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Published on Web 02/10/2009

C−H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Pyrazoles via Sequential Regioselective *C*-Arylation and *N*-Alkylation Enabled by SEM-Group Transposition

Roman Goikhman, Teresa L. Jacques, and Dalibor Sames*

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

Received December 9, 2008; E-mail: sames@chem.columbia.edu

Abstract: Pyrazoles are important azole heteroarenes frequently found in pharmaceuticals and protein ligands, and there has been a growing interest in new synthetic methods for their preparation. We report the first catalytic intermolecular C−H arylation of pyrazoles, namely SEM-protected pyrazoles and *N*-alkylpyrazoles, which lays the foundation for a new approach to the synthesis of complex arylated pyrazoles, where new arene rings are directly attached to predetermined positions of the heteroarene nucleus ("topologically obvious synthesis"). Through a systematic search, we identified a palladium-pivalate catalytic system as the most effective protocol and mapped the reactivity of all three C−H bonds of the pyrazole (C-5 > C-4 ≫ C-3). To circumvent the low reactivity of the C-3 position, we developed a "SEM switch", which transposes the SEM-protecting group from one nitrogen to the other in one step, and in the process transforms the unreactive C-3 position to the reactive C-5 position. The SEM switch thus enables sequential arylation of C-5 and C-3 position, providing rapid access to protected or free 3,4,5-triarylpyrazoles (the C-4 arene ring is readily introduced by bromination and Suzuki coupling). Furthermore, *N*-alkylation of SEM-protected pyrazoles allows for regioselective introduction of the amine substituent, addressing the low regioselectivity of *N*-alkylation of pyrazoles lacking sufficient steric bias. Thus, the catalytic C−H arylation combined with the protecting group transposition and *N*-alkylation provides a rapid route to fully substituted pyrazoles with complete regiocontrol of all substituents. The particular strength of this strategy is the ability to commence the synthesis from either the parent pyrazole or practically any pyrazole intermediate.

Introduction

Azole heteroarenes are structural units frequently found in biologically active compounds, including natural products, protein ligands, and pharmaceuticals.[1] These structures represent indispensable components of the modern medicinal chemistry repertoire.[2] Pyrazoles, while rarely found in nature, serve as important core structures of many pharmaceuticals and pharmaceutical leads with a wide range of biological activities[2b] (e.g., cholesterol lowering,[3] anti-inflammatory,[4] anticancer,[5] antidepressant, and antipsychotic agents[6]). As a result, there is a continuing interest in the development of versatile methods to access highly substituted pyrazoles. Traditionally, pyrazoles have been synthesized via condensation reactions of 1,3-dicarbonyls and hydrazines or by cycloadditions of diazoalkanes and alkynes.[7] Although recent efforts greatly expanded the generality of de novo approaches, each method has its scope and efficiency limitations.[8]

We propose a conceptually different approach to the assembly of complex arylated pyrazoles based on direct C−H bond arylation (Figure 1). Following this logic on a strategic level, new aromatic rings would be directly attached to the existing pyrazole core at desirable positions ("*topologically obvious synthesis*"),[9] which suggests a rapid entry into functionalized heterocycles and an approach enabling efficient synthesis of series of pyrazole analogs and regioisomers.

In order to realize this goal, we developed the first catalytic method for intermolecular *C*-arylation of pyrazoles and explored its regioselectivity trends. On the basis of these results, a general approach was devised for the synthesis of mono-, di-, and

(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: Chichester, U.K., 1997.
(2) (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996, Vol 5. (b) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Pyrazoles as Drugs: Facts and Fantasies. In *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; Italian Society of Chemistry: Roma, 2002; Vol. 6, pp 52–98.
(3) Sliskovic, D. R.; Roth, B. D.; Wilson, M. W.; Hoefle, M. L.; Newton, R. S. *J. Med. Chem.* **1990**, *33*, 31–38.
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(5) Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem.* **2000**, *2*, 318–329.
(6) Moore, K. W.; Bonner, K.; Jones, E. A.; Emms, F.; Leeson, P. D.; Marwood, R.; Patel, S.; Patel, S.; Rowley, M.; Thomas, S.; Carling, R. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1285–1290.
(7) *Science of Synthesis*; Stanovnik, B., Svete, J. D. Eds.; Thieme: Stuttgart, 2002; Vol. 12, pp 22−81, pp 84−91.
(8) (a) Aggarwal, V. K.; De Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381–5383. (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675–78. (c) Deng, X.; Mani, N. S. *Org. Lett.* **2008**, *10*, 1307–1310.
(9) (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077–1101.

10.1021/ja8096114 CCC: $40.75

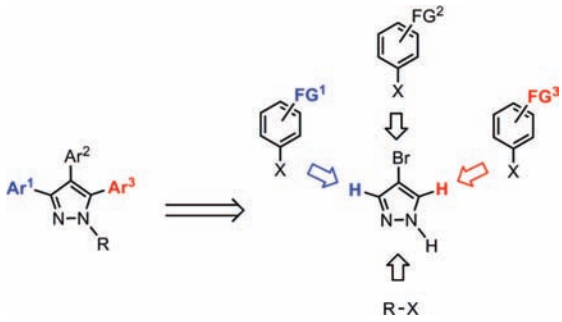

Figure 1. A new approach to synthesis of complex pyrazoles via direct C−H arylation.

triarylpyrazoles (Scheme 1). The first aryl group can be installed regioselectively in the 4-position of pyrazole by bromination and Suzuki coupling; other substituents can also be introduced at this position due to its high nucleophilicity. The first direct C−H arylation takes place with good selectivity at the 5-position, providing a concise approach to unsymmetrical diarylpyrazoles. The subsequent arylation is however inefficient, owing to the low reactivity of the 3-position. To address this problem, we have developed a simple one-step protocol to shift the SEM-group from one nitrogen to the other, which transforms the unreactive position 3 to the reactive position 5, and enables the second C−H arylation to proceed in an efficient manner, affording a short route to protected and free triarylpyrazoles (Scheme 1).[10] Furthermore, regioselective introduction of a nitrogen substituent becomes possible by the *N*-alkylation of unsymmetrical SEM-pyrazoles (Scheme 1). Thus, this strategy allows for rapid assembly of fully substituted pyrazoles with complete regio-control of all C- and N-substituents. Complex pyrazoles with different number and position of aryl rings can be readily synthesized from common precursors by choosing the desirable haloarene donor and the order of the arylation and alkylation reactions.

Results

Development of C−H Arylation Protocol for SEM-Protected Pyrazoles. We have previously reported catalytic methods for direct *C*-arylation of indoles, pyrroles, and imidazoles using palladium[11] and rhodium[12] catalysts and carboxylate bases. However, these protocols were inefficient for arylation of pyrazoles, calling for the development of new conditions.[13−15] We rationalized the low reactivity of pyrazoles in terms of the relatively high Lewis basicity of these compounds and the ability to deactivate the catalyst. We chose to examine SEM-protected pyrazoles as the substrates [SEM = 2-(trimethylsilyl)ethoxymethyl] due to the stability of this protecting group under the catalytic arylation conditions[11c,16] as well as the ability of SEM group to be transposed from one nitrogen to another, enabling sequential arylations as outlined above.

Systematic examination of the reaction parameters (metal catalyst, ligand, base, and solvent) for the coupling of SEM-pyrazole and bromobenzene led to a robust method which uses the following conditions: 5 mol % $Pd(OAc)_2$, 7.5 mol % P(*n*-Bu)Ad_2, and 3 equiv. KOPiv, in DMA as the solvent and heating at 140 °C (Figure 2). Once again, an unbiased search for catalytic C−H arylation conditions identified a carboxylate salt as the best base, consistent with the previous results in our group that demonstrated the importance of carboxylate base in the metalation step of heteroarenes.[11,12] Furthermore, these conditions are very similar to those developed independently by Fagnou and colleagues for arylation of benzene aromatics.[17] Following Fagnou's lead, potassium pivalate can be replaced with potassium carbonate and a substoichiometric amount of pivalic acid, resulting in a more practical procedure; both versions of this protocol (PivOK or PivOH/K_2CO_3) afford comparable yields of arylated SEM-pyrazoles.

Regioselectivity of *C*-Arylation of SEM-Protected Pyrazoles. The next key question centered on establishing the regioselectivity of the catalytic C−H arylation method (Figure 2). The parent SEM-pyrazole **1** when submitted to the catalytic conditions gave a mixture of products, which indicated the higher reactivity of the 5-position relative to the 4-position, and very low reactivity of the 3-position (Figure 2B). In addition to the monoarylated products, the bis-arylation product **4** was also formed in a significant amount. This trend was confirmed by examining the reaction of 1-SEM-3-phenylpyrazole **5**, which gave a 5:2 ratio of products **6** and **7**. In contrast, compound **3** was arylated at the 5-position with high selectivity to provide compound **4** in 80% yield; the regioisomer stemming from arylation at the 3-position was not detected, and only a small amount of the *bis*-arylation product **7** was formed (16:1 ratio, **4**:**7**). Arylation of compound **2** was also selective, taking place at the 4-position to afford product **4** as the major product; however, the yield was lower compared to arylation of the 5-position. These results demonstrate that the arylation is inefficient at the 3-position, which is consistent with the low reactivity of this site (to both electrophiles and strong bases),

(10) As recently reported, THP protecting group and its transposition has been used to achieve pyrazole lithiation and regioselective preparation of N-THP-pyrazolylboronate esters. McLaughlin, M.; Marcantonio, K.; Chen, C.-y.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309–4312.

(11) (a) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900. (b) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057. (c) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979–1982. (d) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476–1479.

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(13) The development of catalytic methods for C-H arylation of arenes and heteroarenes is an active area of research. For recent reviews, see: (a) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (d) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238.

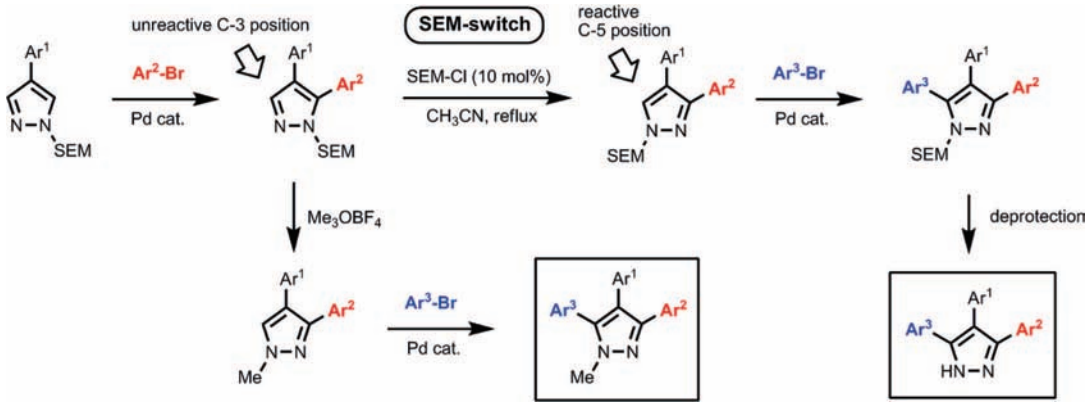
(14) Recent examples of azole C-arylation reported by others. (a) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207–5209. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973. (c) Cerna, I.; Pohl, R.; Kleptarova, B.; Hocek, M. *Org. Lett.* **2006**, *8*, 5389–5392. (d) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589–1591. (e) Chuprakov, S.; Chernyak, N.; Dudnik, A. S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 2333–2336. (f) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–51. (g) Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, *72*, 8543–8546. (h) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473–1476. (i) Blaszykowski, C.; Aktoudianakis, E.; Alberico, D.; Bressy, C.; Hulcoop, D. G.; Jafarpour, F.; Joushaghani, A.; Laleu, B.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 1888–1897.

(15) Intramolecular C-arylation of pyrazoles have been reported via an alkylation/arylation sequence. Blaszykowski, C.; Aktoudianakis, E.; Bressy, C.; Alberico, D.; Lautens, M. *Org. Lett.* **2006**, *8*, 2043–2045.

(16) The SEM group is also a directing group for lithiation of azoles including pyrazoles. (a) Edwards, M. P.; Doherty, A. M.; Ley, S. V.; Organ, H. M. *Tetrahedron* **1986**, *42*, 3723–3729. (b) Fugina, N.; Holzer, W.; Wasicky, M. *Heterocycles* **1992**, *34*, 303–314. (c) Gerard, A.-L.; Bouillon, A.; Mahatsekake, C.; Collot, V.; Rault, S. *Tet. Lett.* **2006**, *47*, 4665–4669. (d) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392–5395.

(17) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.

Scheme 1. Sequential *C*-Arylation Enabled by SEM Group Switch Provides a Rapid Access to Triarylpyrazoles with Complete Control of Regioselectivity



while arylation can be achieved at both C-4 and C-5 positions with preference for the latter.

These reactivity trends laid the foundation for the general synthetic strategy shown in Scheme 1. The information provided by these reactions is sufficient for planning regioselective elaboration of either the parent pyrazole or substituted pyrazoles.

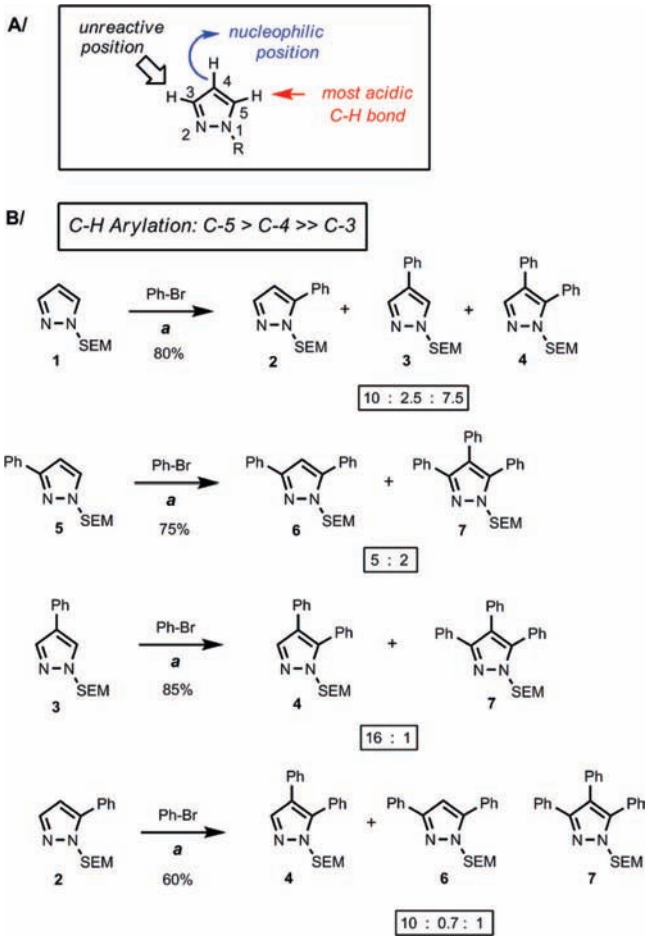


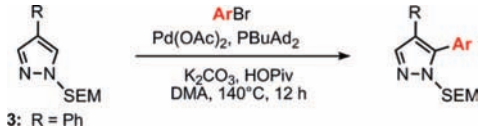
Figure 2. (A) General reactivity properties of pyrazole. (B) Reactivity profile of pyrazoles toward palladium-catalyzed C−H arylation. The C-5 position exhibits the highest reactivity. (a) Reaction conditions: Pyrazole, PhBr (1.5 equiv.), $Pd(OAc)_2$ (5 mol %), P(*n*-Bu)Ad_2 (7.5 mol %), K_2CO_3 (3 equiv.), HOPiv (25 mol %), 2.5 M DMA, 140 °C for 12 h. Isolated yields are shown except for substrate **1**, where the substrate conversion and the product ratio was determined by ^{1}H NMR of the crude mixture. All product ratios were confirmed by ^{1}H NMR of crude mixtures.

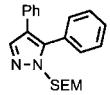
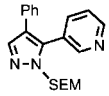
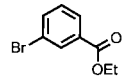
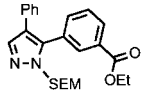
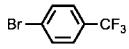
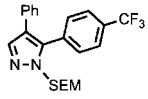
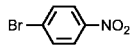
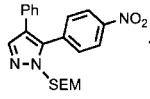
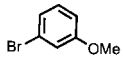
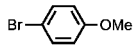
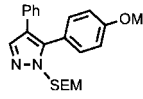
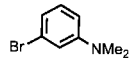
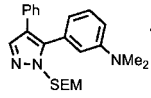
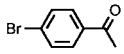
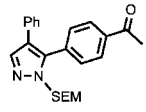
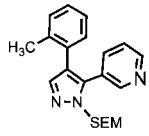
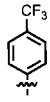
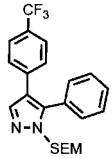
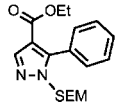
Rationale for the Observed Regioselectivity. Although this work focuses on the method and strategy development, we provide some context for the potential rationale for the observed selectivity preferences. It is well established that the 4-postion of pyrazole is most nucleophilic and readily undergoes electrophilic substitution, while the 5-position carries the most acidic C−H bond which can be selectively deprotonated by strong bases (e.g., lithiation).[18] The previous results suggest that both the palladium-acetate[11b] and the rhodium-pivalate[12] catalytic systems developed in our laboratory, as well as related systems developed by others, proceed via an electrophilic-like mechanism,[19] in the context of indoles, pyrroles, and imidazoles, where the metal acts as an electrophile, breaking the aromaticity, and the carboxylate ligand as the base, removing the proton. Alternatively, Fagnou's laboratory generated compelling evidence which shows that the palladium-pivalate system, in the context of benzene arenes, selectively targets acidic C−H bonds via a "σ-deprotonation mechanism" where the metal-carboxylate moiety directly engages the C−H bond.[17,20] The C-5 selectivity may thus be explained by the preference of the catalytic system for the acidic C−H bonds; however, an alternative rationale akin to the one proposed for C-2 arylations of indoles involving an electrophilic-like mechanism with the migration of palladium to the position adjacent to the nitrogen, is also reasonable.[11b] Importantly, the ability to accommodate both electron-deficient benzenes and electron-rich heteroarenes suggests substantial plasticity of the palladium-pivalate catalytic system, which may also account for the ability to arylate both C-5 and C-4 positions of the pyrazole system. The phosphine ligand modulates the reactivity of this catalytic system; in the context of pyrazoles, strong σ-donor phosphines also protect the catalyst against the inhibition by the basic sp^2 nitrogen of the substrate. Detailed mechanistic studies to answer these mechanistic questions are under way in our laboratories and will be reported in the future.

Arene Donor Substrate Scope. Compound **3** was used to examine the reaction scope of the arylation method; it was

(18) (a) *Science of Synthesis*; Stanovnik, B., Svete, J. D., Eds.; Thieme: Stuttgart, 2002; Vol. 12, pp 173−203. (b) Gupta, R. R.; Kumar, M.; Gupta, V. *Heterocyclic Chemistry*; Springer: Berlin, 1998; p 452. (c) Behr, L. C.; Fusco, R.; Jarboe, C. H. Pyrazoles, pyrazolines, pyrazolidines, indazoles, and condensed rings. In *The Chemistry of Heterocyclic Compounds*; Wiley, R. H., Ed.; Interscience Publishers: New York, 1967; Vol. 22 pp 107−109.
(19) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159–1162.
(20) The palladium-carbonate system also showed preference for acidic C-H bonds: Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.

Table 1. Arylation Substrate Scope[a]



Entry	R	ArBr	Product		Isolated Yield, %
1	Ph			**4**	80% (5% bis)
2	Ph			**8**	65% (15% bis)
3	Ph			**9**	82%
4	Ph			**10**	74% (13% bis)
5	Ph			**11**	58%
6	Ph			**12**	76%
7	Ph			**13**	35%
8	Ph			**14**	74%
9	Ph			**15**	58%
10	o-tol			**16**	79%
11				**17**	69% (8% bis)
12	COOEt			**18**	75%

[a] Reaction conditions: Pyrazole, ArBr (1.5 equiv.), $Pd(OAc)_2$ (5 mol %), P(*n*-Bu)Ad_2 (7.5 mol %), K_2CO_3 (3 equiv.), HOPiv (25 mol %), 2.5 M DMA, 140 °C for 12 h. Isolated yields are an average of at least two separate reactions.

synthesized in short order by bromination of free (NH)-pyrazole at the 4-position,[21] *N*-alkylation with SEM-Cl, and the Suzuki reaction with phenylboronic acid (see Supporting Information).

Scheme 2. SEM Group Transposition (SEM switch)

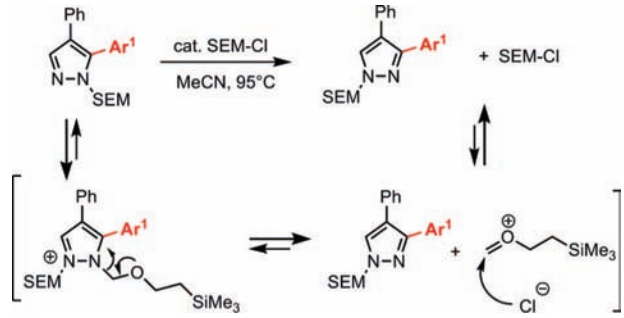
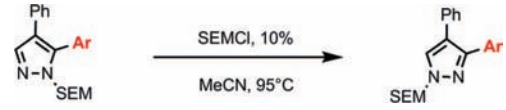
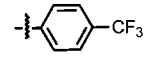
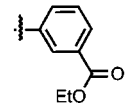


Table 2. SEM Switch Scope



Entry	Aryl Group	Product	% Conversion[a]
1		**19**	85%
2		**20**	90% (84%)[b]
3		**21**	91% (80%)[c]
4		**22**	90%

[a] Determined by ^1H NMR. [b] Isolated yield (flash chromatography). [c] Isolated yield (HPLC).

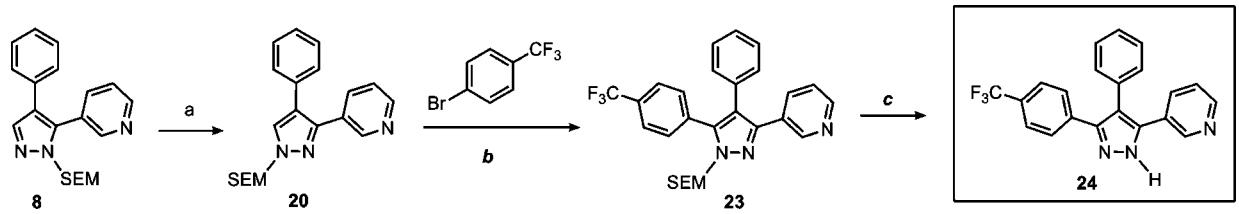
The arylation reactions may be performed on the benchtop under argon, and the scope of the reaction is quite broad, tolerant of a wide variety of functional groups on the bromoarene donor, including ketone, ester, nitro, dimethylamino, and pyridyl groups (Table 1). Electron-deficient and electron-neutral bromoarenes perform best in the reaction, whereas bromoarenes with electron-donating substituents in the *para*-position or steric bulk in the *ortho*-position give lower yields of desired products.

Pyrazole Substrate Scope. Substitution on the phenyl ring in the 4-position of the pyrazole is also tolerated as illustrated by the *ortho*-tolyl- and *para*-trifluoromethylphenyl-substrates, which give the corresponding products **16** and **17**, respectively, in good yields (Table 1, entry 10 and 11). Furthermore, the method is compatible with substituents other than aryl groups as demonstrated by efficient arylation of the substrate containing electron-withdrawing ester functionality directly attached to the pyrazole nucleus in the 4-position, affording product **18** in 75% isolated yield (Table 1, entry 12). Thus, this method allows for synthesis of 4,5-diaryl-SEM-pyrazoles in one step from readily available 4-aryl-SEM-pyrazoles.

SEM-Group Transposition (SEM-group switch). After the installment of the second arene ring, the subsequent arylation would have to take place at the 3-position, which bears the last available C−H bond. However, as shown in Figure 2, the

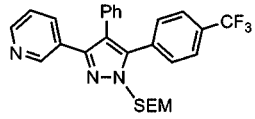
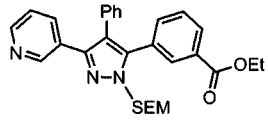
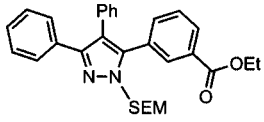
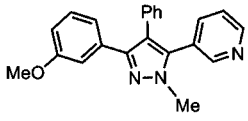
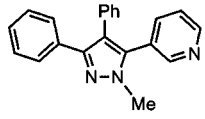
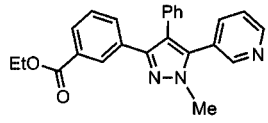
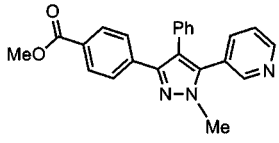
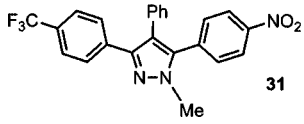
(21) Zhao, Z.-G.; Wang, Z.-X. *Synth. Commun.* **2007**, *37*, 137–147.

Scheme 3. Synthesis of Triarylpyrazoles via Sequential *C*-Arylation[a]



[a] Conditions: (a) Pyrazole, SEMCl (10 mol %), MeCN, 95°C, 24 h; 84% yield. (b) Pyrazole, ArBr (1.5 equiv.), $Pd(OAc)_2$ (5 mol %), P(*n*-Bu)Ad_2 (7.5 mol %), K_2CO_3 (3 equiv.), HOPiv (25 mol %), 2.5 M DMA, 140°C, 12 h; 77% yield. (c) 3N HCl, EtOH, reflux, 3 h, 75% yield. In DMSO-d_6, compound **24** exists as a mixture of tautomers. Yields are an average of at least two separate isolated yields.

Table 3. *C*-Arylation of Diarylpyrazoles, Substrate Scope[a]

Entry	Product	Isolated Yield
1	 **23**	77%
2	 **25**	88%
3	 **26**	64%
4	 **27**	70%
5	 **28**	67%
6	 **29**	53%
7	 **30**	54%
8	 **31**	43%

[a] Reaction conditions: Pyrazole, ArBr (1.5 equiv.), $Pd(OAc)_2$ (5 mol %), P(*n*-Bu)Ad_2 (7.5 mol %), K_2CO_3 (3 equiv.), HOPiv (25 mol %), 2.5 M DMA, 140 °C, 12 h. Yields are an average of at least two separate isolated yields.

arylation of this site is not feasible due to its low reactivity; no reaction or very low yields of the desired product were obtained. To solve this problem, we considered switching the SEM group from one nitrogen atom to another, which would transform the unreactive position 3 to the reactive position 5 (Scheme 2).

It has been reported that a mixture of unsymmetrical N-protected imidazoles could be equilibrated by heating in the presence of alkylating agents, leading to formation of the thermodynamic product.[22] Applying this approach to SEM-pyrazoles, we were able to achieve the SEM switch by heating the starting material with 10 mol % of SEM-Cl in acetonitrile. Alkylation of the pyrazole nitrogen by SEM-Cl forms a pyrazolium salt, which enables the equilibration of the two regioisomers, ultimately producing the thermodynamically favored, less hindered product (Scheme 2). The SEM-switch gives an average of ~90% conversion, as demonstrated with four different substrates (Table 2). The two isomers were frequently difficult to separate via flash chromatography; in such cases, reverse-phase HPLC was used to separate and purify these compounds. However, when triarylpyrazoles are desirable, separating the two regioisomers is not necessary, as the "unswitched material" may readily be removed after the subsequent arylation. The SEM-group switch transforms in one step an unreactive compound to a reactive substrate, avoiding the need for deprotection and reprotection, and enables the two sequential C−H arylations.

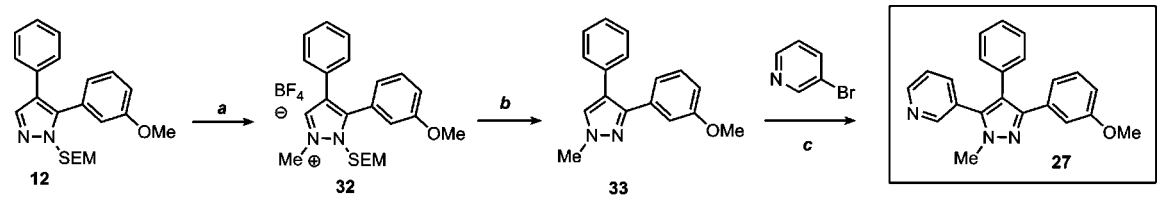
The Second *C*-Arylation and Preparation of 3,4,5-Triarylpyrazoles. Scheme 3 illustrates the brevity of the sequential arylation scheme for preparation of 3,4,5-triarylpyrazoles. Compound **8**, available in one arylation step from starting material **3**, was submitted to the SEM-group transposition to provide compound **20**. The second arylation with 4-bromotrifluoromethylbenzene proceeded in high yield under the standard catalytic conditions to give SEM-protected triarylpyrazole **23**, which after deprotection furnished triarylpyrazole **24**. Thus, all three arene rings are introduced to the pyrazole nucleus with complete regiochemical control; two of the rings are attached directly via C−H bond functionalization.

The scope of the arylation catalytic method was further examined in the context of 1-SEM-3,4-diarylpyrazole substrates (Table 3). Good to excellent yields of SEM-protected triarylpyrazoles were obtained with a variety of functional groups on both the pyrazole substrate and the bromoarene donor.

Deprotection of SEM-Pyrazoles. Free (NH)-pyrazoles are readily accessible by the deprotection of the SEM group, which is accomplished by the action of hydrochloric acid in ethanol.[23] To confirm the generality of this protocol in the

(22) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529–5532.
(23) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392–5395.

Scheme 4. Sequential *C*-Arylation and *N*-Methylation Provides a Rapid Access to 1-Methyl-3,4,5-Triarylpyrazoles with Complete Regioselectivity Control[a]



[a] Conditions: (a) Pyrazole, Me_3O-BF_4 (1.2 equiv.), CH_2Cl_2, RT, 1 h. (b) 3N HCl, EtOH, reflux, 1 h; 70% yield over 2 steps. (c) Pyrazole, ArBr (1.5 equiv.), $Pd(OAc)_2$ (5 mol %), P(*n*-Bu)Ad_2 (7.5 mol %), K_2CO_3 (3 equiv.), HOPiv (25 mol %), 2.5 M DMA, 140 °C for 12 h; 70% yield. Yields are an average of at least two separate isolated yields.

context of complex pyrazoles, triarylpyrazoles **23** and **25** (Table 3) as well as diarylpyrazoles **4**, **8**, and **10** (Table 1) were deprotected to afford high yields of the corresponding free pyrazoles (Supporting Information, section VI). It is well-known that free pyrazoles exist as a mixture of tautomers.[24,25] While the signal for the NH proton is broad in $CDCl_3$, the two peaks are resolved in DMSO-d_6 (δ 13−14.5 ppm); in the case of compound **24**, both tautomers are present in a 56:44 ratio (Supporting Information).

Regioselective *N*-Alkylation/*C*-Arylation Sequence Enabled by the SEM Group. The sequential arylation mediated by the SEM-group switch, described above, provides a rapid access to protected and free triarylpyrazoles and offers an attractive alternative to the de novo approaches. However, when *N*-alkylated products are desirable, the *N*-alkylation of free N−H pyrazoles that lack a sufficient steric bias—such as the triarylpyrazole **24** (Scheme 3)—suffers from lack of regioselectivity, giving a mixture of two regioisomers. To address this issue, we considered the idea of using the SEM group to selectively introduce the alkyl group at the desired nitrogen of the pyrazole. We tested a number of methylating reagents (dimethyl sulfate, methyl iodide, and trimethyloxonium tetrafluoroborate), out of which Me_3O-BF_4 gave best results, yielding *N*-methylated pyrazolium salts at room temperature in dry dichloromethane. For example, compound **12** was methylated and deprotected to produce a single regioisomer of the alkylated pyrazole, namely the compound **33** (Scheme 4). This two-step procedure not only selectively alkylates the nitrogen of choice, but also serves to transform the unreactive 3-position of the pyrazole to the reactive 5-position. The *N*-methylpyrazole **33** was then arylated with 3-bromopyridine to afford complex pyrazole **27**. Thus, the regioselective *N*-alkylation is incorporated into the sequential arylation scheme to afford the fully substituted pyrazole as a single isomer.

One limitation of this approach is that other nucleophilic functions present in the substrate would also undergo methylation; namely, pyridyl and dimethylamino groups are not compatible with the methylation reaction conditions. For anilines, this problem can be solved by introducing the nitrophenyl ring (Tables 1 and 3), and reducing the nitro group after the alkylation step. Another solution is to conduct the alkylation earlier in the sequence and thus introduce the alkylation-prone groups by *C*-arylation after the *N*-alkylation step as illustrated in Scheme 4. The pyridine ring is attached in the last step of the sequence, combining the utility of the regioselective *N*-alkylation with direct C−H arylation.

Conclusions

Pyrazoles are an important class of heteroarenes frequently found in pharmaceuticals and protein ligands, and there has been a growing interest in new synthetic methods for their preparation. We here present a strategically new approach based on the synthetic logic enabled by direct C−H bond functionalization, where new substituents are directly attached to predetermined positions of the heteroarene nucleus.[9] This approach enables functionalization of all five pyrazole positions with complete regiocontrol and allows for the efficient synthesis of analog series and regioisomeric series from common precursors. The particular strength of this strategy is the ability to commence the synthesis from either the parent pyrazole or practically any pyrazole intermediate.

Owing to the intrinsic reactivity preferences of pyrazole, the sequential *C*-arylation of free N−H pyrazoles or *N*-alkylated pyrazoles is not possible, and therefore we devised a strategy based on the SEM-protecting group and its transposition. The SEM group fulfills three major roles: first, it protects the pyrazole amine group and thus enables the *C*-arylation (free pyrazoles are not good substrates); second, it enables the regioselective sequential C−H arylation via the SEM group switch; and third, it allows for regioselective *N*-methylation which can be coupled to subsequent *C*-arylation. In summary, the catalytic C−H arylation combined with the protecting group transposition and *N*-alkylation provides a rapid route to fully substituted pyrazoles with complete regiocontrol of all substituents.

Significant advances have recently been reported for the de novo synthesis of pyrazoles, both in terms of regiocontrol and scope.[8] Also, major improvements have been achieved in the area of Suzuki coupling of pyrazoles; many of the problems associated with inefficient preparation of azolyl boronate esters and the low yielding coupling process have recently been addressed.[10,26] Our approach is complementary to these methods, and together they will greatly enable molecular designers to rapidly access a wide variety of complex pyrazole compounds. It is apparent that the sequential *C*-arylation approach will also

(24) (a) Trofimenko, S.; Yap, G. P. A.; Jove, F. A.; Claramunt, R. M.; García, M. A.; Santa Maria, M. D.; Alkorta, I.; Elguero, J. *Tetrahedron* **2007**, *63*, 8104–8111. (b) Vors, J.-P.; Gerbaud, V.; Gabas, N.; Canselier, J. P.; Jagerovic, N.; Jimeno, M. L.; Elguero, J. *Tetrahedron* **2003**, *59*, 555–560. (c) Aguilar-Parrilla, F.; Cativiela, C.; Diaz de Villegas, M. D.; Elguero, J.; Foces-Foces, C.; Laureiro, J. I. G.; Cano, F. H.; Limbach, H.-H.; Smith, J. A. S.; Toiron, C. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1737–1742. (d) Habraken, C. L.; Moore, J. A. *J. Org. Chem.* **1965**, *30*, 1892–1896.

(25) For considerations regarding the binding of tautomers to protein targets, see: Chimenti, F.; Fioravanti, R.; Bolasco, A.; Manna, F.; Chimenti, P.; Secci, D.; Befani, O.; Turini, P.; Ortuso, F.; Alcaro, S. *J. Med. Chem.* **2007**, *50*, 425–428.

(26) (a) Kudo, N.; Perseghini, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284. (b) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488. (c) Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.

be applicable to imidazoles and triazoles; these results will be described in separate publications in the near future.

Acknowledgment. We thank the National Institute of General Medical Sciences (NIGMS) for support of this work. We also thank Dr. Barry Touré (Novartis) for important intellectual contributions. Dr. Denis Gribkov is acknowledged for performing the preliminary experiments.

Supporting Information Available: Reaction conditions, compound characterization, and remaining authors for ref 4. This material is available free of charge via the Internet at http://pubs.acs.org.

JA8096114