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Regioselective Palladium-Catalyzed Arylation of 4-Chloropyrazoles

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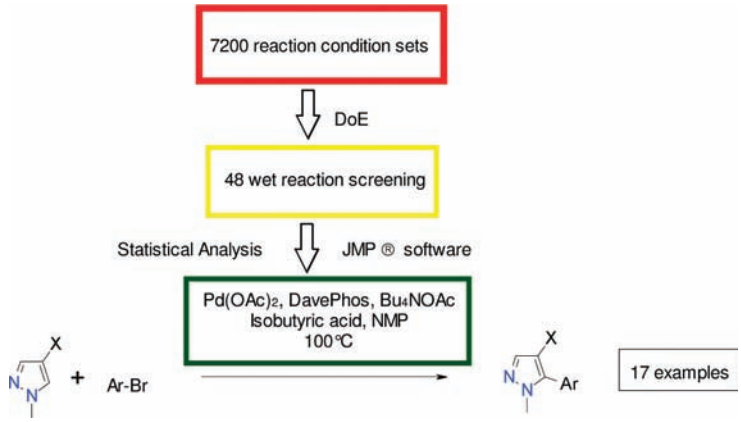
ABSTRACT



A highly regioselective Pd-catalyzed arylation of *N*-methylpyrazoles with aryl bromides is described. This transformation was studied extensively via automated reaction screening. A Design of Experiments (DoE) approach for optimizing the critical parameters was applied, resulting in excellent conditions for preparing selectively 5-arylpyrazoles in moderate to excellent yields under mild conditions.

Heteroaryl derivatives, including aryl pyrazoles, are important building blocks in organic synthesis due to their biological properties.[1] Although a number of synthetic methods have been developed to construct pyrazoles possessing an aryl group on the ring,[2] many of these approaches are based on time-consuming multistep procedures or structure-limited ring transformation reactions. Direct introduction of an aryl group onto the pyrazole nucleus via palladium-mediated cross-coupling reaction has been demonstrated via Suzuki,[3] Stille,[4] and Negishi[4,5] reactions. Metal-catalyzed arylation and heteroarylation of C−H bonds have been shown to be a

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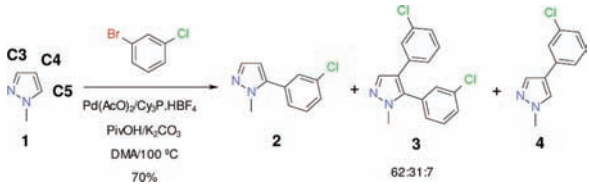
powerful synthetic tool for the functionalization of aromatic compounds and heterocycles.[6] To the best of our knowledge, the first pyrazole arylation at C5 has been recently reported by Sames and co-workers,[7] where trisubstituted pyrazoles were obtained by C−H activation after protecting group migration. Activation at C4 has been reported by Santelli et al.[8]

In connection with a drug discovery program, we required a methodology to quickly access 5-aryl-1-methyl-pyrazoles to facilitate our structure−activity relationship (SAR) studies. For that purpose, we started a research effort exploring the C−H activation methodology on the *N*-methylpyrazole ring. In this manuscript, our research group describes the selective C5 arylation of *N*-methylpyrazoles mediated by palladium complexes.

1-Methylpyrazole (**1**) was initially selected as starting material for direct C−H palladium-mediated model validation. Experimental conditions reported in the literature by Fagnou[6b] et al. were applied to 3-bromochlorobenzene, and a mixture of three different arylated pyrazole derivatives were isolated (Scheme 1). A general reactivity rule could be stated

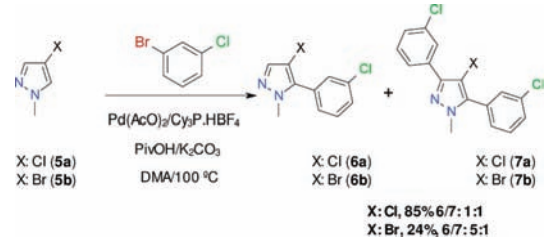
Scheme 1



for 1-methylpyrazole (**1**) based on experimental results (yield of isolated compounds). Direct C−H arylation reactivity for 1-methylpyrazole under palladium-mediated conditions was C5 > C4 ≫ C3 (same relationship was found by Sames and co-workers[7] with a pyrazole analogue).

To expand the SAR after the first arylation, we then chose 4-chloro-1-methyl-pyrazole (**5a**) and 4-bromo-1-methylpyrazole (**5b**) as scaffolds for further functionalization. An arylated compound at C5 and bisarylated compound at C5 and C3 were surprisingly isolated (Scheme 2). The outcome of that test clearly indicates that electron withdrawing groups (EWGs) such as Cl or Br enhance C3 reactivity.

Scheme 2



While better selectivity was observed for bromo derivative **5b** (5/1 ratio, **6b/7b**), chloropyrazole (**5a**) (selectivity: 1/1 (**6a/7a**)) displayed more promising conversion (higher yield), presumably due to its higher electronegativity. On the basis of this, 3-chloro-1-methylpyrazol (**5a**) was selected for the subsequent study and optimization due to its better conversion profile. However, the chloro substituent at C4 improves C3 reactivity, so an optimization study was mandatory for selectivity improvement. On the basis of our experience in automation tools, a statistical study was applied for the design of experiments[9] and optimization of the process, focused on an optimal set of conditions that maximize conversion and selectivity values.

Optimization screening was performed to improve the C5/C3 selectivity profile, maximizing C5 direct arylation. Solvent, base, catalyst, ligand, and additive were screened. A statistical study, using JMP software,[10] was done for a much better optimization, and a Design of Experiments (DoE) design was performed using several factors (Table 1). Experimental conditions selected were compiled from

Table 1. Factors Selected for DoE Design

solvent	base	catalyst	ligand	additive
NMP	Bu_4NOAc	$Pd(AcO)_2$	DavePhos	pivalic acid
DMA	Et_3N	Pd_2dba_3	XantPhos	chloroacetic acid
THF	$^iPr_2EtN$	$PdCl_2(PPh_3)_2$	$PCy_3{\cdot}HBF_4$	acetic acid
dioxane	KF	$PdCl_2dppf$	$(^tBu)_2MeP{\cdot}HBF_4$	isobutyric acid
IPA	Na_2CO_3		no ligand	no additives
water/IPA	$NaHCO_3$		$(^tBu)_3P{\cdot}HBF_4$	
	CSF			
	Cs_2CO_3			
	Cy_2MeN			
	K_3PO_4			

literature reports and our own experience; then, 6 solvents, 10 bases, 4 catalyst, 5 ligands, and 4 additives were included in the study for optimization screening. A total of 7200 reactions could be performed for full combination of the entire experimental conditions selected; however, DoE design

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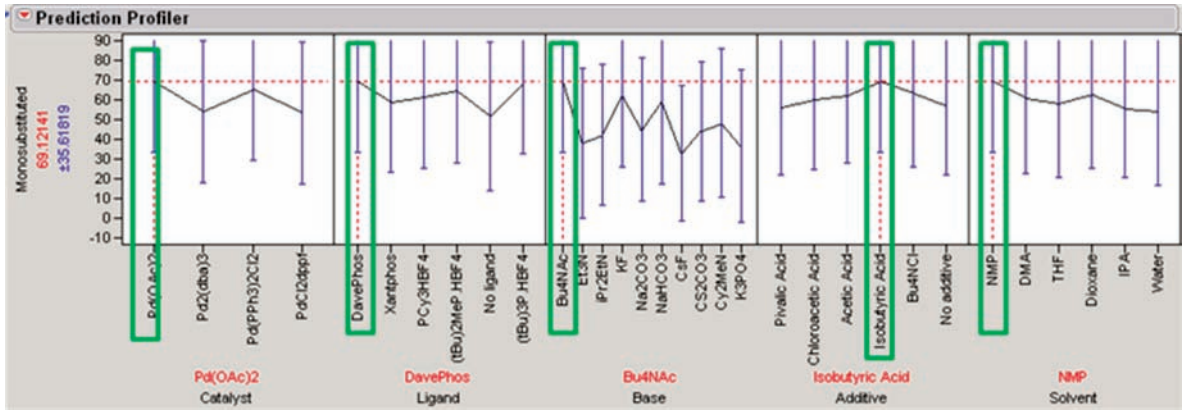


Figure 1. Best predicted conditions.

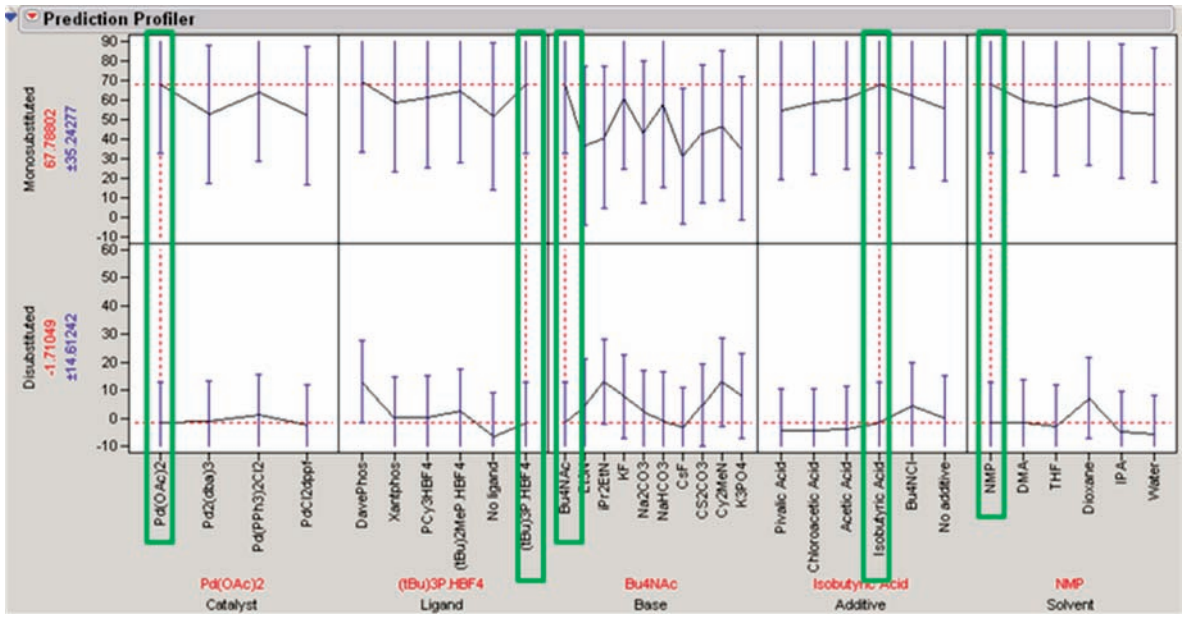


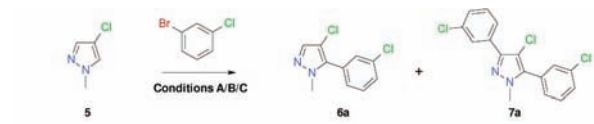
Figure 2. Trends generated by JMP software. Emphasized in red are the best conditions predicted to maximize C5/C3 selectivity.

was successfully applied to reduce all combinations to 48 reactions with an acceptable D-efficiency.

All selected reactions (48) were run (first at 80 °C and then at 100 °C), and all of them were analyzed by LCMS, providing a set of conversion data and isomer ratios at 100 °C. Results were analyzed with JMP software, and a trend was obtained for all factors (Figure 1). The more important factor is the choice of base. Bu_4NOAc performed as the optimal base for C−H activation of 4-chloro-1-methylpyrazole (**5a**). In general there are no statistical differences in catalyst, ligand, additive, or solvent selected.

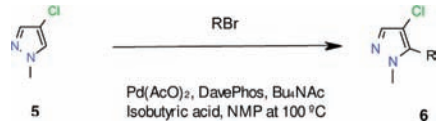
With the objective of obtaining the best combination for conversion and selectivity, two sets of experimental conditions were predicted: (a) based on conversion: $Pd(AcO)_2$, DavePhos, Bu_4NAc, isobutyric acid, NMP at 100 °C (Figure 1) and (b) based on selectivity: $Pd(AcO)_2$, t-$Bu_3P{\cdot}HBF_4$, Bu_4NAcO, isobutyric acid, NMP at 100 °C (Figure 2). Both sets of conditions were not previously performed in our scenario of experimental reactions, so both approaches were run at 500 mg scale for subsequent confirmation and model validation (Scheme 3). Reactions proceeded smoothly to provide corresponding C5 arylated pyrazole (**6a**) in excellent yield and very good selectivity. No statistical differences

Scheme 3



Conditions A: $Pd(AcO)_2$, DavePhos, Bu_4NAc, Isobutyric acid, NMP at 100 °C: **94%** yield (**6a**), **96/4** (**6a:7a**)
Conditions B: $Pd(AcO)_2$, $tBu_3P.HBF_4$, Bu_4NAc, Isobutyric acid, NMP at 100 °C: **91%** yield (**6a**), **93/7** (**6a:7a**)
Conditions C: $Pd(AcO)_2$, DavePhos, Bu_4NAc, Isobutyric acid, NMP at 150 °C: **80%** yield (**6a**), **85/15** (**6a:7a**)

Table 2. Effect of Substituents[a]



entry	RBr	product	yield
1		 6c	10
2		 6a	94
3		 6d	77
4		 6e	62
5		 6f	83
6		 6g	75
7		 6h	13
8		 6i	45
9		 6j	65
10		 6k	-
11		 6l	73
12		 6m	65
13		 6n	29
14		 6o	70
15		 6p	90
16		 6q	-
17		 6r	90
18		 6s	90
19		 6t	46

[a] 4-Chloro-1-methylpyrazole (1.0 equiv), RBr (1.0 equiv); $Pd(OAc)_2$ (1%), DavePhos (2%), Bu_4NAc (2.0 equiv), isobutyric acid (0.3 equiv), NMP (0.3 M), 100 °C, 24 h.

were observed for both sets of conditions. Attempts to increase the diarylated product **7a** using 3 equiv of 3-bromochlorobenzene under conditions C (Scheme 3) at 150 °C provided a 85/15 mixture of products **6a**/**7a**; this result supported our optimized experimental conditions for monoarylation.

Finally, conditions A were selected as preferred conditions to establish the scope of the transformation. A pool of *orto*-, *meta*-, and *para*-electron-rich (entries 13−18) and electron-poor (entries 1−12, 19) bromo-arenes were selected for direct palladium-catalyzed arylation (Table 2). An ample tolerance of functional groups was successfully demonstrated (Cl, F, CN, NO_2, Me, MeO). The reaction worked well with *meta*- and *para*-substituted derivatives providing C5 arylated pyrazoles in good to excellent yields without influence of electronic effects. On the other hand, *ortho*-substitution showed low conversions (entries 1, 7, and 13) or no reaction (entries 10 and 16). An exception was 2-fluorobromobencene that was successfully transformed in 62% yield due to the strong activation effect and the small steric hindrance of the fluoro group (entry 4). Additionally, the method successfully arylated a heteroarene partner 3-bromopyridine in moderate yield, which constitutes an interesting example due to the ubiquitous polyheteroarene scaffolds found in biologically active compounds.

In conclusion, using DoE techniques coupled with statistical methodology, we were able to find a set of conditions to successfully arylate model 4-chloro-1-methylpyrazole. These conditions were applied to prepare a small library of 5-arylchloropyrazoles in moderate to excellent yields. Thus, the developed procedure permits the selective introduction of either electron-poor or electron-rich aryl bromides under mild conditions without influence of electronic effects. The most important effect for a successful reaction is the steric hindrance of the bromo-arene. Moreover, the presence of a chloride substituent in the final products would allow for further derivatization to interesting polysubstituted pyrazoles.

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Supporting Information Available: Experimental procedures and characterization data for all compounds isolated. This material is available free of charge via the Internet at http://pubs.acs.org.

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