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Pd-Catalyzed Direct Cross-Coupling of Electron-Deficient Polyfluoroarenes with Heteroaromatic Tosylates

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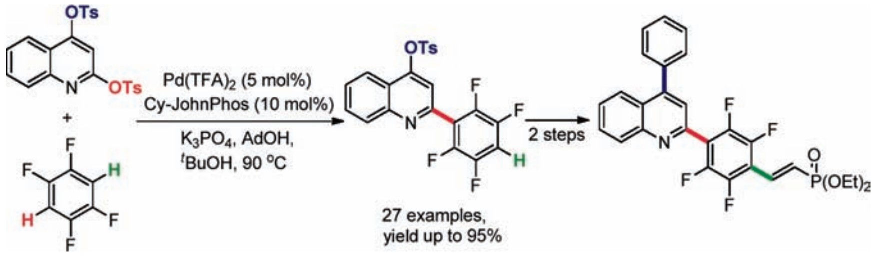
ABSTRACT



We report a Pd-catalyzed direct cross-coupling of electron-deficient polyfluoroarenes with heteroaromatic tosylates. The notable features of this reaction are its high reaction efficiency, excellent chemoselectivity, operational simplicity, and mild reaction conditions. We have applied this protocol to prepare the semiconducting materials in a highly efficient manner.

Heterobiaryl structures are omnipresent in a wide range of biologically active compounds, natural products, and functional materials. Among them, azines (e.g., pyridine, quinoline) and diazines (e.g., quinoxaline, quinazoline) bearing an aromatic ring adjacent to a nitrogen atom constitute a distinct class of structural motif owing to their importance in medicinal chemistry and material sciences.[1] Hence, it is of great synthetic interest to develop efficient reactions to access them. The most common method used to prepare such a class of heterobiaryls is the transition-metal-catalyzed cross-coupling of a metalated arene/heteroarene with a halogenated heteroarene/arene.[2] However, this traditional process suffers from intrinsic limitations in terms of step economy and the stability and availability of azine/diazine organometallics.[2a,b] In addition, many Pd-catalyzed reactions do not work well with 2-halopyridine analogues, owing to the easy formation of a stable dimeric Pd-complex that effectively removes the Pd from the catalytic cycle.[3] In this regard, Pd-catalyzed direct arylation of an azine *N*-oxide[4] or *N*-iminopyridinium ylide[5] with aryl halides has recently been developed. Additionally, the direct coupling of azines to aryl halides or aryl metals, which represents a better

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(1) For selected reviews, see: (a) Torborga, C.; Bellera, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Hill, M. D.; Movassaghi, M. *Chem.—Eur. J.* **2008**, *14*, 6836. (c) Thomas, S. W., III; Joly, G. D.; Swager, T. M. *Chem. Rev.* **2007**, *107*, 1339. (d) Fairlamb, I. J. S. *Chem. Soc. Rev.* **2007**, *36*, 1036. (e) Pozharski, A. F.; Soldartenko, A. T.; Katritsky, A. *Heterocylces in Life and Society*; Wiley: New York, 1997.

(2) For selected examples, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302 and references therein. (c) Hodgson, P. B.; Salingue, F. H. *Tetrahedron Lett.* **2004**, *45*, 685.

(3) Bozell, I. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, *56*, 2584.

(4) For Pd-catalyzed direct arylation of pyridine *N*-oxide, see: (a) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *127*, 18020. (b) Leclerc, J.-P.; Fagnou, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 7781. (c) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (f) Ackermann, L.; Fenner, S. *Chem. Commun.* **2011**, *47*, 430.

(5) Larivee, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52.

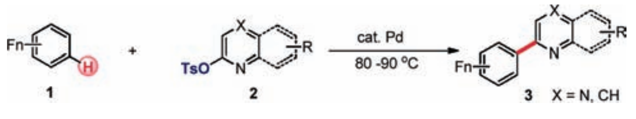
(6) For a carboxy-directed palladium-catalyzed arylation of pyridine using aryl halides, see: (a) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275. For a rhodium-catalyzed direct arylation of pyridine using aryl halides, see:(b) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926. For nickel-catalyzed direct arylation of pyridine using arylzincs, see:(c) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (d) For a radical arylation of azines with aryl boron acids, see: Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

10.1021/ol201706t

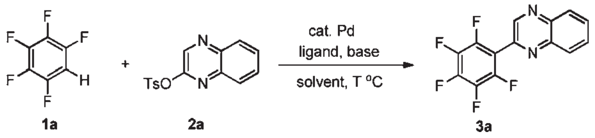
reaction efficiency, has also been accomplished using different transition-metal catalysts.[6] From the point of view of synthetic convenience, the direct heteroarylation of Ar−H using heteroaromatic tosylates would be an attractive alternative, because the heterocyclic alcohols, such as quinoxalinols, quinolinols, and pyridinols, are readily available and inexpensive, the corresponding heteroaromatic tosylates are chemically stable, highly crystalline, and easily prepared. However, the construction of such arylated azine or diazine structures through the present strategy (e.g., direct heteroarylation of polyfluoroarenes using heteroaromatic tosylates) has never been reported, despite important progress that has been achieved on the cross-couplings of aryl metals with heteroaromatic sulfonates[7] or phosphonium salts.[8] Consequently, developing new methods to access this valuable heterobiaryl moiety for widespread synthetic applications are still highly desirable.

It has been demonstrated that the installation of a polyfluoroaryl group *ortho* to a nitrogen atom of azines or diazines can make the heterobiaryl based electronic and optoelectronic materials possess several advantages with respect to their nonfluorinated counterparts, such as enhanced photoluminescence efficiency, minimized self-quenching behavior, and lowered HOMO and LUMO energy levels.[9] However, the preparation of these polyfluoroarylated azines or diazines requires prefunctionalized polyfluoroarenes and several synthetic steps.[10] Therefore, developing highly efficient methods by using simple polyfluoroarenes to directly construct this key structural motif is a topic of immense importance in organic synthesis.[11] Recently, an important example of a copper-catalyzed cross-coupling of pentafluorobenzene with 2-pyridyl halides was reported.[11c,d] However, the reaction was restricted by harsh reaction conditions (120−150 °C) and the availability of pyridyl halides. Herein, we describe a Pd-catalyzed direct cross-coupling of electron-deficient polyfluoroarenes with heteroaromatic tosylates under mild reaction conditions. This approach provides a concise and convenient protocol for the preparation of a wide range of polyfluoroarylated azine/diazine structures with high efficiency (Scheme 1).

Scheme 1. Pd-Catalyzed Direct Cross-Coupling of Polyfluoroarenes with Heteroaromatic Tosylates



We began this study by choosing electron-deficient pentafluorobenzene **1a** and 2-quinaxolinyl tosylate **2a** as model substrates (eq 1). Compound **2a** was prepared from commercially available quinoxalin-2-ol with tosyl chloride.

 (1)

Initially, the use of Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), and Cs$_2$CO$_3$ (1.2 equiv) in toluene at 120 °C failed to afford desired product **3a**. After a survey of reaction parameters, we found that the catalytic activity was highly sensitive to the components of the catalyst system (see Table S1 in the Supporting Information). The Buchwald Cy-JohnPhos ligand **L**, P(biphenyl-2-yl)Cy$_2$, and K$_3$PO$_4$ were the best choice. Other ligands, such as SPhos, XPhos, DavePhos, RuPhos, tricyclohexylphosphine, and bidentate ligand, dppe, were less effective. The absence of a phosphine ligand led to no **3a**, indicating the pivotal role of a phosphine ligand in the catalytic cycle. The reaction temperature also had an impact on the reaction efficiency,[12] and a 72% NMR yield of **3a** was afforded when the reaction temperature decreased to 80 °C with the use of Pd(OAc)$_2$ (10 mol %), P(biphenyl-2-yl)Cy$_2$ (20 mol %), and K$_3$PO$_4$ (1.2 equiv) in dioxane. Interestingly, when the Pd(OAc)$_2$ loading was decreased to 5 mol %, an alcoholic solvent, *t*BuOH,[13] was found to be the optimum reaction medium. Further optimization revealed that the optimal isolated yield (73%) was achieved by use of 3 mol % of Pd(TFA)$_2$ and 6 mol % of **L** with 1.2 equiv of 1-adamantanecarboxylic acid (AdOH) as an additive at 90 °C.[14,15]

Under the optimum reaction conditions, a variety of pentafluorophenylated azine and diazine structures were obtained with high efficiency (Table 1).

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(7) For examples, see: (a) Bhayana, B.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2009**, *11*, 3954. (b) Gogsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4886.

(8) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300.

(9) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003.

(10) For selected examples, see: (a) Chen, J.; Cammers-Goodwin, A. *Tetrahedron Lett.* **2003**, *44*, 1503. (b) Hamilton, C. W.; Laitar, D. S.; Sadighi, J. P. *Chem. Commun.* **2004**, 1628. (c) Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Takagishi, H.; Okuda, S.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 605. (d) Dash, J.; Reissig, H.-U. *Chem.—Eur. J.* **2009**, *15*, 6811.

(11) For recent examples for transition-metal-catalyzed direct arylation of polyfluroroarenes with arylhalides, see: (a) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (d) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (e) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116. For oxidative cross-coupling of polyfluoroarenes with electron-rich heteroarenes, see:(f) He, C.-Y.; Fan, S.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 12850.

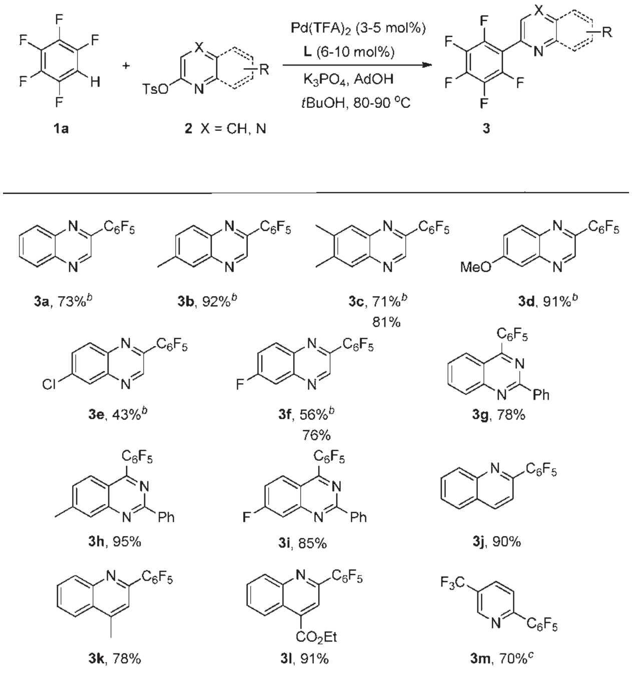
(12) Decreasing the reaction temperature is beneficial to the reaction; for details, see Supporting Information Table S1.

(13) ^{t}BuOH is often used as a (co)solvent in cross-coupling reactions of aryl tosylates; see: (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (b) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059 and ref 7a.

(14) Using 5 mol% Pd(OAc)$_2$ and 1.2 equiv of AdOH furnished the reaction in a slightly lower yield (60% isolated yield). PivOH can also be used as an additive but is less effective.

(15) It has been demonstrated that phosphine-ligated arylpalladium carboxylates LPd(Ar)(OCOR) were typically proposed to react with arenes to form biarylpalladium complexes through a concerted metalation−deprotonation (CMD) pathway. The role of AdOH or PivOH was proposed to function as a proton shuttle during the aryl C−H cleavage step. See: Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496.

Table 1. Pd-Catalyzed Direct Cross-Coupling of Pentafluorobenzene with Various Heteroaromatic Tosylates[a]



3a, 73%[b]

3b, 92%[b]

3c, 71%[b] 81%

3d, 91%[b]

3e, 43%[b]

3f, 56%[b] 76%

3g, 78%

3h, 95%

3i, 85%

3j, 90%

3k, 78%

3l, 91%

3m, 70%[c]

[a] Reaction conditions (unless otherwise specified): **1a** (2.0 equiv), **2** (0.3 mmol, 1.0 equiv), $Pd(TFA)_2$ (5 mol %), P(biphenyl-2-yl)Cy_2 **L** (10 mol %), K_3PO_4 (1.2 equiv), and AdOH (1.2 equiv) in *t*BuOH (1.5 mL) at 90 °C for 12 h. [b] Using 3 mol % of $Pd(TFA)_2$ and 6 mol % of **L**. [c] Reaction run at 80 °C for 36 h.

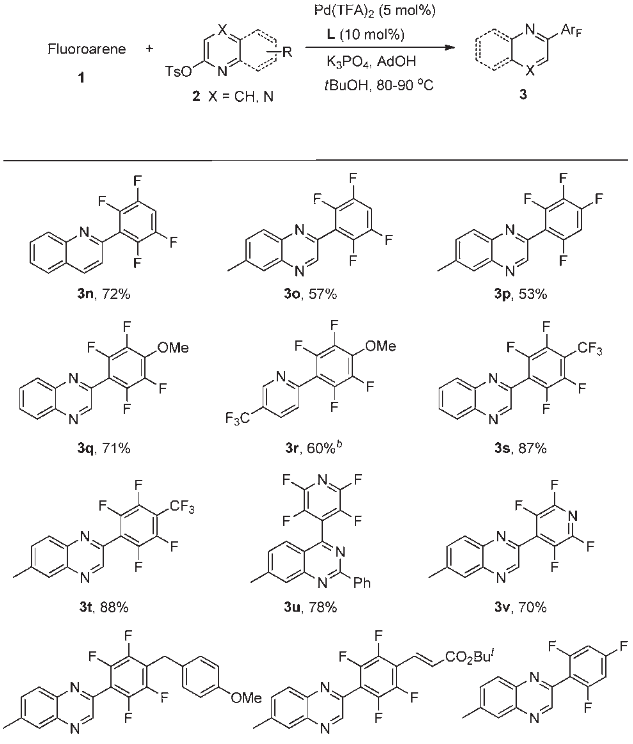
Substrates of 2-quinaxolinyl tosylates bearing an electron-donating group furnished the reaction smoothly in good yields with only utilization of 3 mol % Pd-catalyst (entries **3b**–**d**). While for electron-withdrawing group substituted 2-quinaxolinyl tosylates, lower yields were afforded (entries **3e**–**f**). This can be addressed by increasing the loading of $Pd(TFA)_2$ to 5 mol % (entry **3f**). 4-Quinazolinyl tosylates did not interfere with the coupling, and good to excellent yields were obtained (entries **3g**–**i**). Azines are also suitable substrates for the reaction (entries **3j**–**m**). Importantly, although product **3e** was obtained in a reasonable yield, it revealed a good chemoselectivity at 2-quinaxolinyl tosylate over aryl chloride, thus providing a good opportunity for further transformations by utilizing traditional techniques (entry **3e**).

To further probe the applicability of this methodology, couplings of various fluoroarenes **1** bearing three or four fluorines with heteroaromatic tosylates were also tested (Table 2).

To our delight, fluoroarenes **1** containing more than one reaction site provided good yields of monoazine- or diazine-substituted products without observation of bis(heteroaryl)fluoroarenes (entries **3n**–**p**). However, due to the poor reactivity of 1,3,5-trifluorobenzene,[16] only a 27% yield of **3y** was afforded (entry **3y**). The nature of the substituents on the fluoroaromatic ring did not influence the reaction efficiency, and both electron-rich and -poor groups furnished the reaction in good yields (entries **3q**–**t**). We were pleased to observe that polyfluoropyridine was viable for the direct heteroarylation, forming bisheterocycles **3u** and **3v** in good yields (entries **3u**–**v**). Benzylated fluoroarene is also a suitable substrate and provided **3w** in a reasonable yield (entry **3w**). Notably, an α,*β*-unsaturated ester is compatible with the catalytic system with no formation of a Heck reaction byproduct, thus demonstrating the utility of this protocol in the synthesis of highly functionalized heteroarylpolyfluoroarenes (entry **3x**).

The importance of this protocol can also be featured by the rapid access of semiconducting materials through sequential C–H bond and C–O bond activation from simple and inexpensive starting materials. As shown in Scheme 2, chemoselective functionalization of inexpensive quinoline-2,4-diyl bis(tosylate) **4** under the standard reaction conditions afforded monofluoroarylated quinoline-4-yl tosylate **5**. The resulting compound **5** was subsequently

Table 2. Pd-Catalyzed Direct Cross-Coupling of Fluoroarenes with Various Heteroaromatic Tosylates[a]



3n, 72%

3o, 57%

3p, 53%

3q, 71%

3r, 60%[b]

3s, 87%

3t, 88%

3u, 78%

3v, 70%

3w, 49%[c]

3x, 80%[c]

3y, 27%[d]

[a] Reaction conditions (unless otherwise specified): **1** (3.0 equiv), **2** (0.3 mmol, 1.0 equiv), K_3PO_4 (1.2 equiv), and AdOH (1.2 equiv) in *t*BuOH (1.5 mL) at 90 °C for 12 h. **L**, P(biphenyl-2-yl)Cy_2. [b] Reaction run at 80 °C for 36 h. [c] Using 1.2 equiv of **1**. [d] Using 10 mol % of $Pd(TFA)_2$ and 20 mol % of **L**.

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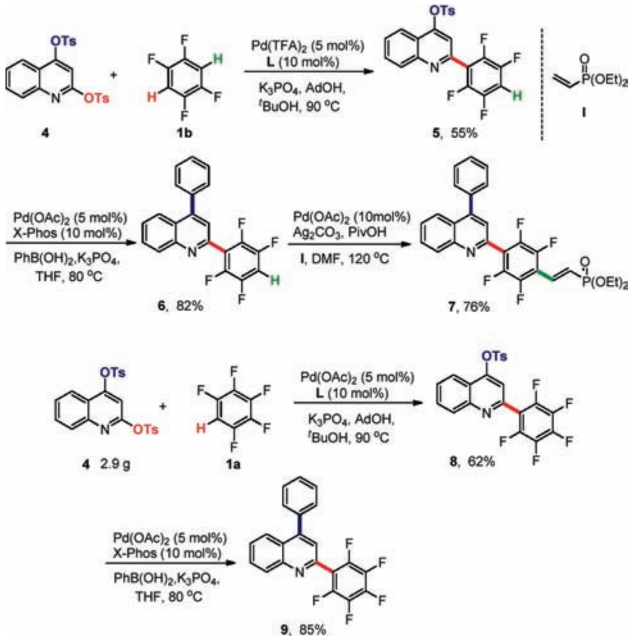
[16] (a) Hyla-Kryspin, I.; Grimme, S.; Buker, H. H.; Nibbering, N. M. M.; Cottet, F.; Schlosser, M. *Chem.—Eur. J.* **2005**, *11*, 1251. (b) Schlosser, M.; Marzi, E. *Chem.—Eur. J.* **2005**, *11*, 3449.

[17] Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506.

Scheme 2. Synthesis of Semiconducting Polyfluorophenylquinolines **7** and **9** through Chemoselective Functionalization of Quinoline-2,4-diyl Bis(tosylate) **4**



treated with phenylboronic acid in the presence of a Pd-catalyst,[13a] followed by the oxidative olefination via sequential C–H activation,[17] to give a semiconducting polyfluorophenylquinoline derivative **7**[18] in a highly efficient manner. A 2-g-scale synthesis of **8** was also performed in good yield (62%), thus indicating the good reliablility of the process (Scheme 2). Similarly, phenylation of **8** provided a semiconducting compound **9**[18] efficiently. These transformations demonstrated that compounds **5** and **8** are very useful and can be used as versatile building blocks to access a wide range of functional materials through the present strategy.

In conclusion, we have developed a straightforward and convenient method for Pd-catalyzed direct heteroarylation of electron-deficient polyfluoroarenes. The reaction makes direct use of a simple polyfluoroarenes and readily available and inexpensive heteroaromatic tosylates without the requirement of several synthetic steps to prepare cross-coupling partners. Application of the method leads to the semiconducting materials in a highly efficient manner. Because of the high reaction efficiency, excellent chemoselectivity, and the ease of conducting such reactions, this protocol provides a useful and facile access to polyfluoroaryl azine and diazine structures of interest in functional materials of electronic devices. Further studies to expand the substrate scope and their applications are now in progress.

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Supporting Information Available. Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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[18] Stefopoulos, A. A.; Kourkouli, S. N.; Economopoulos, S.; Ravani, F.; Andreopoulou, A.; Papagelis, K.; Siokou, A.; Kallitsis, J. K. *Macromolecules* **2010**, *43*, 4827.