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# Sequential $S_NAr$ Reaction/Suzuki–Miyaura Coupling/C–H Direct Arylations Approach for the Rapid Synthesis of Tetraaryl-Substituted Pyrazoles

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**Abstract:** A rapid synthesis of 1,3,4,5-tetraaryl-substituted pyrazoles has been achieved through a sequence of $S_NAr$ reaction/Suzuki–Miyaura coupling/Pd-catalyzed direct arylations that used 3-iodo-1*H*-pyrazole as a scaffold. Pyrazoles with four different aryl groups were synthesized in a straightforward manner with no extra synthetic steps, such as protection/deprotection or the introduction of activating/directing groups, using readily available substrates and reagents. The developed synthetic approach enabled the structurally diverse synthesis of multiaryl-substituted pyrazoles without using a glovebox technique.

Multiaryl-substituted pyrazoles are an important class of compounds, because they are frequently used in pharmaceutical drugs,[1] agricultural chemicals,[2] and as ligands for transition-metal catalysts.[3] In addition, they are attractive elements for fluorescent materials.[4] The most conventional approach[5] to the synthesis of multiaryl-substituted pyrazoles—condensation of 1,3-diketone or $\alpha,\beta$-unsaturated carbonyl compounds with substituted hydrazines—often suffers from insufficient regioselectivity.[6] Although many synthetic approaches for multiaryl-substituted pyrazoles have been reported, the development of a more divergent, regioselective, protection/deprotection-free, short synthetic route remains important.

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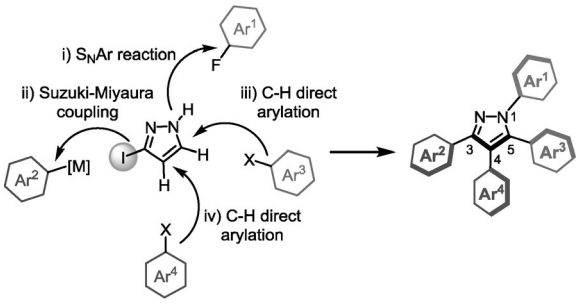
Sequential cross-coupling approaches that are based on a readily available heteroaromatic scaffold are powerful methods for the syntheses of multiaryl-substituted heteroaromatics. Schmitt and co-workers demonstrated the synthesis of pentaaryl-substituted pyridines by five Suzuki–Miyaura cross-coupling reactions starting from readily available 2-chloro-3-hydroxypyridine.[7] Knochel and co-workers reported the regioselective functionalization of an oxazole scaffold to obtain triaryl-substituted oxazoles using TMP bases complexed by LiCl (TMP = 2,2,6,6-tetramethylpiperidyl).[8] Itami and co-workers reported the synthesis of tetraaryl-substituted thiophenes starting from 3-methoxy thiophene through sequential C–H direct arylations and a subsequent Suzuki–Miyaura coupling.[9] The research groups of Fagnou,[10] Itami,[11] and Murai[12] achieved the sophisticated synthesis of fully aryl substituted thiazoles by sequential C–H direct arylations.

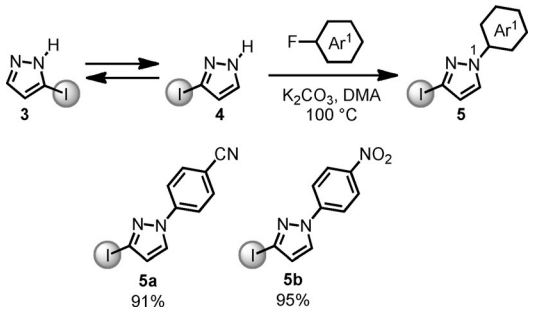
With respect to multiaryl-substituted pyrazole synthesis, McLaughlin et al. reported the construction of 3,4,5-triaryl pyrazoles through three Suzuki–Miyaura coupling reactions based on the rearrangement of a THP protecting group (THP = tetrahydropyran).[13] Sames and co-workers demonstrated the synthesis of 3,4,5-triaryl pyrazoles through a Suzuki–Miyaura coupling and the following two C5 direct arylations using the "SEM switch" method {SEM = 2-(trimethylsilyl)ethoxymethyl}.[14] To date, however, a synthesis of pyrazoles containing four different aryl groups by four sequential cross-couplings based on a readily available pyrazole scaffold has not been demonstrated.

We have reported diversity-oriented syntheses for drug discovery and materials development based on Pd-catalyzed cross-coupling reactions.[15] Herein, we wish to report a regioselective, protection/deprotection-free, sequential $S_NAr$ reaction/Suzuki–Miyaura coupling/C–H direct arylations approach to the synthesis of 1,3,4,5-tetraaryl-substituted pyrazoles that uses readily available, 3-iodo-1*H*-pyrazole as a scaffold.

We planned to install four aryl groups, $Ar^1$-$Ar^4$, via a $S_NAr$ reaction at the N1-position, Suzuki–Miyaura coupling[16] at the C3-position, C–H direct arylation at the C5-position,[14,17] and C–H direct arylation at the C4-position[18,19] using 3-iodo-1*H*-pyrazole as the scaffold (Scheme 1). Sames and co-workers[14] and Gorelsky[20] demonstrated a trend in the reactivity of three C–H bonds of pyrazole against C–H direct arylation based on a concerted metalation and deprotonation (CMD) mechanism (C5 > C4 ≫ C3). We theorized that the use of a Suzuki–Miyaura



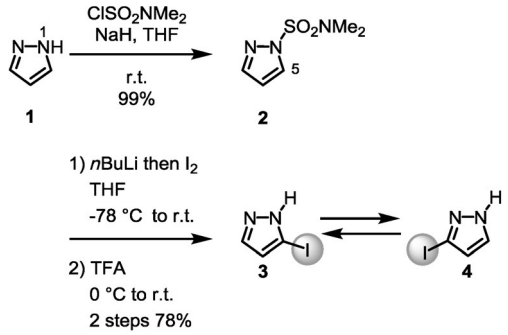

**Scheme 1.** Synthetic plan for tetraaryl-substituted pyrazoles through a sequential cross-coupling approach based on a 3-iodo-1*H*-pyrazole scaffold.




**Scheme 3.** SNAr reaction at the N1-position of the pyrazole scaffold. DMA: N,N-dimethyl acetamide.

coupling could accomplish the high-yielding installation of an $Ar^2$ group at the C3-position. The key to success was in regioselectively activating the C5-position without activating the C4-position as well as to install $Ar^4$ group in a high yield at the sterically hindered C4-position. In the present study, only commercially available reagents that could be treated without glovebox techniques were examined for the rapid combinatorial synthesis of a pyrazole library.

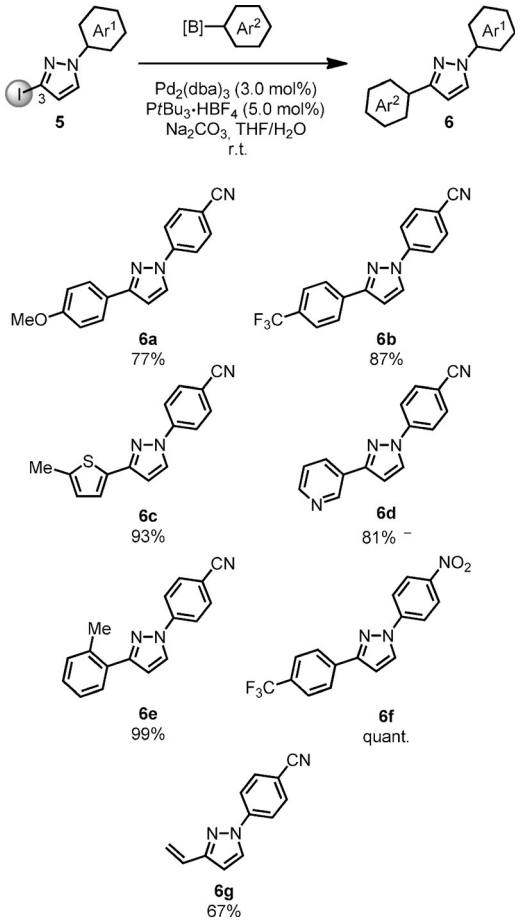
The pyrazole scaffold was prepared in accordance with a previously reported procedure,[21] as shown in Scheme 2. The introduction of a sulfonamide group at the N1-position, iodination at the C5-position, and the following acidic removal of the sulfonamide group afforded the desired pyrazole scaffold as a mixture of tautomers **3** and **4**. The desired scaffold was readily prepared in a gram scale (6.9 g).




**Scheme 2.** Synthesis of the pyrazole scaffold. THF: tetrahydrofuran, Bu: butyl, TFA: trifluoroacetic acid.

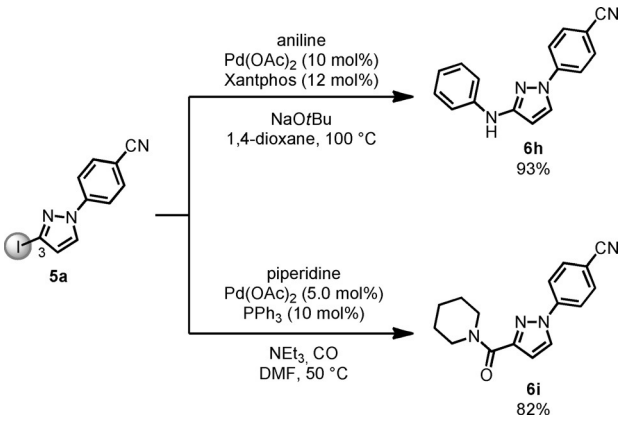
A $S_NAr$ reaction at the N1-position was examined, as shown in Scheme 3. $Ar^1$ groups containing electron-withdrawing nitrile and nitro groups were introduced in excellent yields. As previously mentioned, the iodo pyrazole scaffold was a mixture of tautomers, but products **5a** and **5b** were obtained as single regioisomers. This result was consistent with previous reports.[17f,22]

Suzuki–Miyaura coupling at the C3-position was investigated, as shown in Scheme 4. We recently reported the combination of tris(dibenzylideneacetone)dipalladium $[Pd_2(dba)_3]$,[23] $P(tBu)_3{\cdot}HBF_4$,[24] and $Na_2CO_3$ in THF/$H_2O$ (1:1)[15d] for a Suzuki–Miyaura coupling of bromo-thiophenes. This combination was




**Scheme 4.** Suzuki–Miyaura coupling at the C3-position of 1-aryl-3-iodopyrazole **5**. *Reaction conditions: 10 mol% $[Pd_2(dba)_3]$, 24 mol% $PCy_3{\cdot}HBF_4$, $K_3PO_4$, 1,4-dioxane/$H_2O$ 100 °C, 18 h. Cy: cyclohexyl.

useful for the Suzuki–Miyaura coupling of iodo pyrazole **5**. Electron-donating, electron-withdrawing, sterically hindered, and heteroatom-containing aryl groups as well as a simple alkenes were introduced in good-to-excellent yields (67%-quant.). With respect to the synthesis of **6d**, our conditions afforded the desired product in a low yield, whereas Fu and coworkers conditions[25] afforded the desired product in a good yield (81%). Multi-substituted pyrazoles containing either an amino group or a carboxamide group at their C3-position are often found in bioactive compounds.[26,27] Therefore, the Buch-




**Scheme 5.** Pd-catalyzed amination and carbonylative amidation at the C3-position of **5a**. Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.[30]

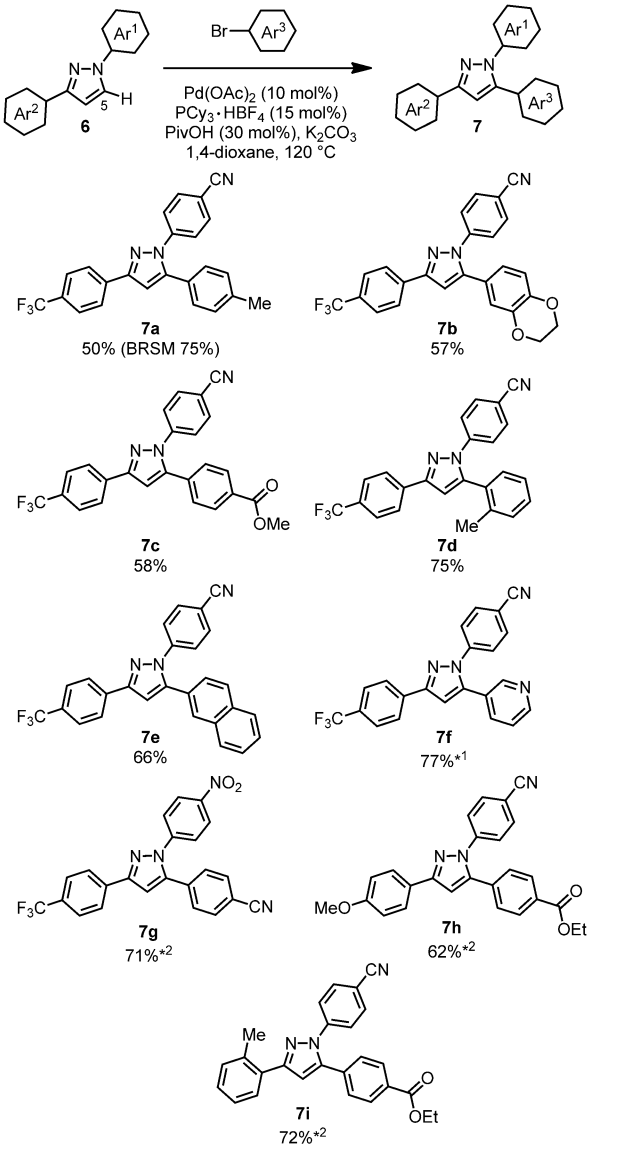
wald–Hartwig amination[28] and carbonylative amidation[29] were examined, as shown in Scheme 5. As expected, the desired compounds **6h** and **6i** were obtained in good yields.

Although the C–H direct arylations of pyrazoles at the C5-position have been reported,[17] C–H direct arylations at the C5-position of 1,3-diaryl pyrazoles have not. The reaction conditions were optimized using **6b**. The combinations of phosphine ligands ($PPh_3$, $PCy_3{\cdot}HBF_4$, $P(t\text{Bu})_3{\cdot}HBF_4$, di(1-adamantyl)-*n*-butylphosphine (cataCXium A),[31] 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos)[32]) and solvents (DMA, 1,4-dioxane) were examined. The combination of cataCXium A and DMA caused an undesired double arylation both at the C4- and C5-positions (see the Supporting Information), whereas the combination of $PCy_3{\cdot}HBF_4$ and 1,4-dioxane afforded the desired coupling product **7a** in the highest yield (50%, BRSM 75%) and high regioselectivity (double arylated product/**7a** = 1:30). The substrate scope of the optimized reaction conditions was examined, as shown in Scheme 6. Electron-donating, electron-withdrawing, sterically hindered, and heteroatom-containing $Ar^3$ groups were introduced in satisfactory-to-good yields (57–75%).

The introduction of an $Ar^4$ group at the sterically hindered C4-position of 1,3,5-triaryl pyrazole was examined, as shown in Scheme 7. Santelli and co-workers reported the direct arylation of 1,3,5-trimethyl pyrazole at the C4-position.[18b] In our case, however, the C4-position was sterically more hindered by two adjacent C3- and C5-aryl groups. In the examination of C–H direct arylations at the C5-position, we observed a substantial degree of over-arylation at the C4-position when using the combination of cataCXium A ligand in a DMA solvent, as previously described. Therefore, we employed this combination for C–H direct arylation at the C4-position, as shown in Scheme 7. As a result, electron-donating, electron-withdrawing, and heteroatom-containing aryl groups were introduced in satisfactory to good yields (39–84%).

Thus, we developed a sequential coupling approach for the synthesis of tetraaryl-substituted pyrazoles. The developed approach afforded the desired tetraaryl-substituted pyrazoles in good yields (4-steps; 22–58% yields based on **4**).

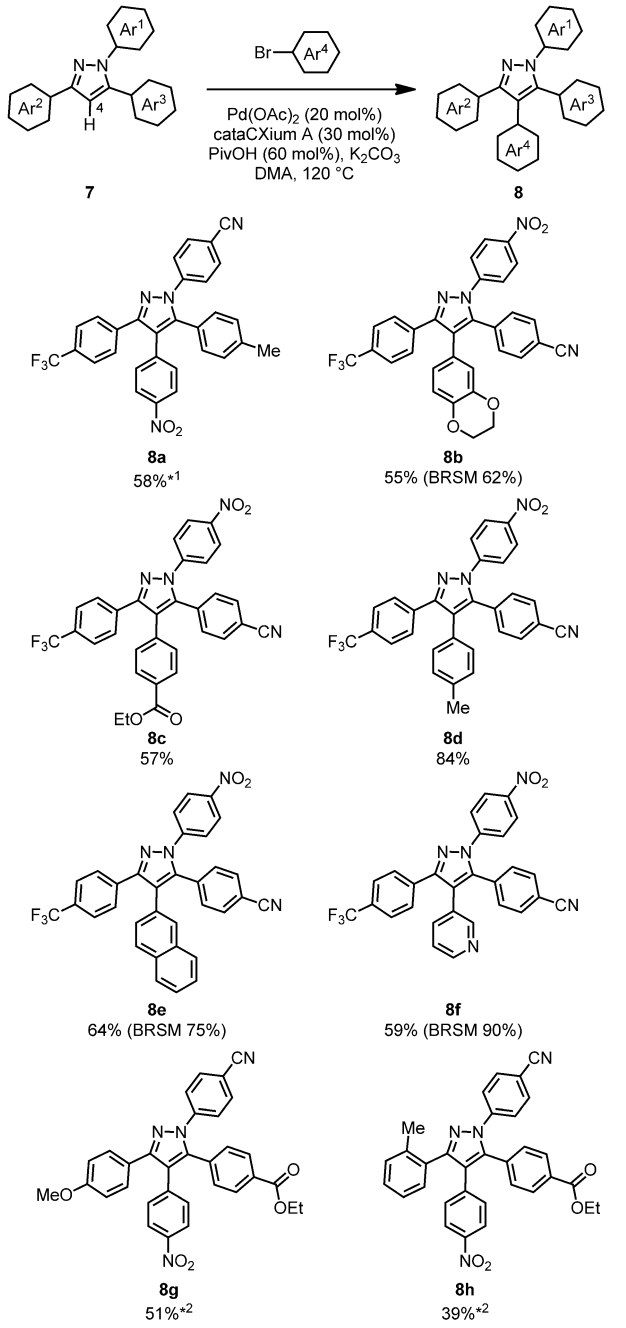
The structure of tetraaryl-substituted pyrazole **8a** was unambiguously determined by X-ray crystallographic analysis as




**Scheme 6.** C–H direct arylation at the C5-position of 1,3-diaryl-substituted pyrazole **6**. *1: Reaction conditions: 20 mol% $Pd(OAc)_2$, 30 mol% $PCy_3{\cdot}HBF_4$, and 60 mol% PivOH. *2: The ratio of substrate **6** to ArBr was 1.5:1. The yield was calculated based on the Ar-Br. BRSM: based on recovered starting material; PivOH: pivalic acid.

shown in Figure 1. All four aryl groups were introduced at the desired positions. They were distorted from coplanarity by 36.78(9)° (4-CNPh), 47.15(6)° (4-MePh), 63.34(7)° (4-$NO_2$Ph), and 22.13(14)° (4-$CF_3$Ph) with respect to the central pyrazole ring, which was probably due to the steric repulsion among the aryl rings.

In summary, we have successfully demonstrated a regioselective, protection/deprotection-free, divergent synthesis of tetraaryl-substituted pyrazole based on a 3-iodo-1*H* pyrazole scaffold (**4**). This is the first example of the synthesis of pyrazoles with four different aryl groups through four sequential cross-coupling reactions. Our developed approach employed readily available substrates and reagents, and a glovebox technique was not required. The 3-iodo-1*H* pyrazole scaffold enabled the




**Scheme 7.** C–H direct arylation at the C4-position of 1,3,5-triaryl-substituted pyrazole **7**. *Reaction conditions: 10 mol% $Pd(OAc)_2$, 15 mol% cataCXium A, and 30 mol% PivOH. *2: The ratio of substrate **7** to ArBr was 1.5:1.

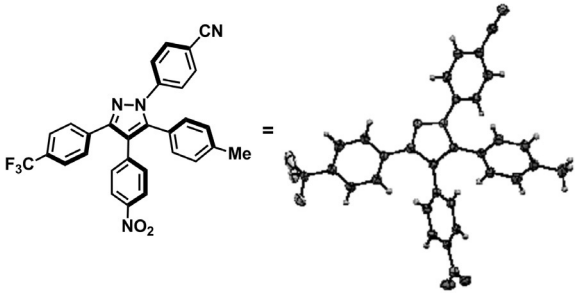


**Figure 1.** X-ray crystallographic analysis of **8a**.[33]

installation of alkene, amine, and carboxamide groups at the C3-position. The developed approach would be a valuable aid as a rapid lead generation in drug discovery and materials development based on multiaryl-substituted pyrazoles.

**Keywords:** C-H activation · cross-coupling · heterocycles · palladium · synthetic methods

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[33] CCDC 1406276 (**8a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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