High-Speed, Highly Fluorous Organic Reactions

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The rapidly growing field of combinatorial chemistry has precipitated the development of new techniques aimed at improving the efficiency of performing chemical reactions and separations in both the solid- and liquid-phase.[1] Solid-phase chemistry has a great advantage at the separation stage because the product is easily separated by filtration. But the same heterogeneity that is useful in separation can sometimes be a liability in the reaction stage.

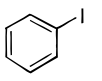
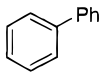
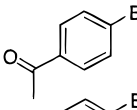
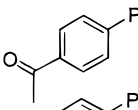
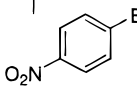
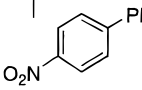
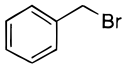
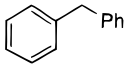
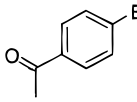
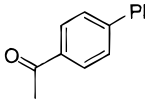
Recently introduced fluorous synthesis techniques[2] capitalize on the immiscibility of fluorous (highly fluorinated) phases with organic solvents and water at room temperature. Fluorous molecules or molecules equipped with fluorous tags will seek the fluorous phase in a separation stage but can under heating in a reaction stage often be dissolved in organic solvents and combined with organic reactants. Thus, fluorous techniques are a means of integrating synthetic and purification strategy in combinatorial chemistry.[2a−c] Fluorous and solid-phase techniques can often speed the separation process to the point where the reaction times limit sample throughput in a combinatorial or parallel synthesis. Convenient methods to promote rapid reactions then become important. The new microwave technique provides such a method. The efficiency of microwave flash-heating chemistry in dramatically accelerating reactions rates has recently been proven in several different fields of synthetic organic chemistry,[3] among them solid-phase, liquid-phase, and fluorous palladium-catalyzed reactions.[4]

Early work in fluorous chemistry employed $CH_2CH_2C_6F_{13}$ tags (shortened F-13),[2,5] which had sufficient fluorine content to drive a number of trialkyltin and phosphine reagents and catalysts into a fluorinated phase in a convenient liquid−liquid extraction. However, the degree of fluorination is critical for achieving a high partitioning of the tagged compounds into the fluorous phase,[6] and the F-13 tag proved to be too small with respect to liquid−liquid extraction for some compounds. The $CH_2CH_2C_{10}F_{21}$ (F-21) tag was introduced to enable an increased partitioning into the fluorous phase, and this was used with success in fluorous Ugi (Flugi) and fluorous Biginelli (Fluginelli) reactions, provided hybrid fluorous/organic solvents were used.[5] However, initial attempts to use the highly fluorous F-21 tin compounds in Stille and radical reactions were largely unsuccessful.[7] Very sluggish reactions and poor yields were encountered in organic solvents with traditional thermal heating techniques.[7]

We now report that flash-heating by microwave irradiation promotes rapid reactions of highly fluorous tin compounds. The usefulness of the microwave technique is exemplified by a series of Stille- and radical-mediated reactions as shown below.

Stille-couplings with organohalides **1a**−**d** and $PhSn(CH_2CH_2C_{10}F_{21})_3$ (**2a**) under standard conditions (DMF, $Pd(PPh_3)_2Cl_2$, LiCl) were all finished within 6 min of single-mode microwave irradiation at 50 W (Table 1). In a typical run with iodobenzene **1a** and **2a** (entry 1),

Table 1. Microwave Promoted Stille-Couplings with F-21 Compound 2a[a]

Entry	Organo halide	Time (min)/ Effect (W)[b]	Product	Isolated yield (%)[c]
1.	 **1a**	6/50	 **3a**	78
2.	 **1b**	6/50	 **3b**	71
3.	 **1c**	6/50	 **3c**	69
4.	 **1d**	6/50	 **3d**	46
5.	 **1b**[d]	6/50	 **3b**	75

[a] For experimental details, see Experimental Section. [b] Continuous irradiation at 2450 MHz. [c] >95% by GC/MS. [d] $Pd(OAc)_2$ and $P(m\text{-}PhSO_3Na)_3$ instead of $Pd(PPh_3)_2Cl_2$ as precatalyst.

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(1) (a) Felder, E. R.; Poppinger, D. In *Approaches in Advanced Drug Research*; Testa, B., Meyer, U. A., Eds.; Academic Press: San Diego, 1997; Vol. 30, pp 111−199. (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489−509. (c) Borman, S. *Chem. Eng. News* **1998**, *76*, (14), 47−67.

(2) (a) Studer, A.; Hadida, S.; Ferrito, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823−826. (b) Studer, A.; Curran, D. P. *Tetrahedron* **1997**, *53*, 6681−6696. (c) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1175−1196. (d) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641−650.

(3) (a) Majetich, G.; Wheless, K. In *Microwave-Enhanced Chemistry*; Kingston, H. M.; Haswell, S. J., Eds; American Chemical Society: Washington, DC, 1997; pp 455−505. (b) For the first example of a microwave-heated tin hydride mediated radical reaction, see: Bose, A. K.; Manhas, M. S.; Ghosh, M.; Shah, M.; Raju, V. S.; Bari, S. S.; Newaz, S. N.; Banik, B. K.; Chaudhary, A. G.; Barakat, K. J. *J. Org. Chem.* **1991**, *56*, 6968−6970.

(4) (a) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219−8222. (b) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584. (c) Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 5583−5587. (d) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076−5079. (e) Villemin, D. Presented at the International Conference on Microwave Chemistry, Prague, September 1998; paper PL 5.

(5) Studer, A.; Jeger, P.; Wipf, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 2917−2924.

(6) The concentration of fluorous tin compounds enables a very convenient collection of the toxic tin compounds from the reaction mixture. Other methods for removing tin substrates: Crich, D.; Sun S. *J. Org. Chem.* **1996**, *61*, 7200−7201.

(7) Attempts to reduce adamantyl bromide with the F-21 tin hydride under standard stoichiometric conditions for F-13 reagents were irreproducible. In most cases, the starting materials were recovered, but in one experiment small amounts of adamantane were formed. Stille-couplings with the F-21 phenyl tin reagent gave biphenyl in much slower rates and lower yields than the F-13 reagents. Hadida, S. and Kim, S.-Y. Unpublished results, University of Pittsburgh.

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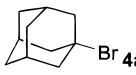
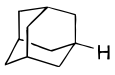
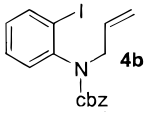
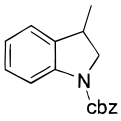
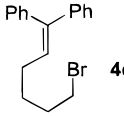
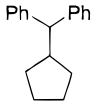
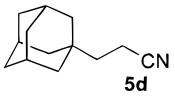
Table 2. Microwave Promoted Radical Reactions with F-21 Compound 2b[a]

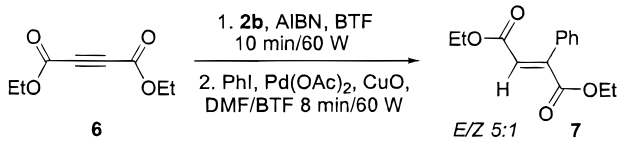
Entry	Organo halide	Reagents	Time (min)/ Effect (W)[b]	Product	Isolated yield (%)[c]
1.	 **4a**	**2b**	5/35	 **5a**	81
2.	 **4b**	**2b**	5/35	 **5b**	93
3.	 **4c**	**2b**	5/50	 **5c**	78
4.	**4a**	0.1 equiv **2b**[d] + 	10/60	 **5d**	64/77[e]

[a] For experimental details, see Experimental Section. [b] Continuous irradiation at 2450 MHz. [c] >95% by GC/MS. [d] $NaBH_3CN$ added to recycle the tin hydride. [e] 64% isolated yield by extraction, 77% isolated yield by filtration.

biphenyl **3a** was isolated in 78% yield after standard three-phase liquid extraction (water, CH_2Cl_2, FC-84) and chromatography. The yields of the related products in entries 2 and 3 were somewhat lower due to the formation of biphenyl as a side product, arising from phenyl migration from triphenylphosphine[4c,8] in the oxidative addition complex and homocoupling between two molecules of **2a**. Entry 4 showed an additional formation of benzylic side products (diphenylmethane and bibenzyl). Careful chromatography is thus necessary when nonpolar Stille-coupled products are formed. This purification problem was eased by the employment of $Pd(OAc)_2$ and a sulfonated ligand ($P(m\text{-}PhSO_3Na)_3$, entry 5)[9] that afford a water-soluble byproduct of aryl migration and a water-soluble palladium catalyst. A slightly higher yield was encountered with the sulfonated catalytic system (entry 5) compared to the corresponding reaction with $Pd(PPh_3)_2Cl_2$ (entry 2).

The radical-mediated reduction of **4a** and cyclization of **4b**,**c** with $HSn(CH_2CH_2C_{10}F_{21})_3$ (**2b**) in benzotrifluoride (BTF) yielded products **5a**−**c** in high yields after 5 min of microwave heating (Table 2). The tin hydride **2b** can also be used in catalytic amounts,[10] as shown in the addition reaction of **4a** with acrylonitrile (entry 4). In this case, a higher yield was found after workup by filtration through standard silica gel as compared to three-phase separation (77% vs 64%). This workup, perhaps the most convenient fluorous/organic separation reported to date, presumably succeeds because the fluorous tin compounds are insoluble in the organic eluting solvent and simply adhere to the top of the column. One-pot, microwave-assisted fluorous hydrostannylation of diethyl acetylenecarboxylate **6**, followed by Stille-coupling of the resulting fluorous vinyl stannane with phenyl iodide, delivered **7** in an overall isolated yield of 44% (*E*/*Z* 5:1) (Scheme 1). This is the first example of a vinylic stannane in a Stille-coupling performed under microwave irradiation.

Scheme 1



With these highly fluorous F-21 tin reagents, microwave irradiation is more than an expedient to reduce reaction times; reactions conducted under traditional heating either did not work at all or did not work nearly as well.[7] We believe that the advantage with single-mode microwave heating, compared to traditional heating, is due to rapid heating, superheating of the solvent, smaller temperature gradients in the reaction mixture and the absence of wall effects. The organic and fluorous phases that form a biphase system at room-temperature coalesce upon heating, giving a homogeneous solution with a high organic/fluorous interface area,[11] which also could contribute to the success of the microwave-heating experiments. Upon cooling, the biphase system will reemerge.

In conclusion we have demonstrated that microwave heating allows for the use of F-21 tags as an alternative to the F-13 tags in Stille-coupling and radical reactions. The high reaction rate promoted by microwave flash-heating and the subsequent efficient purification procedures should make the high-speed, highly fluorous reaction concept attractive for combinatorial chemistry. The F-21 tin reagents are fluorinated to the degree that they begin to cross the line between "fluorous" and "Teflon-bound" tin reagents. They are highly insoluble in organic solvents and their solubility in hybrid solvents such as BTF is poor. The ability to promote highly fluorous reactions with microwave heating is crucial since it allows for the exploitation of silica gel filtration or the high partition coefficients in the liquid−liquid extraction in the separation stage of a reaction process.

Experimental Section

Microwave heating was carried out with a MicroWell 10 single-mode microwave cavity[12] from Labwell AB, Sweden, producing continuous irradiation at 2450 MHz. All reactions were performed under nitrogen in heavy-walled Pyrex tubes[13] with a perforated stopcock with septa. In the event of overpressurization, this septum would burst. The inner diameter of the Pyrex tubes was approximately 5 mm and the height of the solvent in the tube between 4 and 6 cm. Great care should be taken when performing pressurized reactions using microwave heating.[14] The reactions were performed without stirring. All

(8) (a) Andersson, C.-M.; Hallberg, A., Daves, G. D., Jr. *J. Org. Chem.* **1987**, *52*, 3529−3536. (b) Kelkar, A. A.; Hanaoka, T. a.; Kubota, Y.; Sugi, Y. *J. Mol. Catal.* **1994**, *88*, L113−L116. (c) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Beller, M.; Fischer, H. *J. Organomet. Chem.* **1995**, *491*, C1−C4. (d) Morita, D. K.; Stille J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576−8581. (e) Herrmann, W. A.; Brossmer, C.; Reisinger, C. P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem. Eur. J.* **1997**, 1357−1364. (f) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.

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(10) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303−304.

(11) It has been suggested that microwave heating may assist in the creation of an active interface and promote transport processes between liquid interfaces. Leskovsek, S.; Smidovnik, A.; Koloini, T. *J. Org. Chem.* **1994**, *59*, 7433−7436.

(12) Stone-Elander, S. A.; Elander, N.; Thorell, J. O.; Solås, G.; Svennebrink, J. *J. Labelled Cmpd. Radiopharm.* **1994**, *34*, 949−960.

(13) Pyrex tubes are recommended for microwave-assisted organic synthesis. Baghurst, D. R.; Mingos, D. M. P. *J. Chem. Soc., Dalton Trans. 1* **1992**, 1151−1155.

(14) For safety instructions and precautions see: Kingston, H. M.; Walter, P. J.; Engelhart, W. G.; Parsons, P. J. In *Microwave-Enhanced Chemistry*; Kingston, H. M., Haswell, S. J., Eds.; American Chemical Society: Washington, DC, 1997; pp 697−745.

chemicals, except **2a** and **2b**[15] were commercially available and used without further purification. The silica used in circular chromatography was purchased from Merck (Kieselgel 60 PF_{254}, 1.07749). The silica used for filtration was purchased from Merck (Kieselgel 60, 1.09385). All isolated products have previously been characterized and corresponded satisfactory with MS and NMR literature data.

General Procedure for Stille-Coupling Reactions (Table 1).[16] To a heavy-walled Pyrex tube were added the following. Entries 1−4: **1a**−**d**, 0.10 mmol; **2a**, 0.12 mmol (220.4 mg); $Pd(PPh_3)_2Cl_2$, 0.0020 mmol (1.4 mg); LiCl, 0.3 mmol (12.7 mg); DMF, 1.0 mL. Entry 5: **1b**, 0.10 mmol (19.9 mg); **2a**, 0.12 mmol (220.4 mg); $Pd(OAc)_2$, 0.0020 mmol (0.45 mg); P(*m*-$PhSO_3Na)_3$, 0.0040 mmol (2.3 mg); LiCl, 0.3 mmol (12.7 mg); DMF, 1.0 mL. The reaction mixture was flushed with nitrogen and the screw-cap tightened thoroughly (finger-tight) before mixing with a Whirlimixer. Heating was then applied by means of microwave irradiation. The reaction tube was allowed to cool in the microwave cavity for a couple of minutes before any handling of the reaction mixture took place. The solvent was removed under reduced pressure when the tube had reached rt and the reaction mixture was thereafter purified by three-phase extraction. FC-84 (10 mL) and water (10 mL) were added and extracted three times with 20 mL of dichloromethane. The products were further purified by circular chromatography. Eluting solvents for chromatography: **3a**, isohexane; **3b**, isohexane/ethyl acetate 9:1; **3c**, isohexane/ethyl acetate 19:1; **3d**, isohexane.

General Procedure for Radical-Mediated Reactions (Table 2).[17] To a heavy-walled Pyrex tube were added the following. Entries 1−3: **4a**−**c**, 0.10 mmol; **2b**, 0.12 mmol (211.3 mg); AIBN, 0.010 mmol (1.6 mg); benzotrifluorid (BTF), 1.0 mL. Entry 4: **4a**, 0.10 mmol (21.5 mg); **2b**, 0.010 mmol (17.6 mg); acrylonitrile, 0.5 mmol (26.5 mg); $NaBH_3CN$, 0.13 mmol (4.1 mg); AIBN, 0.010 mmol (1.6 mg); BTF/*t*-BuOH (1/1), 1.0 mL. All reactions, except the second reaction of entry 4, were worked up as described under General Procedure for Stille-Coupling Reactions. **5d** was worked-up in accordance to the General Procedure for Stille-Coupling Reactions in the first reaction and by filtration through silica with ethyl acetate as solvent in the other. Eluting solvents for chromatography: **5a**, isohexane; **5b**, isohexane/ethyl acetate 2:1; **5c**, isohexane/ethyl acetate 5:1; **5d**, isohexane/ethyl acetate 2:1.

Procedure for the Hydrostannylation and Vinylic Stille-Coupling (Scheme 1).[18] To a heavy-walled Pyrex tube were added the following. Step 1: **6**, 0.10 mmol (17.0 mg); **2b**, 0.12 mmol (211.3 mg); AIBN, 0.010 mmol (1.6 mg); benzotrifluorid (BTF), 0.6 mL. The reaction mixture was heated by microwave irradiation (10 min/60 W) and was allowed to cool to room temperature before the reagents for step 2 were added directly to the Pyrex tube. Step 2: PhI, 0.5 mmol (102.0 mg); $Pd(OAc)_2$, 0.0020 mmol (0.45 mg); CuO, 0.3 mmol (23.9 mg); DMF, 0.5 mL. The reaction mixture was irradiated (8 min/60 W) and allowed to cool, and product **7**[18] was extracted and purified as described under General Procedure for Stille-Coupling Reactions. Eluting solvent for chromatography: **7**, isohexane/ethyl acetate 5:2.

Acknowledgment. We thank the Swedish Natural Science Research Council and the Swedish Foundation for Strategic Research for financial support.

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(15) Syntheses and characterizations of the F-13 and F-21 compounds can be found in (a) Curran, D. P.; Hadida, S. *J. Am. Chem. Soc.* **1996**, *118*, 2531−2532. (b) Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 8341−8349. (c) Curran, D. P.; Hadida, S.; Kim, S.-Y.; Luo, Z. *J. Am. Chem. Soc.*, in press.

(16) The corresponding yields obtained with $PhSn(CH_2CH_2C_6F_{13})_3$ and thermal heating: **3a**, 90%; **3b**, 90%; **3c**, 94%; **3d**, 77%. For further details, see ref 15b.

(17) The corresponding yields obtained with $HSn(CH_2CH_2C_6F_{13})_3$: **5a**, 90%; **5d**, 89%; see ref 15a. **5b** and **5c** were isolated from reactions in supercritical CO_2 in 99% and 87%, respectively. See Hadida, S.; Super, M. S.; Beckman, E. J.; Curran, D. P. *J. Am. Chem. Soc.* **1997**, *119*, 7406−7407.

(18) (a) NMR and MS of **7**: Gellerstedt, G.; Hardell, H. L.; Lindfors, E. L. *Acta Chem. Scand.* **1980**, *B34*, 669−673. (b) NMR of **7**: Savoia, D.; Trombini, C.; Umani-Ronchi, A.; Verardo, G. *J. Chem. Soc., Chem. Commun.* **1981**, 541−542.