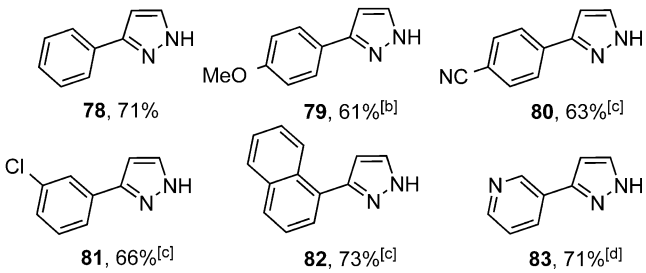
R = SO_2NMe_2, **1**				**3**	**4**	**5**	**6**	**7**	**8**
R = Ts, **42**					**43**	**44**	**45**	**46**	**47**
R = $C(O)NMe_2$, **48**					**49**	**50**	**51**	**52**	**53**
R = Boc, **54**					**55**	**56**	**57**	**58**	**59**
R = THP, **60**					**61**	**62**	**63**	**64**	**65**
R = Bn, **66**					**67**	**68**	**69**	**70**	**71**
R = Me, **72**					**73**	**74**	**75**	**76**	**77**

Entry	R	Method	Conversion[b]	3,3′-bpy	C-5	C-4	C-3	C-5, C-4	C-5, C-3
1	SO_2NMe_2	A	100	–	90	–	–	6	4
2	SO_2NMe_2	B	21	30	12	55	–	3	–
3	Ts	A	Trace[c]	–	–	–	–	–	–
4	Ts	B	NR[d]	–	–	–	–	–	–
5	$C(O)NMe_2$	A	NR[d]	–	–	–	–	–	–
6	Boc	A	NR[d,e]	–	–	–	–	–	–
7	THP	A	13	–	100	–	–	–	–
8	THP	B	NR[d]	–	–	–	–	–	–
9	Bn	A	66	–	61	–	23	–	16
10	Bn	B	88	30	28	18	–	24	–
11	Me	A	20	–	60	–	25	–	15
12	Me	B	100	22	43	9	–	26	–

[a] Relative product ratios were determined with ^1H NMR analysis from the crude reaction mixtures.
[b] LC-MS analysis on the conversion of 3-bromopyridine using mesitylene as an internal standard.
[c] Poor solubility of *N*-Ts pyrazole into the reaction medium. Small amount of product detected with LC-MS.
[d] NR = no reaction.
[e] Full Boc-deprotection occurred.

Table 4. Direct C–H arylation of *N*-SO_2NMe_2 pyrazole followed by deprotection.[a]





[a] Isolated yields.
[b] 6 mol% of PCy_3 was used instead of PPh_3.
[c] *N*-Protection removed with TFA:CH_2Cl_2 (1:1 ratio) at room temperature.
[d] 3 mol% $Pd(OAc)_2$, 6 mol% of 2-ethylhexanoic acid and 12 mol% of PPh_3 were used.

mides as well as some acidic functional group-containing substrates have their limitations in these reactions. Deprotection of C-5 arylated pyrazoles gives C-3 arylated pyrazole products which have wide use in the construction of bioactive targets.

Experimental Section

Typical Procedure for Direct C–H Arylation of Pyrazoles (Table 2)

***N,N*-Dimethyl-5-phenyl-1*H*-pyrazole-1-sulfonamide (9):** A microwave vial equipped with a stir bar was charged with *N,N*-dimethyl-1*H*-pyrazole-1-sulfonamide **1** (0.42 mL, 3.0 mmol), bromobenzene (0.32 mL, 3.0 mmol), potassium carbonate (0.622 g, 4.5 mmol), 2-ethylhexanoic acid (0.048 mL, 0.30 mmol), palladium acetate (0.034 g, 0.15 mmol) and xylenes (9 mL). Triphenylphosphine (0.157 g, 0.60 mmol) was added, nitrogen was blown into the vial for 10 seconds and vial was sealed. The reaction mixture was stirred at room temperature for 5–15 min, then heated to 130 °C and stirred for 4 h. The reaction was allowed to cool to room temperature and analyzed with LC-MS. The reaction mixture was diluted with ethyl acetate (10 mL) and filtered through celite. Solvents were evaporated under vacuum. The crude product was analyzed with ^{1}H NMR to reveal 93:5:2 (C-5:C-5, C-4:C-5, C-3) selectivity. Purification of the crude product with column chromatography using 20–50% ethyl acetate/heptanes afforded **9** as a white crystalline solid; yield: 0.611 g (81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 1.6 Hz, 1H), 7.49–7.55 (m, 2H), 7.37–7.44 (m, 3H), 6.35 (d, J = 1.6 Hz, 1H), 2.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 141.5, 129.8, 129.7, 129.2, 128.1, 109.5, 39.1; HR-MS (ESI-TOF): m/z = 252.0829, calcd. for $C_{11}H_{14}N_3O_2S$ $[M+H]^+$: 252.0807.

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