JOC*Note*

A Simple, Modular Method for the Synthesis of 3,4,5-Trisubstituted Pyrazoles

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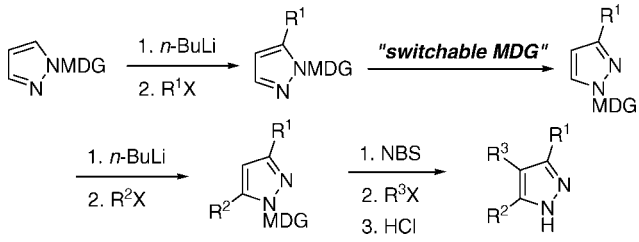

A modular approach for the regiocontrolled preparation of pyrazoles bearing substituents on all three carbon atoms is described. Central to this method is the use of a switchable metal-directing group (MDG) to enable sequential direct lithiation of the 3- and 5-positions of the pyrazole ring. Pyrazole boronic esters obtained from these lithiated intermediates can undergo efficient Suzuki cross-coupling under the developed nonaqueous conditions, which minimize undesirable protolytic deboronation. Halogenation of the 4-position provides the means for substitution at the remaining carbon atom.

In recent years, the pyrazole ring system has proven to be an increasingly popular heterocycle for the synthesis of pharmaceutically active compounds.[1] In support of drug development programs at Merck, we had reason to investigate potential methods for the preparation of functionalized pyrazoles. Specifically, we required a simple method by which the pyrazole ring could be elaborated in a regiocontrolled fashion to provide polysubstituted pyrazole derivatives. Our general approach to this problem (Figure 1) was to develop a modular synthesis based around the concept of a *switchable* metal-directing group (MDG). We envisaged that controlled access to metalated pyrazoles would open the door to a variety of reactions for further functionalization, including cross-coupling technologies.[2]

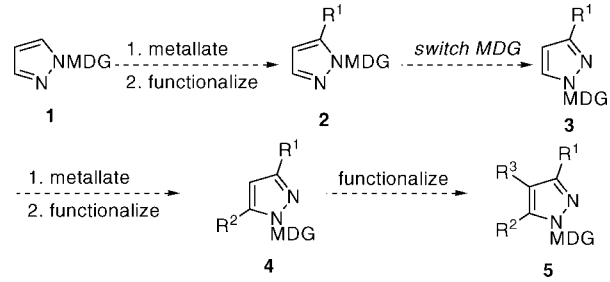

FIGURE 1. Modular approach to polyfunctionalized pyrazoles.

Of particular interest was the Suzuki cross-coupling reaction since this is well-established as a dependable process applicable to many substrate types.[3] However, at the outset of our studies in this area, the preparation and use of pyrazole boronic acids had received limited attention in the literature. One report[4] by Young and co-workers at Merck, which served as the basis for our own efforts, described the use of *N*-THP pyrazole in the preparation of pyrazole-5-boronic acid. The overall yield for this process from pyrazole was 38%, and an attempt to cross-couple the prepared boronic acid with an aryl bromide afforded only 32% yield.

More recently, two reports relevant to our research appeared in the literature. Building upon Young's work, Rault described the preparation of a pyrazole boronate ester **6** and demonstrated its use in Suzuki cross-coupling reactions, although the yields were only moderate and required relatively high catalyst loadings (5 mol %).[5] Concurrently, Fu documented an excellent general procedure for the Suzuki cross-coupling of nitrogen-containing heterocycles that were previously known to be difficult substrates for this reaction.[6] This report featured only one example of a pyrazole-5-boronic acid participating in a cross-coupling with bromobenzene. Given our need to prepare a variety of pyrazole-based intermediates for use in drug discovery work, we required a more general and robust method for the synthesis of these derivatives. In this Note, we are now able to disclose our own results toward an efficient means for elaboration of the pyrazole nucleus.

We initially set out to define the optimal conditions for the preparation of pyrazole boronate **6**. In the best procedure, *N*-THP-pyrazole can be obtained in essentially quantitative yield by treatment of pyrazole with 1.05 equiv of 3,4-dihydro-2*H*-

(1) Elguero, J. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol. 5.

(2) The directed metalation/cross-coupling tactic has been extensively studied by Prof. Snieckus. For recent examples, see: (a) Blanchet, J.; Macklin, T.; Ang, P.; Metallinos, C.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 3199–3206. (b) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588–1594. For an example of regioselective pyrazole metalation, see: (c) Paulsen, A. F.; Eskildsen, J.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **2002**, *67*, 3904–3907.

(3) Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (d) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11–59. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 9633–9695. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. (g) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419–2440.

(4) Young, M. B.; Barrow, J. C.; Glass, K. L.; Lundell, G. F.; Newton, C. L.; Pellicore, J. M.; Rittle, K. E.; Selnick, H. G.; Stauffer, K. J.; Vacca, J. P.; Williams, P. D.; Bohn, D.; Clayton, F. C.; Cook, J. J.; Krueger, J. A.; Kuo, L. C.; Lewis, S. D.; Lucas, B. J.; McMasters, D. R.; Miller-Stein, C.; Pietrak, B. L.; Wallace, A. A.; White, R. B.; Wong, B.; Yan, Y.; Nantermet, P. G. *J. Med. Chem.* **2004**, *47*, 2995–3008.

(5) Gérard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tetrahedron Lett.* **2006**, *47*, 4665–4669.

(6) Kudo, N.; Perseghini, N.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284.

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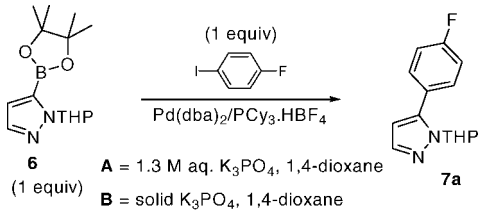


	% Assay Conv. (ArI)	% Assay Yield (**7a**)
Conditions A:	60	58
Conditions B:	> 99	98

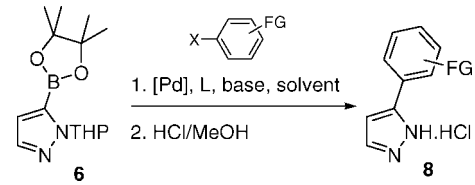
FIGURE 2. Comparsion of aqueous versus nonaqueous solvent systems for Suzuki coupling of pyrazole boronate **6** (yields determined by quantitative LC analysis).

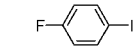
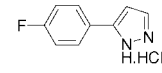
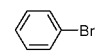
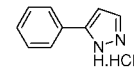
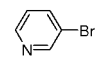
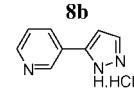
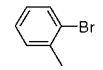
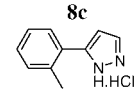
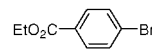
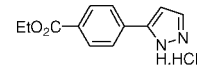
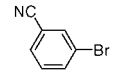
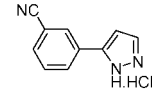
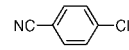
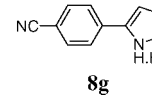
pyran (DHP) and catalytic TFA in toluene at 80 °C.[7] Concentration of the reaction mixture affords a crude product that is sufficiently pure for direct use in the ensuing regioselective deprotonation reaction (THP = MDG). Treatment with *n*-BuLi in THF lithiates the 5-position of the pyrazole ring. Quenching with B(O*i*-Pr)$_3$ and then pinacol/AcOH yields the boronic ester, which greatly facilitates isolation (relative to the boronic acid). The pinacol boronate **6** is a stable solid that is easily isolated (80% yield) by crystallization from heptane.

With ready access to boronate **6**, the applicability of known procedures for Suzuki cross-coupling was studied. In our hands, the use of aqueous solvents for this reaction led to protolytic deboronation as a troublesome side reaction, and the conversion of aryl halide suffered accordingly (Figure 2).[8] Consequently, we attempted the same cross-coupling under alternative conditions and discovered that protolytic deboronation is effectively suppressed by eliminating bulk water from the system (Figure 2). This modification allows for efficient cross-coupling using only 1 equiv of **6**, and high yields were realized for a variety of aryl chlorides, bromides, and iodides (Table 1). For convenience, the crude cross-coupled products were deprotected and isolated/characterized as the corresponding HCl salts **8**.[9] The efficiency of the developed cross-coupling conditions is clearly demonstrated by the high purity of the "crude" products isolated from these reactions. The overall isolated yield for the coupling/deprotection/salt formation sequence is shown in Table 1.

Having secured a series of monoarylated pyrazole HCl salts, we turned our attention toward the development of techniques for further elaboration of the pyrazole ring (Figure 3). To this end, we investigated the possibility that reintroduction of the THP group (**8b** to **9b**) would be selective for the other nitrogen atom of the pyrazole ring. This would potentially allow for a second metalation of the ring and subsequent functionalization. In the event, subjection of the monoarylated free-base pyrazole to the previously developed conditions for installation of the *N*-THP group led to highly selective reaction at the nitrogen furthest from the aryl substituent and afforded compound **9b** in high yield.

TABLE 1. Synthesis of Monoarylated Pyrazoles[a]



entry	aryl halide	product	yield (%)[b]
1		 **8a**	84
2		 **8b**	81
3		 **8c**	70
4		 **8d**	81
5		 **8e**	88
6		 **8f**	82
7		 **8g**	85

[a] Reaction conditions: Boronate **6** (100 mol %), aryl halide (100 mol %) Pd(dba)$_2$ (2 mol %), PCy$_3$·HBF$_4$ (2.4 mol %), K$_3$PO$_4$ (300 mol %), 1,4-dioxane (10 mL/g), 80 °C, 16 h, then extractive workup and treatment with HCl/MeOH at rt. [b] Yields refer to isolated material.

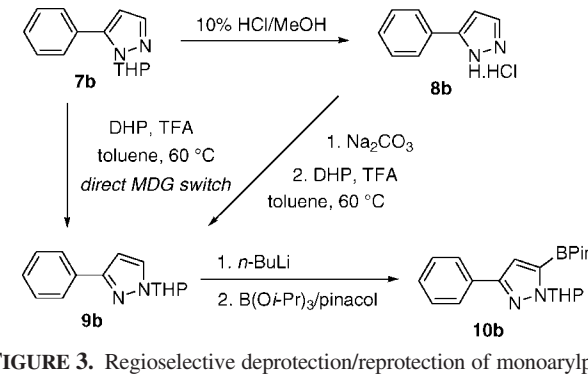


FIGURE 3. Regioselective deprotection/reprotection of monoarylpyrazole **7b** and demonstration of the direct MDG switch (**7b** to **9b**) followed by boronate (**10b**) formation (BPin = pinacol boronate).

With this knowledge, we postulated that under the appropriate conditions it would be possible to simply equilibrate the THP group onto the thermodynamically most stable position in a single process (**7b** to **9b**), without the need for a two-step deprotection/reprotection sequence.

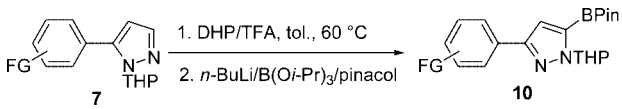
To our satisfaction, treatment of **7b** with 1 equiv of DHP and 5 mol % of TFA in toluene at 60 °C directly furnished **9b** in good yield. It was established that the newly positioned MDG in **9b** again served to facilitate pyrazole ring deprotonation using

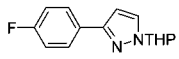
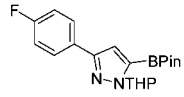
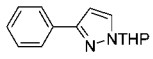
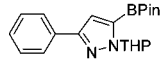
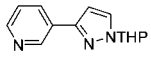
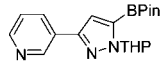
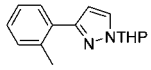
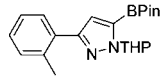
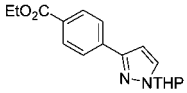
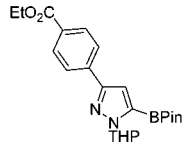
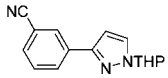
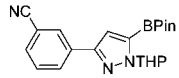
(7) Important modifications to the existing literature procedure that are relevant to larger-scale operation of this chemistry include reduced excess of DHP (1.05 vs 1.5 equiv) and controlled addition of this reagent at 80 °C to avoid a serious exotherm observed using an "all-in" mode (see Supporting Information for further details). Distillative workup was also eliminated. For further details regarding the kinetic profile of this reaction, see: Schafer, W. A.; Hobbs, S.; Rehm, J.; Rakestraw, D. A.; Orella, C.; McLaughlin, M.; Ge, Z.; Welch, C. J. *Org. Process Res. Dev.* **2007**, *11*, 870–876.

(8) Proteolytic deboronation of heterocyclic substrates can be problematic and was observed by Prof. Fu when employing a pyrazole-4-boronic acid substrate (ref 6).

(9) Alternatively, the THP-pyrazoles are stable to chromatography and can be isolated (pure) using this technique.

TABLE 2. THP Switch and Boronic Ester Synthesis[a]



entry	switched product	yield (%)[b]	boronate	yield (%)[b]
1	 **9a**	86	 **10a**	79
2	 **9b**	78	 **10b**	72
3	 **9c**	68	 **10c**	67
4	 **9d**	81	 **10d**	72
5[c]	 **9e**	85	 **10e**	82
6[c]	 **9f**	83	 **10f**	81

[a] Reaction conditions: DHP (100 mol %), TFA (5 mol %), toluene (10 mL/g), 60 °C for 2−3 h. Isolate switched intermediate and treat THF solution (10 mL/g) with *n*-BuLi (105 mol %) at −50 °C then $B(Oi\text{-}Pr)_3$ (110 mol %), pinacol (110 mol %), and AcOH (200 mol %) at rt. [b] Yields refer to isolated material. [c] LDA (105 mol %) used as the base, added to mixture of substrate/$B(Oi\text{-}Pr)_3$ at −60 °C.

n-BuLi and the resultant lithiated species could be smoothly transformed into the corresponding pinacol boronic ester **10b**. This novel MDG switch and subsequent metalation proved to be fairly general for a series of monoarylated pyrazoles obtained from the initial cross-couplings (Table 2). Notably, heteroatom-bearing substrates such as **9a** or **9c** can be selectively metalated and converted into boronic esters. Substrates featuring more reactive functional groups (**9e** and **9f**) can also be utilized, provided LDA is used as the base.[10]

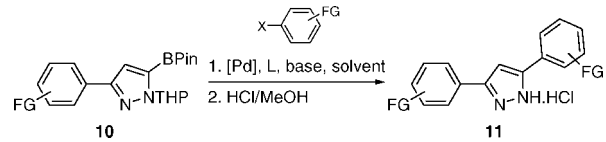
Introduction of a second aryl substituent onto these intermediates (**10**) via Suzuki cross-coupling was again efficiently accomplished using the developed nonaqueous conditions. Table 3 depicts the variety of 3,5-diarylated pyrazoles (**11**) that were synthesized, and again, the crude products were directly converted to their HCl salts for ease of isolation.

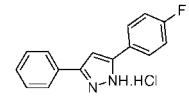
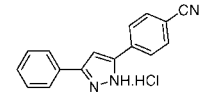
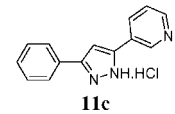
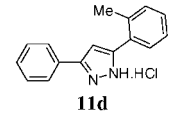
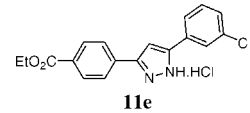
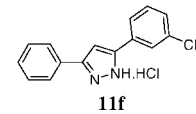
Further complexity can be introduced by way of the 4-bromo derivatives, which can be easily prepared by NBS treatment of the THP-protected 3,5-diarylpyrazoles (e.g., **12**). Suzuki cross-coupling of these 4-bromo compounds (**13**) allows for introduction of a third distinct aryl substituent onto the pyrazole ring in good yield (Figure 4).

In summary, we have described an efficient and modular strategy for the functionalization of all three carbon atoms of pyrazole. Central to this approach is the novel use of an easily switchable metal-directing group to enable sequential direct lithiation of the 3- and 5-positions of the pyrazole ring. A key aspect of this work is the development of an effective procedure for the Suzuki cross-coupling of pyrazole boronic esters, which overcomes the problem of competitive deboronation typically encountered under previously described conditions. The flexibility and generality of the developed method was demonstrated by the efficient and regiocontrolled preparation of numerous mono-, di-, and triarylated pyrazoles, which are of potential utility as heterocyclic building blocks for the synthesis of pharmaceutically active compounds.

(10) Ethyl ester **7e** suffered double addition of *n*-BuLi leading to a tertiary alcohol.

TABLE 3. Synthesis of 3,5-diarylated pyrazoles[a]



entry	boronate	X	product	yield (%)[b]
1	**10a**	Br	 **11a**	83
2	**10b**	Cl	 **11b**	88
3	**10c**	Br	 **11c**	78
4	**10d**	Br	 **11d**	88
5	**10e**	Br	 **11e**	79
6	**10f**	Br	 **11f**	81

[a] Reaction conditions: Boronate (100 mol %), aryl halide (100 mol %) $Pd(dba)_2$ (2 mol %), $PCy_3.HBF_4$ (2.4 mol %), K_3PO_4 (300 mol %), 1,4-dioxane (10 mL/g), 80 °C, 16 h, then extractive workup and treatment with HCl/MeOH at rt. [b] Yields refer to isolated material.

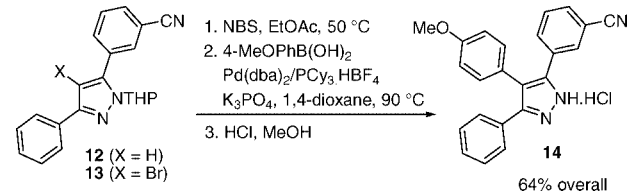


FIGURE 4. Elaboration to triarylpyrazole **14**.

Experimental Section

Suzuki Cross-Coupling of Pyrazole Boronic Esters and HCl Salt Formation. To an 8 mL vial equipped with a stirbar and septum were charged the pyrazole boronate (**6** or **10a**−**f**) (1 mmol),

aryl halide (1 mmol), K_3PO_4 (300 mol %), $Pd(dba)_2$ (2 mol %), $PCy_3.HBF_4$ (2.4 mol %), and 1,4-dioxane (3 mL). The heterogeneous mixture was agitated and purged with N_2 for 10 min before it was heated to 80 °C for 16 h. After this time, LC analysis of the gray mixture normally indicated >98% conversion. The mixture was diluted with brine (30 mL) and MTBE (70 mL), and the separated organic was dried over Na_2SO_4. The filtered MTBE solution was concentrated under reduced pressure, and the crude residue was treated with HCl in MeOH (10 mL of stock solution) at rt. Isolation of the HCl salts (**8**) was achieved by dilution with MTBE and filtration of the resultant slurry. **5-(4-Fluorophenyl)-1*H*-pyrazole hydrochloride (8a):** Following this general procedure, **8a** was obtained as an off-white solid (84%): mp = 162−163 °C; ^{1}H NMR (400 MHz, DMSO) δ 6.98 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 8.4, 5.6 Hz, 2H), 7.98 (dd, J = 8.4, 5.6 Hz, 2H), 8.08 (d, J = 2.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO) δ 103.5, 116.1 (d, J_{CF} = 20.1 Hz), 126.0, 128.6 (d, J_{CF} = 10.0 Hz), 133.8, 146.1, 163.6 (d, J_{CF} = 251.6 Hz). HRMS calcd for $C_9H_8FN_2$ $[M + H]^+$ 163.06715, found 163.06749.

THP Switch. To an 8 mL vial equipped with a stirbar and septum was charged the substrate **7** (1 mmol) followed by toluene (3 mL), DHP (100 mol %), and TFA (5 mol %). The mixture was heated at 60 °C for 3 h, then LC analysis indicated complete switching of the THP group. The mixture was diluted into saturated aqueous $NaHCO_3$ (30 mL) and MTBE (70 mL), and then the separated organic phase was washed with brine (30 mL) and dried over Na_2SO_4. The filtered MTBE solution was concentrated under reduced pressure, and the switched THP product **9** was isolated following flash chromatography on silica gel using an appropriate mixture of EtOAc/hexanes as the eluent. **3-(4-Fluorophenyl)-1-(tetrahydropyran-2-yl)-1*H*-pyrazole (9a):** Following this general procedure, **9a** was obtained as a colorless oil (86%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58−1.77 (m, 3H), 2.02−2.23 (m, 3H), 3.69−3.77 (m, 1H), 4.07−4.14 (m, 1H), 5.43 (dd, J = 10.0, 2.4 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 7.04−7.11 (m, 2H), 7.63 (d, J = 2.4 Hz, 1H), 7.77−7.82 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 22.6, 25.1, 30.7, 68.0, 87.9, 103.3, 115.5 (d, J_{CF} = 20.1 Hz), 127.6, 129.1, 129.8, 150.9, 162.7 (d, J_{CF} = 241.5 Hz). HRMS calcd for $C_9H_8FN_2$ $[(M - THP) + H]^+$ 163.06715, found 163.06724.

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Supporting Information Available: Characterization data and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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