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Rapid and Amenable Suzuki Coupling Reaction in Water Using Microwave and Conventional Heating

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It is possible to prepare biaryls in good yield very rapidy (5−10 min) on small (1 mmol) and larger (10−20 mmol) scales from aryl halides and phenylboronic acid using water as a solvent and palladium acetate as catalyst. The reaction can be performed equally well using microwave and conventional heating, showing that using these conditions probably no nonthermal microwave effects are associated with the impressive speed of the reaction.

The Suzuki reaction (palladium-catalyzed cross coupling of aryl halides with boronic acids) is one of the most versatile and utilized reactions for the selective construction of carbon−carbon bonds, in particular for the formation of biaryls.[1] As the biaryl motif is found in a range of pharmaceuticals, herbicides, and natural products as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki reaction has received much recent attention. One area of research interest has been in the use of water as a solvent for the Suzuki reaction.[2] Water, being cheap, readily available, nontoxic, and nonflammable, has clear advantages as a solvent for use in chemistry.[3,4] There are however problems such as solubility of substrates and stability of the metal catalysts in water, but these problems have to some extent been overcome by the use of phase-transfer catalysts and water-soluble phosphine ligands or the design of novel heterogeneous catalysts.[5] Suzuki reactions of water-soluble aryl iodides have been performed in water using simple palladium salts[6,7] or amphiphilic polymer-supported palladium catalysts.[8] Badone and co-workers have investigated the effects of solvent, including water, on the rate of the ligandless palladium acetate catalyzed Suzuki reaction of a range of aryl bromides, iodides, and triflates.[9] They report that when using water as a solvent the addition of 1 equiv of tetrabutylammonium bromide (TBAB) to the reaction mixture greatly accelerates the reaction.[10] They find that aryl bromides can be coupled with phenylboronic acid to yield biaryls fairly rapidly (1 h) and in good yields whereas with aryl iodides the reaction does not reach completion. The role of the ammonium salts is thought to be twofold. First, they facilitate solvation of the organic substrates in the solvent medium. Second, they are thought to enhance the rate of the coupling reaction by activating the boronic acid to reaction by formation of $[ArB(OH)_3]^-[R_4N]^+$. TBAB has been used recently in conjunction with a palladium oxime catalyst for the Suzuki coupling of aryl chlorides with phenylboronic acid in water.[11] In addition to the Suzuki couplings performed in neat water as the solvent, there have been a number of reports[12−14] of the use of water as a cosolvent for the reaction, again focused on the use of aryl iodides and activated bromides, with two recent reports[15,16] of the use of aryl chlorides.

With its high dielectric constant water is also potentially a very useful solvent for microwave-mediated synthesis. The use of microwave ovens as tools for synthetic chemistry is a fast growth area.[17,18] Since the first reports

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[1] For recent reviews see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[2] For a review of palladium-catalyzed reactions in water, see: Genet, J.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305.

[3] For an introduction to the use of water as a solvent in organic synthesis, see: (a) *Organic Synthesis in Water*; Greico, P. A., Ed.; Blackie Academic & Professional: London, 1998. (b) Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1997.

[4] For an introduction to the use of organometallic catalysts in aqueous-phase catalysis, see: *Aqueous-Phase Organometallic Catalysis, Concepts and Applications*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

[5] For recent examples see: (a) Gulyas, H.; Szollosy, A.; Hanson, B. E.; Bakos, J. *Tetrahedron Lett.* **2002**, *43*, 2543. (b) Brauer, D. J.; Hingst, M.; Kottsieper, K. W.; Like, C.; Nickel, T.; Tepper, M.; Stelzer, O.; Sheldrick, W. S. *J. Organomet. Chem.* **2002**, *645*, 14.

[6] Bumagin, N A.; Bykov, V. V. *Tetrahedron* **1997**, *53*, 14437.

[7] Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.*, **2002**, *67*, 2721.

[8] Uozumi, Y.; Danjo, H.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 3384.

[9] Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170.

[10] The use of TBAB in palladium-mediated catalysis has been reported on a number of occasions, in particular for the Heck reaction. See, for example: Jeffery, T. *Tetrahedron Lett.* **1994**, *35*, 3051.

[11] Botella, L.; Nájera, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 179.

[12] Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757.

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[14] Campi, E. M.; Jackson, W. R.; Marcuccio, S. M.; Naeslund, C. G. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2395.

[15] LeBlond, C. R., Andrews, A. T.; Sun, Y.; Sowa, J. R. *Org. Lett.* **2001**, *3*, 1555.

[16] Alonso, D. A.; Nájera, C.; Pacheco, M. A. *J. Org. Chem.* **2002**, *67*, 5588.

[17] For reviews on the area see: (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, 717. (b) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (c) Lindström, P.; Tierney, J.; Wathey B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.

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of microwave-assisted synthesis in 1986,[19,20] the technique has been accepted as a method for reducing reaction times often by orders of magnitude and for increasing yields of product compared to conventional methods.[21,22] As a result, this has opened up the possibility of optimizing new reactions in a very short time. With microwave promotion, efficient heating of the sample itself is possible, whereas transfer of heat through reaction vessel walls is necessary with conventional heating systems, e.g., an oil bath. This internal heat transfer results in minimized wall effects (no thermal boundary layer), and reaction mixtures can be heated to high temperatures rapidly. The first reports of Suzuki couplings using microwave promotion were by Larhed and Hallberg, using $Pd(PPh_3)_4$ as the catalyst, homogeneous and polymer-supported aryl iodides and bromides as substrates, and a mixture of water, ethanol, and DME as solvent.[23,24] With reaction times of only approximately 3−4 min, good yields of product were obtained. There have been reports of microwave-assisted solvent-free Suzuki coupling protocols using palladium-doped alumina[25] and KF on alumina in conjunction with palladium catalysts.[26] Microwave heating has been used to facilitate the coupling in water of arylboronic acids with the poly(ethylene glycol) esters of an aryl iodide and triflate and also a bromothiophene.[27] In the same report, 4-iodobenzoic acid methyl ester was coupled with a range of boronic acids in water/poly(ethylene glycol) mixtures. Sodium tetraphenylborate has been used as a phenylation reagent for microwave-mediated aqueous-phase biaryl synthesis.[28] We have recently reported that it is possible to couple a range of aryl halides, including chlorides, with phenylboronic acid in neat water using microwave heating with palladium acetate as the catalyst and TBAB as an additive.[29] The total reaction time is between 5 and 10 min, and low palladium loadings are used. We were next interested in extending the methodology, comparing our reactions performed using microwave heating with those using conventional thermal heating and in investigating the effects on the yields and reaction times of scaling up the reaction to make larger quantities of biaryls. We report the results of these studies here.

Microwave-Assisted Suzuki Couplings

A key advantage of modern scientific microwave apparatuses is the ability to control reaction conditions very specifically, monitoring temperature, pressure, and reaction times. This meant that we were able to screen a wide range of conditions very fast and with close monitoring. As a result, we could optimize the reaction very easily. Our initial investigations were undertaken using 1 mmol of aryl halide and 1 mmol of boronic acid, the reactions being performed in 10 mL sealed tubes using 2 mL of water. When using aryl iodides and bromides, we find that the best yields of biaryl are formed when the temperature is ramped from room temperature to 150 °C and then held at this temperature for 5 min.[30] The time taken for the reaction mixture to reach the target temperature of 150 °C varies depending on the aryl halide substrate but is within the period of 30−40 s. For aryl chlorides we find that it is necessary to increase the temperature to 175 °C to obtain reasonable yields of biaryl product. At temperatures above 150−175 °C we observe significant deactivation of the catalyst and the onset of decomposition of the organic substrates and products. We find that the optimum catalyst loading is 0.4 mol %. At the high temperatures used in the reactions, if higher catalyst loadings are used, there is a problem with competitive hydrodeboronation of the boronic acid, giving, in the case of phenylboronic acid, benzene. This obviously leads to poor yields of the desired biaryl. The microwave power used is very important. We find that the optimum power is 60 W, above which rapid deactivation of the catalyst occurs and below which yields of biaryl drop significantly and extended reaction times are required. We find that although good yields of product are formed using 0.5 equiv of TBAB, it is better to use 1 equiv of TBAB. The conditions used are applicable to a wide range of substrates bearing different functional groups.

We were keen to develop the methodology for the preparation of grams of material. As a starting point for the scale-up of the reaction from 1 to 10 mmol, we chose to study the coupling of 4-bromoacetophenone with phenylboronic acid. Due to the quantity of starting materials required, we moved from performing the reactions in sealed 10 mL tubes to using larger open vessels. A 50 mL round-bottomed flask was placed inside the microwave cavity and a double-surface reflux condensor attached to this. In the initial experiment, a ratio of aryl halide to phenylboronic acid to TBAB to $Pd(OAc)_2$ to Na_2CO_3 identical to that in the optimized 1 mmol reaction, namely, 1:1:1:0.004:3.8, respectively, was used. A volume of 10 mL of water was used. The reaction was performed using a continuous microwave power of 60 W and the reaction run for a total time of 10 min, stirring the reaction mixture throughout. The temperature increased from room temperature to a maximum of 110 °C over a period of 3.5 min and then stayed at this temperature for the remainder of the time. A yield of 4-acetylbiphenyl of 90% was obtained, this comparing with a yield of 91% when the reaction is performed on a 1 mmol scale in a sealed tube. Having shown that it was possible

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(18) For a review on the concepts see: Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213.

(19) Gedye, R.; Smith, F.; Westaway, K.; Humera, A.; Baldisera, L.; Laberge, L.; Rousell, L. *Tetrahedron Lett.* **1986**, *26*, 279.

(20) Giguere, R.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.

(21) For some recent examples see: (a) Westman, J. *Org. Lett.* **2001**, *3*, 3745. (b) Kuhnert, N.; Danks, T. N. *Green Chem.* **2001**, *3*, 98. (c) Loupy, A.; Regnier, S. *Tetrahedron Lett.* **1999**, *40*, 6221.

(22) Stadler, A.; Kappe, A. C. *Eur. J. Org. Chem.* **2001**, 919.

(23) Hallberg, A.; Larhed, M. *J. Org. Chem.* **1996**, *61*, 9582.

(24) Hallberg, A.; Lindeberg, G.; Larhed, M. *Tetrahedron Lett.* **1996**, *37*, 8219.

(25) Kabalka, G. W.; Pagni, R. M.; Wang, L.; Namboodiri, V.; Hair, C. M. *Green Chem.* **2000**, *2*, 120.

(26) Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, *42*, 639.

(27) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885.

(28) Villemin, D.; Gómez-Escalonilla M. J.; Saint-Clair, J.-F. *Tetrahedron Lett.* **1996**, *37*, 8219.

(29) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973.

(30) *Caution: The water is heated well above its boiling point, so all necessary precautions should be taken when such experiments are performed. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective metal cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to a temperature below the boiling point of the solvent before removal from the microwave cavity and being opened to the atmosphere.*

to scale-up the reaction without loss of yield or need for greatly extended reaction times, we wanted to try to decrease the quantities of TBAB and base used in the reaction. Reducing the quantity of TBAB used from 1 to 0.25 equiv had no effect on the product yield. The quantity of base can be reduced from 3.8 to 1 equiv with no ill effects, but further reduction results, not surprisingly, in lower yields of biaryl.

With the optimized conditions in hand, we screened a representative range of aryl bromides in the reaction. The results are shown in Table 1 together with those from the reactions on a 1 mmol scale in sealed tubes. It is clear that in all cases yields of biaryl are almost identical in the 1 and 10 mmol reactions. All the reactions were performed in air and without degassing the water prior to use and using a 1:1 stoichiometric ratio of aryl halide to boronic acid. This compares favorably with other aqueous Suzuki coupling protocols where oxygen-free conditions and an excess of boronic acid are often used. To extend the scope of the reaction, we also investigated the couplings of phenylboronic acid with representative aryl iodides and chlorides. We find that although it is possible to use aryl iodides in the reaction, albeit with a decrease in yield over the 1 mmol experiments, aryl chlorides do not react. The loss of yield with the aryl iodides is not totally surprising as Badone and co-workers found a similar problem with their Suzuki couplings in water.[9] The reason that the chlorides do not work could well be because the high temperatures needed to activate the chloride substrates are not achievable using the open vessel system.

Conventionally Heated Suzuki Couplings

The fact that the reaction with aryl bromides can be scaled up and performed in open vessels as efficiently as when using higher temperatures and pressures in sealed tubes was of interest to us not only from a synthetic viewpoint. Since the start of the field of microwave-assisted synthesis, far shorter times for reactions as compared to those using “conventional” heating have been reported, and this has sparked debate into the nature of the microwave heating.[31] The acceleration of reactions could simply be an effect of the thermal energy generated by the microwaves interacting with the substrates or could be an effect specific to microwave heating. In most cases the observed differences between microwave and conventional heating can be attributed to simple thermal effects. We were interested in trying to ascertain whether the rates of the reactions we were observing in our Suzuki reaction were simply due to efficient thermal heating. In their $Pd(PPh_3)_4$-catalyzed Suzuki reactions in water/organic solvent mixtures, Larhed and Hallberg show that using conventional heating the reactions take much longer than when using microwave irradiation (6 h and 3−4 min, respectively).[23,24] In their report of cross couplings of boronic acids and poly(ethylene glycol)-supported aryl iodides in water using $Pd(OAc)_2$ as catalyst, Schotten and co-workers[27] do not comment specifically on whether their conditions for conventional heating are optimized or what temperature their microwave reactions reach but do report that reaction times for the microwave-assisted reactions are a matter of 2−4 min as compared to 2 h for the conventional thermal reactions.

Taking the coupling of 4-bromoacetophenone and phenylboronic acid as a starting point, we performed the reaction on a 1 mmol scale using conventional heating. We kept the quantities of catalyst, base, TBAB, and water exactly the same as in the microwave-assisted reaction and performed the reaction in a sealed 10 mL microwave tube. We dipped the tube into an oil bath preheated to 150 °C and held it there for 5 min before removing it and cooling the reaction mixture.[32] An isolated yield of 4-acetylbiphenyl of 94% was obtained. This compares to an isolated yield of 91% when using microwave heating. As well as showing that in this reaction the microwave simply provides an efficient heating method, the fact that the reaction can be performed so fast using conventional heating is very noteworthy. Indeed, to our knowledge this represents the *fastest Suzuki couplings with aryl bromides using conventional heating*. Although not so energy efficient, this offers an alternative to the microwave methodology for the rapid synthesis of biaryls in neat water. To probe the applicability of the methodology to other substrates, we screened a range of aryl bromides bearing electron-withdrawing and -donating groups as well as a sterically crowded example. The results are shown in Table 1

. In each case identical or better yields than those obtained with the microwave method were found. The same is true of an iodo example, but it was possible to couple aryl chlorides with phenylboronic acid only in very low yields (≤5%) using the conventional thermal conditions. We attribute this to the fact that the high temperatures needed to activate the chloride substrates are not readily achievable using the conventional thermal methodology.

We next turned our attention to the larger scale reaction. We performed the coupling on a 10 mmol scale by placing a 50 mL flask containing exactly the same starting materials as in the microwave experiments into a preheated (150 °C) oil bath and held it there for 10 min before removing and cooling it. Again a range of aryl bromide substrates were screened, and yields almost identical to those found when using the microwave methodology were obtained. Finally, we performed the reaction of 4-bromoacetophenone with phenylboronic acid on a 20 mmol scale and again obtained impressive yields of biaryl (91%) after 10 min of heating.

In summary, we have shown that it is possible to prepare biaryls in good yield on small and larger scales from aryl halides and phenylboronic acid using water as a solvent and palladium acetate as catalyst. The reaction can be performed equally well using microwave and conventional heating, showing that using these conditions probably no nonthermal microwave effects are associated with the impressive speed of the reaction. As oil baths are more readily available in laboratories than focused microwave reactors, the conventional thermal

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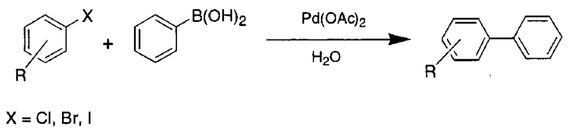
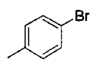
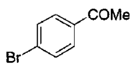
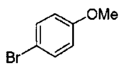
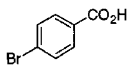
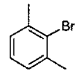
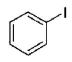
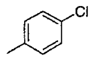
(31) For a review see: Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199.

(32) *Caution: A blast shield should be in place, and vessels designed to withhold elevated pressures must be used. After completion of an experiment, the vessel must be allowed to cool before being opened to the atmosphere.*

TABLE 1. Microwave and Conventionally Heated Suzuki Coupling of Aryl Halides and Arylboronic Acids in Water Using Pd(OAc)$_2$[a]



Entry	Aryl halide	Microwave heated		Conventionally heated	
		Isolated yield (%) 1 mmol scale [a]	Isolated yield (%) 10 mmol scale [b]	Isolated yield (%) 1 mmol scale [c]	Isolated yield (%) 10 mmol scale [d]
1		79	60	98	87
2		91	92	94	91
3		86	64	92	85
4		91[e]	97[e]	92[e]	96[e]
5		73	58	77	82
6		80	62	86	66
7		62[f,g]	≤ 5[g]	≤ 5[g]	≤ 5[g]

[a] 1 mmol of aryl halide, 1 mmol of boronic acid, 3 mmol of Na_2CO_3, 0.4 mol % Pd(OAc)$_2$, 1.0 mmol of TBAB, 2 mL of water. Microwave irradiation 60 W; temperature ramped to 150 °C (taking between 30 and 40 s) and held for 5 min. [b] 10 mmol of aryl halide, 10 mmol of boronic acid, 0.4 mol % Pd(OAc)$_2$, 10 mmol of Na_2CO_3, 2.5 mmol of TBAB, 10 mL of water. Microwave irradiation 60 W continuous; total reaction time 10 min; temperature ramped to 110 °C and held. [c] 1 mmol of aryl halide, 1 mmol of boronic acid, 3 mmol of Na_2CO_3, 0.4 mol % Pd(OAc)$_2$, 1.0 mmol of TBAB, 2 mL of water. Placed into a preheated oil bath at 150 °C and held for 5 min. [d] 10 mmol of aryl halide, 10 mmol of boronic acid, 0.4 mol % Pd(OAc)$_2$, 10 mmol of Na_2CO_3, 2.5 mmol of TBAB, 10 mL of water. Placed into a preheated oil bath at 130 °C and held for 10 min. [e] Without TBAB. [f] Microwave irradiation 60 W; temperature ramped to 175 °C (taking between 30 and 40 s) and held for 5 min. [g] Determined by ^1H NMR.

heating method is perhaps of more synthetic use and offers an easy and fast method for making gram quantities of biaryls.

Experimental Section

General Procedure for the Microwave-Assisted Reactions on a 1 mmol Scale. In a 10 mL glass tube were placed aryl halide (1.0 mmol), phenylboronic acid (122 mg, 1.0 mmol), Na_2CO_3 (315 mg, 3 mmol), $Pd(OAc)_2$ (1 mg, 0.004 mmol), tetrabutylammonium bromide (322 mg, 1.0 mmol), 2 mL of water, and a magnetic stir bar. The vessel was sealed with a septum and placed into the microwave cavity. Microwave irradiation of 60 W was used, the temperature being ramped from rt to 150 °C. Once 150 °C was reached, the reaction mixture was held at this temperature for 5 min. After the mixture was allowed to cool to room temperature, the reaction vessel was opened and the contents were poured into a separating funnel. Water and diethyl ether (30 mL of each) were added, and the organic material was extracted and removed. After further extraction of the aqueous layer with ether, combining the organic washings, and drying them over $MgSO_4$, the ether was removed in vacuo, leaving the crude product. The product was purified and isolated by chromatography after, in the cases where the starting aryl halide was a liquid, first removing unreacted aryl halide by heating the crude residue while under a vacuum on a Schlenk line.

General Procedure for the Microwave-Assisted Reactions on a 10 mmol Scale. In a 50 mL round-bottomed flask were placed aryl halide (10.0 mmol), phenylboronic acid (1.22 g, 10.0 mmol), Na_2CO_3 (1.0 g, 9.4 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), tetrabutylammonium bromide (805 mg, 2.5 mmol), 10 mL of water, and a magnetic stir bar. The flask was then placed into the microwave cavity. Continuous microwave irradiation of 60 W was used for 10 min, the temperature being ramped from rt to 110 °C. After the mixture was allowed to cool to room temperature, the contents of the reaction vessel were diluted with water (100 mL) and the product was extracted with diethyl ether (2 × 100 mL). The combined organic layers were washed with brine (100 mL) and dried over $MgSO_4$ and the ether was removed in vacuo, leaving the crude product, which was purified by column chromatography.

General Procedure for the Conventionally Heated Reactions on a 1 mmol Scale. The method was as for the microwave-assisted procedure except that after the tube was sealed with a septum it was placed into an oil bath preheated to 150 °C rather than into the microwave cavity. The reaction mixture was held in the oil for 5 min before being removed, allowing the vessel and contents to cool, and then the product extracted and purified in a manner identical to that in the microwave protocol.

General Procedure for the Conventionally Heated Reactions on a 10 mmol Scale. The method was as for the microwave-assisted procedure except that after the flask was loaded it was placed into an oil bath preheated to 150 °C rather than into the microwave cavity. The reaction mixture was held in the oil for 10 min before being removed, allowing the vessel and contents to cool, and then the product extracted and purified in a manner identical to that in the microwave protocol.

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Supporting Information Available: Table outlining optimization of conditions for 10 mmol Suzuki coupling reactions using microwave promotion, general experimental details, and ^1H and ^{13}C NMR data for the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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