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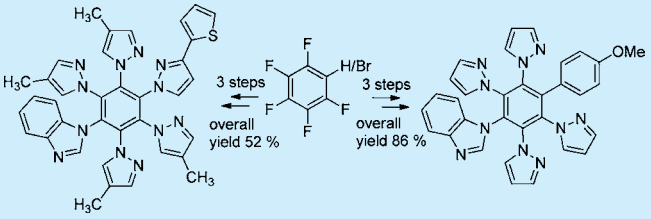
# Sequential Direct $S_NAr$ Reactions of Pentafluorobenzenes with Azole or Indole Derivatives

Frederik Diness*,† and Mikael Begtrup

Department of Drug Design and Pharmacology, University of Copenhagen, Universitetsparken 2, DK-2100 Copenhagen, Denmark

Supporting Information

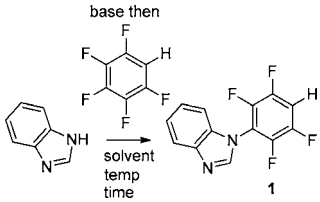
**ABSTRACT:** Sequential regioselective *N*-arylations through high-yielding catalyst-free direct $S_NAr$ reactions of pentafluorobenzene derivatives with azole or indole derivatives are described. The *N*-arylated derivatives were further functionalized through a microwave-assisted cross-coupling reaction via C−H bond activation or Suzuki conditions. The order of the reactions could be reversed, proving full orthogonality between the reactions which led to well-defined fully substituted benzene derivatives.




Complex *N*-arylated azole and pyrrole derivatives are currently being intensively investigated as these are materials for organic light emitting diodes (OLED) and organic electronics in general.[1] A promising new group of these are substituted benzene derivatives bearing four to six azole/pyrrole moieties, which has been explored for self-assembling, redox activity, metal chelation, conductivity, convertible conformation, and optoelectronic properties.[2] However, only benzene derivatives with four to six identical azole or pyrrole moieties are known from the literature,[2] and until now, no facile methods for selective tailoring of complex derivatives (e.g., asymmetric) within this class have been available.[3] Recently, we reported high-yielding catalyst-free *N*-arylation of azole or indole derivatives through direct nucleophilic aromatic substitution ($S_NAr$) of unactivated monofluorobenzene derivatives.[4] Similarly, pentafluorobenzene derivatives have also been explored within this regime. Here we report that these derivatives under optimized mild reaction conditions undergo regioselective high-yielding sequential substitutions. Furthermore, it is demonstrated that the direct $S_NAr$ reactions are fully orthogonal to cross-coupling reactions, which may be conducted in any reaction order.

Initially, benzimidazole was reacted with pentafluorobenzene in DMA using an inorganic base at room temperature (see the reaction scheme in Table 1).[5] The system was to serve as a model for functionalizing of polybenzimidazole with perfluorobenzene derivatives. Application of cesium carbonate or tribasic potassium phosphate which has been superior for reacting monofluorobenzene derivatives,[4] however, led to very slow conversion rates. This may be explained by the low degree of benzimidazole deprotonation by these bases at room temperature. However, the use of 1 equiv of sodium *tert*-butoxide as a stronger and more soluble base gave high conversion within 15 min and led to fair yields of the regioselective monosubstituted product **1**. A screen of solvents proved that combined with sodium *tert*-butoxide, DMF and DMA worked equally well, whereas THF, acetonitrile, ethyl acetate, and 2-propanol gave rise to slow conversion rates and major amounts of byproducts.

**Table 1. Optimization of Direct $S_NAr$ Reaction Conditions**




| entry[a] | base (equiv) | pentafluorobenzene (equiv) | time (min) | yields[b] (conversion)[b] (%) |
|---|---|---|---|---|
| a | $Na_2CO_3$ (1) | 1 | 60 | 6 (6) |
| b | $Na_2CO_3$ (2) | 1 | 60 | 7 (7) |
| c | NaOH (1.1) | 1 | 60 | 74 (78) |
| d | NaOtBu (1.1) | 1 | 60 | 88 (99) |
| e | NaOtBu (1.1) | 1.5 | 60 | 91 (99) |
| f | NaOtBu (1.1) | 5 | 60 | 99 (100) |
| g | NaOtBu (2) | 1 | 60 | 41 (94) |
| h | NaOtBu (1.1) | 1 | 15 | 64 (64) |
| i | NaOtBu (1.1) | 1.5 | 15 | 77 (80) |
| j | NaOtBu (1.1) | 5 | 15 | 99 (99) |

[a]Conditions for reactions in the table: benzimidazole (0.1 mmol), base (see table), pentafluorobenzene (see table), DMF (1 mL), −10 to 0 °C. [b]Evaluated by HPLC (see the Supporting Information).

Further optimization of the reaction conditions (Table 1) showed that reducing the temperature and using an excess of pentafluorobenzene almost eliminated byproduct formation. In the case of sodium carbonate as base (Table 1, entry b), even an excess did not enhance the slow conversion rates. Independent of our work, others have recently published

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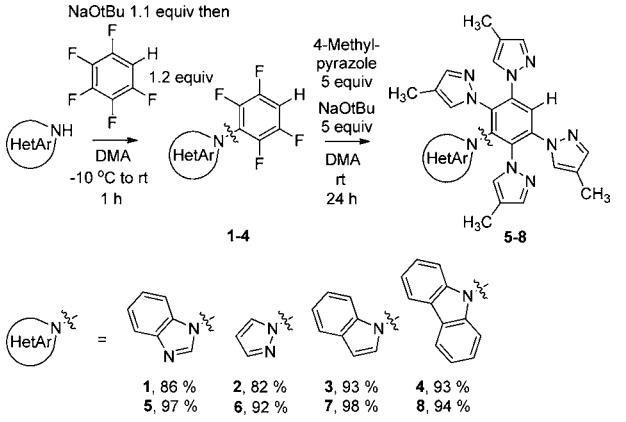
findings that sodium hydroxide is the optimal base for this reaction when large excesses of pentafluorobenzene and base are applied under elevated temperatures.[5b] Our experiments revealed that a large excess of sodium *tert*-butoxide led to major amounts of byproducts (Table 1, entry g). However, when only 1 equiv of pentafluorobenzene and minor exesss of base were used, the use of sodium *tert*-butoxide led to a faster conversion rate than sodium hydroxide (Table 1, entry c) with only minor byproduct formation. Hence, sodium *tert*-butoxide was applied for the final optimizations (Table 1, entries d–j). Under the optimized conditions, the *N*-arylated benzimidazole (**1**) (1-(2,3,5,6-tetrafluorophenyl)-1*H*-benzo[*d*]imidazole) was obtained in 99% yield within 15 min (Table 1, entry j).

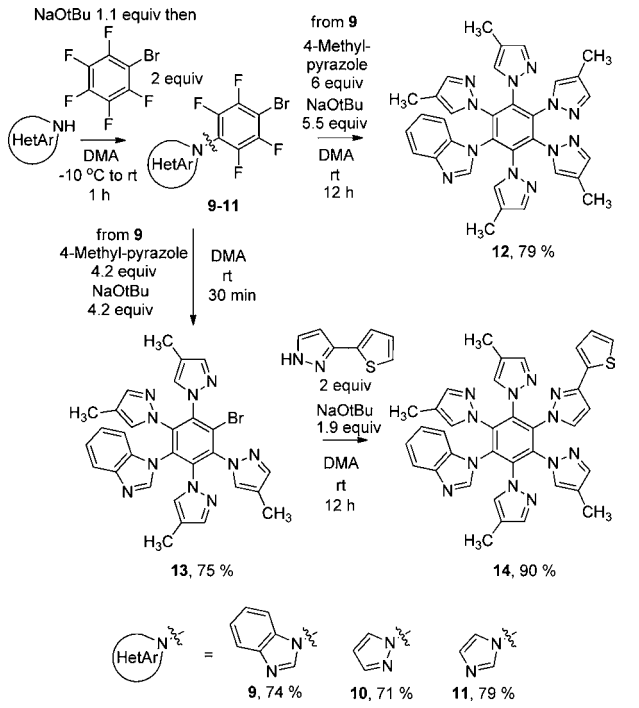
A closer look at the results from all the *N*-arylations revealed that the major byproducts were compounds where additional fluorides had been substituted by the benzimidazole leading to bis- or tris-substituted phenyl derivatives. However, this observation leads to the idea that selective sequential fluorine displacement could be conducted. In order to explore this concept the corresponding tetrafluorophenyl derivatives of pyrazole, benzimidazole, indole, and carbazole were synthesized and isolated in 82–93% yields using only a minor excess of pentafluorobenzene (Scheme 1). Gratifyingly, it was found that addition of excess of a second azole nucleophile within 24 h at room temperature gave the fully substituted products which could be isolated in excellent yields.

**Scheme 1. Sequential $S_NAr$ Reactions of Pentafluorobenzene**




Analogous pentafluorobromobenzene could be applied in the *N*-arylation reaction giving the corresponding 2,3,5,6-tetrafluorobromphenyl containing *N*-aryl products in 71–79% yields (Scheme 2). The pentafluorobromobenzene derived products **9**–**11** were, however, more prone to undergo additional substitutions when 2 equiv of pentafluorobromobenzene were applied in these reactions. It was also noticed that small amounts of the debrominated product (**1**) as well as the 1-bromo-2,3,4,5-tetrafluorophenyl derivative were formed. This regioselectivity of para versus ortho substitution is also observed for reaction with benzotriazole[6] and imidazole.[5a] Despite the numbers of *N*-arylated azole derivatives already reported, compounds **9** and **10** were not previously reported. The monoazole-substituted products (**9**–**11**) smoothly underwent full substitution under the same conditions as above, exemplified by elaborating on the benzimidazole derivative **9**. Surprisingly also the bromo substituent was fully displaced after overnight reaction leading to compound **12**. However, reducing equivalents of nucleophile and base to almost stoichiometric

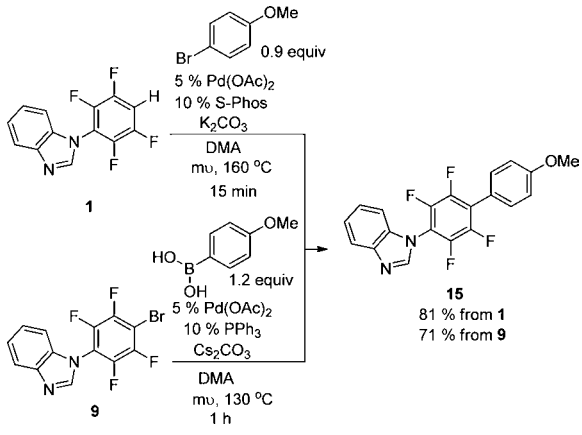
**Scheme 2. Sequential $S_NAr$ Reactions of Pentafluorobromobenzene**




amounts and shortening of the reaction time to 30 min gave the pentasubstituted bromobenzene derivative **13** in 75% yields. Further reaction of **13** lead to the fully substituted **14**, which to our knowledge is the first example of benzene with three different C–N-bonded azole substituents.

Alternative funtionalization of **1** through C–H activation was also explored utilizing cross-coupling reactions (Scheme 3). Cross couplings of fluorobenzene derivatives and aryl halides through C–H activation have been reported both by palladium and copper catalysis.[7] However, the reported reaction conditions include reactions times of 12–24 h and a significant excess of fluorobenzene derivative. Optimization of the reaction conditions for compound **1** using a sealed vessel reaction and microwave heating reduced the reaction time to 15 min. Even reducing the amount of **1** to only 1.1 equiv still gave rise to **15** in 81% yields. The *p*-bromo products **9** also facilely underwent microwave-facilitated cross-coupling under Suzuki conditions.[8]

**Scheme 3. Cross Couplings of $S_NAr$ Products**



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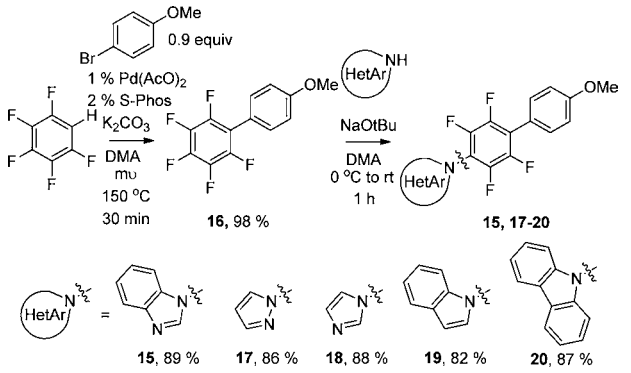
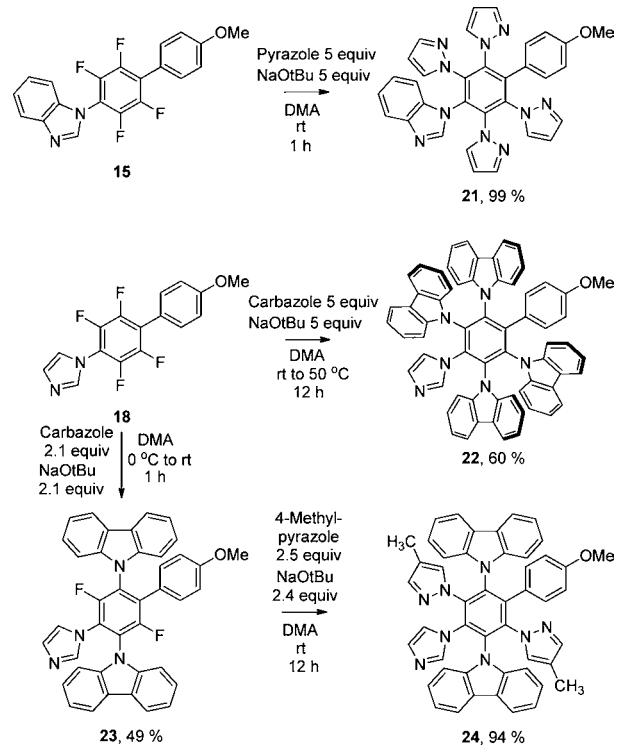
To further expand the scope, the reversed order of the *N*-arylation and the C−C cross coupling reaction was explored. Pentafluorobenzene smoothly underwent cross-coupling with a bromobenzene derivative under the same conditions as above. Reacting the formed 4′-methoxy-2,3,4,5,6-pentafluorobiphenyl (**16**) with a range of azole or pyrole derivatives worked well and gave rise to the para-substituted derivatives (**15** and **17**−**20**) in 82−89% yields (Scheme 4). The starting temperatures for these reactions were raised to 0 °C as compound **16** had reduced solubility in DMA below this temperature.

**Scheme 4. $S_NAr$ Reactions of Biphenyl Derivatives**




The generated tetrafluorobiphenyl derivatives smoothly underwent full substitution here exemplified by per-substitution of compound **15** and **18** with carbazole or pyrazole (Scheme 5). We did not find any limitations in the combination of azole or indole derivatives within these reactions and as seen for **22** even very sterically congested compounds could be obtained by this method. However, many of the more lipophilic products were poorly soluble, which may account for the reduced isolated yields of **22** even though full conversion of **18** was observed. Similar observations have been reported for per-substitution of hexafluorobenzene.[2] The steps of the additional substitutions were found to be governed by a complex combination of steric hindrance, nucleophilicity of the azole, and the fluorination pattern. Pursuing partial substitutions was, however, possible for the reaction of **18** with 2 equiv of carbazole. The reaction was fully regioselective as only the 2,5-regioisomer (**23**) was obtained. This observation is consistent with previous reports which have determined that the C−F bond in fluorobenzene is activated by additional fluoro substituents in the ortho- and meta-positions, whereas fluorine in the para-position adds little if any to the reactivity.[9] A similar substitution pattern is also observed for tetrasubstitution of hexafluorobenzene with pyrazole.[2f]

**Scheme 5. Sequential $S_NAr$ Reactions of Azole−Tetrafluorobiphenyl Derivatives**




The easy access to the difluorinated **23** paved the way for exploration of additional substitution with 2 equiv of a third nucleophile. Such reaction worked smoothly and is exemplified here by reaction with 4-methylpyrazole where the expected product **24** could be obtained in 94% yields.[10] By these means a nonsymmetrical fully substituted benzene derivative with four different substituents could be obtained with full control of regioselectivity.

These results demonstrate that pentafluorobenzene derivatives undergo direct $S_NAr$ substitution of fluorine with azole/indole dervatives without major deactivation of the remaining fluoro substituents. This enables sequential regioselective subsitution of fluorine atoms with up to three different azole and/or indole dervatives. Combined with C−C cross couplings, these catalyst-free *N*-arylation reactions lead to new multi-substituted aryl derivatives with potential use within molecular optoelectronics, material science, and biological applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, HPLC chromatograms, NMR spectra and data, and other characterization data of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: fdi@sund.ku.dk.

### Present Address

†Center for Evolutionary Chemical Biology, Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark.

### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Baldo, M. A.; Thompson, M. E.; Forrest, S. R. *Nature* **2000**, *403*, 750. (b) Chou, P.-T.; Chi, Y. *Chem.—Eur. J.* **2007**, *13*, 380. (c) Tao, Y.; Yang, C.; Qin. *J. Chem. Soc. Rev.* **2011**, *40*, 2943. (d) Xiao, L.; Chen, Z.; Qu, B.; Luo, J.; Kong, S.; Gong, Q.; Kido, J. *Adv. Mater.*

**2011**, *23*, 926. (e) Costa, R. D.; Orti, E.; Bolink, H. J.; Monti, F.; Accorsi, G.; Armaroli, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 8178. (f) Wang, C.; Dong, H.; Hu, W.; Liu, Y.; Zhu, D. *Chem. Rev.* **2012**, *112*, 2208. (g) Uoyama, H.; Goushi1, K.; Shizu, K.; Nomura, H.; Adachi, C. *Nature* **2012**, *492*, 234−238.

(2) (a) Foces-Foces, C.; Llamas-Saiz, A. L.; Claramunt, R. M.; Jagerovic, N.; Jimeno, M. L.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1359. (b) Biemans, H. A. M.; Zhang, C.; Smith, P.; Kooijman, H.; Smeets, W. J. J.; Spek, A. L.; Meijer, E. W. *J. Org. Chem.* **1996**, *61*, 9012. (c) Piet, J. J.; Biemans, H. A. M.; Warman, J. M.; Meijer, E. W. *Chem. Phys. Lett.* **1998**, *289*, 13. (d) Santa María, M. D.; Cornago, P.; Claramunt, R. M.; Elguero, J.; Fernández-Castaño, C.; Foces-Foces, C. *J. Mol. Struct.* **1999**, *478*, 285. (e) Jouaiti, A.; Loï, M.; Hosseini, M. W.; De Cian, A. *Chem. Commun.* **2000**, 2085. (f) Iaashchuk, I.; Sorokin, V. I. *Tetrahedron* **2009**, *65*, 4652. (g) Rit, A.; Pape, T.; Hahn, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 4572. (h) Takase, M.; Yoshida, N.; Nishinaga, T.; Iyoda, M. *Org. Lett.* **2011**, *13*, 3896. (i) Samanta, D.; Shanmugaraju, S.; Joshi, S. A.; Nethaji, M.; Mukherjee, P. S. *Chem. Commun.* **2012**, *48*, 2298. (j) Takase, M.; Narita, T.; Fujita, W.; Asano, M. S.; Nishinaga, T.; Benten, H.; Yoza, K.; Müllen, K. *J. Am. Chem. Soc.* **2013**, *135*, 8031.

(3) For a general review on C−F bond activation, see: Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119.

(4) Diness, F.; Fairlie, D. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 8012.

(5) For related work, see: (a) Fujii, S.; Maki, Y.; Kimoto, H. *J. Fluorine Chem.* **1989**, *43*, 131−144. (b) Liu, C.; Wang, H.; Xing, X.; Xu, Y.; Ma, J.-A.; Zhang, B. *Tetrahedron Lett.* **2013**, *54*, 4649−4652.

(6) Zhao, J.; Song, T.; Zhu, S.; Xu, L. *Tetrahedron* **2011**, *67*, 910.

(7) (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754−8756. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097−5100. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128.

(8) For a review, see: *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer: Berlin, 2006.

(9) (a) Bolton, R.; Sandall, J. P. B. *J. Fluorine Chem.* **1982**, *21*, 459. (b) Chambers, R. D.; Martin, P. A.; Sandford, G.; Williams, D. L. H. *J. Fluorine Chem.* **2008**, *129*, 998.

(10) The structure of **24** was confirmed by extensive studies using 1D and 2D NMR spectroscopy (see the Supporting Information).