Aromatic Fluorination

DOI: 10.1002/anie.201001507

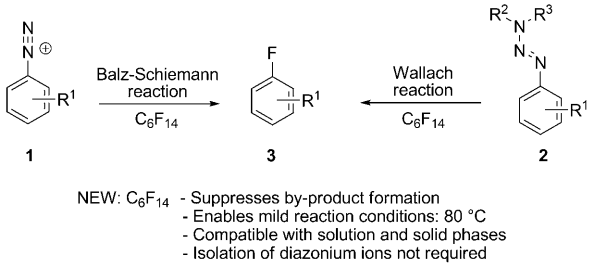
Synthesis of Aryl Fluorides on a Solid Support and in Solution by Utilizing a Fluorinated Solvent**

Marion Döbele, Sylvia Vanderheiden, Nicole Jung, and Stefan Bräse**

The conversion of diazonium tetrafluoroborate salts[1–3] into fluorinated arenes[4] was discovered more than 80 years ago by Balz and Schiemann,[5] and is widely used owing to the importance of fluorinated compounds in the life sciences[6] and material science[7] in academic as well as industrial laboratories.[8,9] This method has also found application for the synthesis of radioactive-labeled compounds.[10]

The yields of the Balz–Schiemann reaction are moderate to good, and a few isolated protocols achieve excellent yields.[11] Therefore many attempts have been made to increase the yields and to lower the reaction temperatures, which in general correspond to the melting points of the tetrafluoroborates, in most cases over 100 °C. Some alternatives rely on, for example, the exchange of the counter ion[12] or the use of other solvents like $BF_3{\cdot}Et_2O$[13] and ionic liquids.[14] Modified conditions, for example photochemical methods,[15,16] have also resulted in improved protocols.

Herein we describe a variant of the Balz–Schiemann reaction which through the utilization of a perfluorinated solvent leads to very good conversions of diazonium salts and triazenes to provide the corresponding aryl fluorides under mild conditions (Scheme 1). In our search for a method that allows the application of the Balz–Schiemann reaction in combinatorial chemistry, we tested different sets of conditions. Our leitmotiv was the cleavage of triazenes to give diazonium ions followed by their conversion in situ into the corresponding fluoroarenes. This approach, known as Wallach reaction,[17] offers some advantages over conventional methods. First, triazenes can be stored for extended periods without decomposition and they constitute safe alternatives to explosive diazonium salts. For example, our DSC/TG and DTA/TG measurements (DSC = dynamic difference calorimetry, DTA = differential thermoanalysis, TG = thermogravimetry) on triazene **9** (see Scheme 4) gave a decomposition temperature of 202.2 °C (beginning at 136 °C up to 266 °C, with a loss of mass of 98 %), while no reaction with O_2 or H_2O takes place. The enthalpy of decomposition for **9** is determined to be roughly 40 kJ g^{-1}. In addition, triazene-masked diazonium ions can be used in reaction sequences in solution as well as on a solid support, and are thus amenable to combinatorial methods.[18] All products of the fluorinating cleavage should first be analyzed in terms of purity, as the isolation of preferably pure crude products plays a pivotal role in combinatorial chemistry.



Scheme 1. Aryl fluorides **3** resulting from diazonium ion **1** and from triazene-masked diazonium ions **2**.

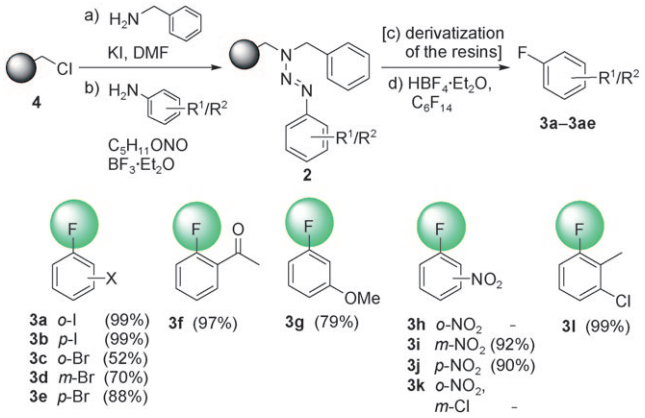
Initial tests were conducted with resin-bound triazenes. We used different solvents (for example, THF, DMF, MeOH) and observed the generation of "traceless" by-products (the reduced cleavage compound). As these compounds account for most of the impurities in the thermal decomposition of diazonium salts as well, we tried to suppress the reduction through the use of a perfluorinated solvent. In perfluorohexane[19] under optimized conditions, cleavage of the aromatic compounds to give the diazonium tetrafluoroborate salts and in situ fluorination led to the crude products in very good purities. A comparative analysis of the yields we obtained with our substrates with recent results of similar fluorinating methods is given in the Supporting Information.[13,20]

Scheme 2 summarizes some attempts of the cleavage of resin-bound aromatic compounds. The fluorinations were performed with a reaction time of 1 hour in perfluorohexane at 100 °C. In the first step, aniline derivatives were converted into diazonium salts through diazotization and then immobilized as triazenes on *N*-benzylaminomethyl-functionalized polystyrene resin. For the direct evaluation of the fluorinating cleavage method the immobilized diazonium compounds **2** were directly cleaved from the solid support without further derivatization. The achieved purities are very good after the reaction was performed once on the resin. Only *ortho*-nitro- and *ortho*-fluoro-substituted substrates did not deliver the fluorinated compounds **3**. Here either the reduced compound or the phenol derivatives were formed. For all other derivatives (also valid for the compounds in Scheme 3) the side reaction yielding the reduced compound could be suppressed. Thus, our fluorination reaction in a perfluori-

[*] M. Döbele, S. Vanderheiden, Dr. N. Jung, Prof. Dr. S. Bräse
Institute of Organic Chemistry, KIT-Campus Süd
Fritz-Haber-Weg 6, 76131 Karlsruhe (Germany)
Fax: (+49) 721-608-8581
E-mail: braese@kit.edu
S. Vanderheiden, Dr. N. Jung, Prof. Dr. S. Bräse
IOC-ComPlat, KIT-Campus Nord
Hermann von Helmholtz Platz 1
76344 Eggenstein-Leopoldshafen (Germany)

[**] We thank Bekir Bulat for synthetic work and Dr. Wolfgang Ebenbeck (Saltigo) for helpful discussions.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001507.



Scheme 2. Syntheses of aryl fluorines via resin-bound arenes (GC/MS purities of the products in brackets). c) For R^1 = I: 1. $ArB(OH)_2$, $[Pd(PPh_3)_4]$, Na_2CO_3, DMF, H_2O, 120 °C, 12 h (1–3 repetitions); 2. alkene, $[Pd(PPh_3)_4]$, NEt_3, DMF, 120 °C, 12 h (1–3 repetitions); 3. alkyne, Cu^ICl, $[Pd(PPh_3)_4]$, NEt_3, DMF, 80 °C, 48 h; for $R^1 = COCH_3$: diethyl cyanomethylphosphonate, KO*t*Bu, DMF, 80 °C, 12 h.

nated solvent becomes the preferred method for the automated synthesis of compound libraries.

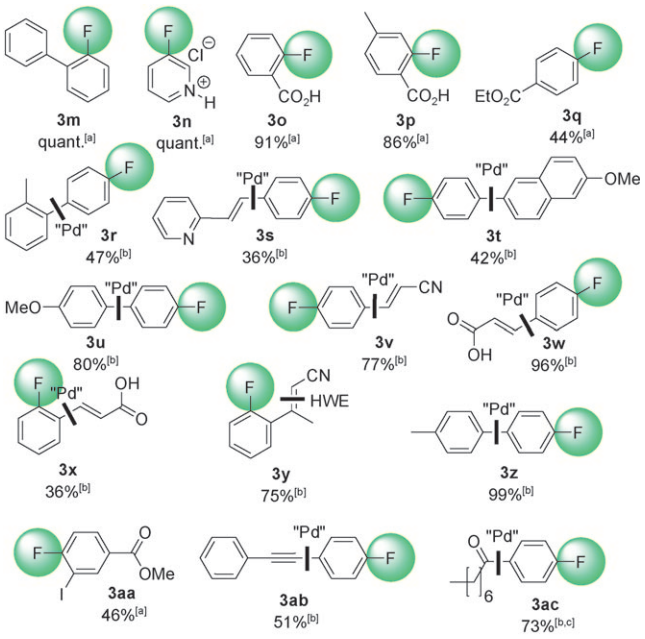
The use of a perfluorinated solvent considerably simplifies the Balz–Schiemann reaction: various compounds can be generated reliably in good purity, and the formation of the reduced by-products is suppressed. This method tolerates traces of water, and it is possible to recycle the solvent since it can be separated readily from the resin and the supernatant.

For the isolation of a small library of fluorinated substances we immobilized less-volatile aniline derivatives and, additionally, resin-bound anilines were further derivatized on a solid support. We chose the Horner–Wadsworth–Emmons, Heck, Suzuki, and Sonogashira reactions to synthesize biaryls, cinnamic acid esters, and other arenes. In the final step the products were cleaved from the support under optimized reaction conditions (80 °C, 12 h). In this way we could synthesize 17 different fluoroarenes, including heteroarenes such as 3-fluoropyridine hydrochloride (**3n**) and (*E*)-2-(4-fluorostyryl)pyridine (**3s**).

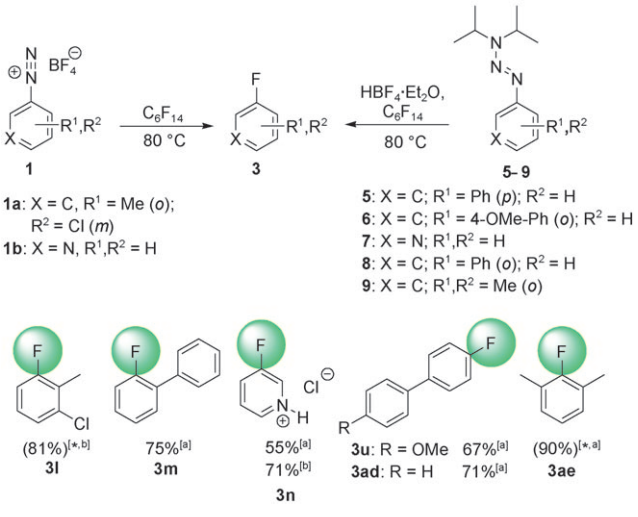
The yields were good to excellent for compounds cleaved directly from the support without further derivitization, but the yields were lower for fluorine compounds that had required an additional cross-coupling reaction. In subsequent experiments the coupling reaction was performed three times to guarantee complete conversion of the aryl iodides. The results after cleavage of the target molecules show that the previous moderate yields could be improved (for example **3v**: one reaction = 34 % yield, three reactions: 77 % yield). Furthermore, using the example of **3m** we could prove that our approach is also appropriate for reactions on a larger scale. Reaction of 2.00 g of resin gave the target compound in 81 % yield.

Fluorinating cleavage was also investigated in the liquid phase. Because of the low solubility of the starting materials, the diazonium salts **1** and the diisopropyl triazenes **5**–**9** were suspended in perfluorohexane and subsequently reacted for 12 hours at 80 °C following the optimized protocol for the solid-phase reaction. The examples in Scheme 4 show good results also for solution-phase reactions, and upscaling was successful as well (**3ad**: 69 %).[*] With regard to the planned application of fluorinating cleavages to automated, solid-phase synthesis this is the method of choice as no separation from the residual diisopropyl amine is required.

The good results in perfluorohexane can be explained by two effects. First, any side reaction of the solvent with reactive intermediates is prevented; neither the reduced by-products nor the chlorinated compounds that would arise in the presence of CH_2Cl_2,[9] for example, form. A second effect is



Scheme 3. Aryl fluorides isolated after cleavage from immobilized triazenes **2**. [a] Yield over one step. [b] Yield over two steps. [c] Formation of the ketone in acidic aqueous media.[21]



Scheme 4. Aromatic fluorination in solution phase. *GC/MS purity of the crude product. [a] Cleavage of **5**–**9**; [b] Cleavage of **1a**: 3-chloro-2-methylbenzene diazonium salt, **1b**: pyridinium-3-diazonium salt.

[*] When the reaction was performed on a 0.7 mmol scale, the yield was 69 %; on a 1.8 mmol scale compound **3ad** was obtained in 47 % yield; in each case the reaction time was 1 hour. Further upscaling might require longer reaction times.

proposed to result from the reaction of aryl radicals with perfluorohexane: The thermal decomposition of diazonium ions is currently thought to proceed by ionic as well as radical pathways.[22,23] The ionic path is evoked to explain the Balz–Schiemann reaction products,[24] while the radical path leads to a diversity of side products.[25] Under standard conditions aryl radicals might react with impurities or water; analogously, the reaction of radicals with fluoroalkanes in fluorinated media gives the desired fluorinated product.

Using a perfluorinated solvent we could apply a new variant of the Balz–Schiemann reaction to generate a small library of fluorinated substances. Either triazenes that were resin-bound or in solution could be converted under very mild conditions, giving the corresponding aryl fluorides in good to very good yields. This easy and cost-effective procedure provides fluorinated arene products, compounds that have been particularly difficult to access in the past, in high purities.

Experimental Section

Synthesis of **3u**:

Standard procedure for solid-phase synthesis according to Scheme 1: The triazene resin **2u** (150 mg, 0.678 mmol g^{-1}, 0.102 mmol) was suspended at room temperature in 4.00 mL perfluorohexane and tetrafluoroboric acid diethyl ether complex (100 mg, 620 μmol) was added. The vial was sealed with a pressure-resistant crimp top and the suspension was shaken at 80 °C for 12 h. After the reaction mixture had cooled down, acetone was added and the mixture was shaken again. The acetone layer was isolated and concentrated in vacuo. and the aryl fluoride was purified by column chromatography (cyclohexane(CH)/ethyl acetate (EA) 99:1–20:1). The target compound **3u** was obtained in 80 % (16.4 mg, 0.081 mmol) yield.

Standard procedure for the solution-phase synthesis according to Scheme 4: Triazene **6** (19.0 mg, 6.10 μmol) was suspended in 4.00 mL perfluorohexane at room temperature and tetrafluoroboric acid diethyl ether complex (200 mg, 1.24 mmol) was added. The vial was sealed with a pressure-resistant crimp top, and the suspension was shaken at 80 °C for 12 h. After the reaction mixture had cooled down, acetone was added and the mixture was shaken again. The acetone layer was isolated and concentrated in vacuo, and the residue was purified by column chromatography (CH/EA 99:1–20:1). The target compound **3u** was obtained in 67 % (8.40 mg, 4.31 μmol) yield.

Synthesis of **3l**:

Standard procedure for the solution-phase synthesis according to Scheme 4: Diazonium salt **1a** (68.0 mg, 283 μmol) was suspended in 2.00 mL perfluorohexane at room temperature and tetrafluoroboric acid diethyl ether complex (100 mg, 620 μmol) was added. The vial was sealed with a pressure-resistant crimp top, and the suspension was shaken at 80 °C for 12 h. After the reaction mixture had cooled down, acetone was added and the mixture was shaken again. The acetone layer was isolated and the purity (81 %) of the target compound **3l** was determined by GC/MS analysis.

Received: March 12, 2010
Revised: April 17, 2010
Published online: July 14, 2010

Keywords: Balz–Schiemann reaction · combinatorial chemistry · perfluorinated solvents · solid-phase synthesis · triazenes

[1] C.-K. Chu, J.-H. Kim, D. W. Kim, K.-H. Chung, J. A. Katzenellenbogen, D. Y. Chi, *Bull. Korean Chem. Soc.* **2005**, *26*, 599 – 602.
[2] R. L. Ferm, C. A. VanderWerf, *J. Am. Chem. Soc.* **1950**, *72*, 4809 – 4810.
[3] P. O'Leary, *Sci. Synth.* **2007**, *31b*, 1361 – 1400.
[4] For alternative sources: a) T. Furuya, T. Ritter, *Org. Lett.* **2009**, *11*, 2860 – 2863; b) T. Furuya, A. E. Strom, T. Ritter, *J. Am. Chem. Soc.* **2009**, *131*, 1662 – 1663.
[5] G. Balz, G. Schiemann, *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1186 – 1190.
[6] Fluorine in life sciences: a) K. Müller, *ChemBioChem* **2004**, *5*, 557 – 726; b) *Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals* (Eds.: A. Tressaud, G. Haufe), Elsevier Science, Amsterdam, **2008**.
[7] a) D. Pauluth, T. Geelhaar, *Nachr. Chem. Tech. Lab.* **1997**, *45*, 9 – 15; b) W. H. de Jeu, *Physical Properties of Liquid Crystalline Materials*, Gordon & Breach, New York, **1980**.
[8] For a recent summary see: a) Balz–Schiemann reaction: G. W. Gribble in *Name Reactions for Functional Group Transformations* (Eds.: J. J. Li, E. J. Corey), Wiley, Hoboken, NJ, **2007**, 552 – 563; b) electrophilic NF fluorinating reagents: G. S. Lal, G. P. Pez, R. G. Syvret, *Chem. Rev.* **1996**, *96*, 1737 – 1756.
[9] Mechanism: C. G. Swain, R. J. Rogers, *J. Am. Chem. Soc.* **1975**, *97*, 799 – 800.
[10] M. Argentini, C. Wiese, R. Weinreich, *J. Fluorine Chem.* **1994**, *68*, 141 – 144; A. Knoechel, O. Zwernemann, *Appl. Radiat. Isot.* **1991**, *11*, 1077 – 1180.
[11] a) A. Hubbard, T. Okazaki, K. K. Laali, *J. Org. Chem.* **2008**, *73*, 316 – 319; b) M. S. Newman, K. C. Lilje, *J. Org. Chem.* **1979**, *44*, 1347 – 1348; c) A. Eirin, F. Fernandez, C. Gonzalez, C. Lopez, *Org. Prep. Proced. Int.* **1992**, *24*, 509 – 516.
[12] C. Sellers, H. Suschitzky, *J. Chem. Soc. C* **1968**, 2317 – 2319.
[13] K. Shinhama, S. Aki, T. Furuta, J.-i. Minamikawa, *Synth. Commun.* **1993**, *23*, 1577 – 1582.
[14] K. Laali, V. J. Gettwert, *J. Fluorine Chem.* **2001**, *107*, 31 – 34.
[15] a) J. Heredia-Moya, K. L. Kirk, *J. Fluorine Chem.* **2007**, *128*, 674 – 678; b) M. Sawaguchi, T. Fukuhara, N. Yoneda, *J. Fluorine Chem.* **1999**, *97*, 127 – 133.
[16] For an overview of fluorination with different fluorination agents: *Houben-Weyl*, *Vol. E10a*, Thieme, Stuttgart, **1999**, pp. 686 – 740.
[17] a) O. Wallach, F. Heusler, *Justus Liebigs Ann. Chem.* **1888**, *243*, 219. More updated variants of the Wallach reaction: b) M. N. Rosenfeld, D. A. Widdowson, *J. Chem. Soc. Chem. Commun.* **1979**, 914 – 916; c) N. Satyamurthy, J. R. Barrio, D. G. Schmidt, C. Kammerer, G. T. Bida, M. E. Phelps, *J. Org. Chem.* **1990**, *55*, 4560 – 4564; d) J. R. Barrio, N. Satyamurthy, H. Ku, M. E. Phelps, *J. Chem. Soc. Chem. Commun.* **1983**, 443 – 444; e) T. Pages, B. R. Langlois, D. Le Bars, P. Landais, *J. Fluorine Chem.* **2001**, *107*, 329 – 335.
[18] S. Bräse, D. Enders, J. Köbberling, F. Avemaria, *Angew. Chem.* **1998**, *110*, 3614 – 3616; *Angew. Chem. Int. Ed.* **1998**, *37*, 3413 – 3415.
[19] Fluorinert72 (CAS 355-42-0) was purchased from ABCR.
[20] P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem.* **2010**, *122*, 2265 – 2268; *Angew. Chem. Int. Ed.* **2010**, *49*, 2219 – 2222.
[21] a) B. Meseguer, D. Alonso-Dìaz, N. Griebenow, T. Herget, H. Waldmann, *Angew. Chem.* **1999**, *111*, 3083 – 3087; *Angew. Chem. Int. Ed.* **1999**, *38*, 2902 – 2906; b) F. Persico, B. D. Wuest, *J. Org. Chem.* **1993**, *58*, 95 – 99.
[22] C. Galli, *Chem. Rev.* **1988**, *88*, 765 – 792.
[23] a) I. Szele, H. Zollinger, *J. Am. Chem. Soc.* **1978**, *100*, 2811 – 2815; b) Y. Hashida, R. G. M. Landells, G. E. Lewis, I. Szele, H. Zollinger, *J. Am. Chem. Soc.* **1978**, *100*, 2816 – 2823; c) K. Laali, I. Szele, H. Zollinger, *Helv. Chim. Acta* **1983**, *66*, 1737 – 1747.
[24] H. Zollinger, *Angew. Chem.* **1978**, *90*, 151 – 160; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 141 – 150.
[25] a) H. Zollinger, *Diazo Chemistry I*, VCH, Weinheim, **1994**, pp. 188 – 212; b) H. Zollinger, *Diazo Chemistry I*, VCH, Weinheim, **1994**, pp. 228 – 230.

