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The Coupling of Arylboronic Acids with Nitroarenes Catalyzed by Rhodium

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ABSTRACT

The coupling of arylboronic acids with electron-deficient nitroarenes was realized for the first time by using a rhodium(I) catalyst under an air atmosphere, achieving unsymmetrical diaryl ethers with yields ranging from poor to good. From a deuterium labeling experiment, the oxygen atom is derived from ambient water. The efficiency of this reaction was demonstrated by its compatibility with fluoro, bromo, chloro, and trifluoromethyl groups.

Diaryl ethers constitute an important building block for the synthesis of natural products, and polymer science and pharmacologically active compounds.[1] Common synthetic routes for the preparation of these compounds involve an Ullmann coupling reaction of aryl halides and phenols with copper in the form of a metal salt.[2] These methods, which suffer from drawbacks as a result of limited application, use copper in stoichiometric amounts. Later, many improved methods have been reported for the synthesis of symmetrical or unsymmetrical diaryl ethers in the presence of copper[3] or palladium[4] catalytic systems that enable the Ullmann coupling reaction. To the best of our knowledge, only three examples have been described in which aryl halides are not coupled to oxygen via a phenol but via an inorganic oxygen source (K_3PO_4/H_2O,[5a] KOH,[5b] or CsOH[5c]) to afford diaryl ethers.[5] By far, transition-metal-catalyzed Ullmann coupling reactions, which generally employ aryl halides and organometallics as coupling partners, have served as the most common methods for constructing biaryl ether unions. However, several problems still remain, such as a high catalyst loading and elevated

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(1) (a) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700. (c) Li, X.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650. (d) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (e) In, J.-K.; Lee, M.-S.; Yang, J.-E.; Kwak, J.-H.; Lee, H.; Boovanahalli, S. K.; Lee, K.; Kim, S. J.; Moon, S. K.; Lee, S.; Choi, N. S.; Ahnc, K. S.; Jung, J.-K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1799. (f) Van Beek, D.; Fossum, E. *Macromolecules* **2009**, *42*, 4016. (g) Su, D.; Lim, J. J.; Tinney, E.; Wan, B.; Young, M. B.; Anderson, K. D.; Rudd, D.; Munshi, V.; Bahnck, C.; Felock, P. J.; Lu, M.; Lai, M.; Touch, S.; Moyer, G.; DiStefano, D. J.; Flynn, J. A.; Liang, Y.; Sanchez, R.; Perlow-Poehnelt, R.; Miller, M.; Vacca, J. P.; Williams, T. M.; Anthony, N. J. *J. Med. Chem.* **2009**, *52*, 7163.

(2) (a) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853. (b) Lindley, J. *Tetrahedron* 1984, *40*, 1433 and references cited therein.

(3) (a) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (b) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913. (c) Ouali, A.; Spindler, J.-F.; Cristau, H.-J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499. (d) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (e) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (f) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863. (g) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906. (h) Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089. (i) Xia, N.; Taillefer, M. *Chem.—Eur. J.* **2008**, *14*, 6037. (j) Altman, R. A.; Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284. (k) Zhang, Q.; Wang, D.; Wang, X.; Ding, K. *J. Org. Chem.* **2009**, *74*, 7187. (l) Benyahya, S.; Monnier, F.; Man, M. W. C.; Bied, C.; Ouazzani, F.; Taillefer, M. *Green Chem.* **2009**, *11*, 1121.

(4) (a) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (b) Harkal, S.; Kumar, K.; Michalik, D.; Zapf, A.; Jackstell, R.; Rataboul, F.; Riemeier, T.; Monsees, A.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 3237. (c) Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 4321. (d) Hartwig, J. F. *Nature* **2008**, *455*, 314.

(5) (a) Chen, G.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2007**, *48*, 473. (b) Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694. (c) Tlili, A.; Monnier, F.; Taillefer, M. *Chem.—Eur. J.* **2010**, *16*, 12299.

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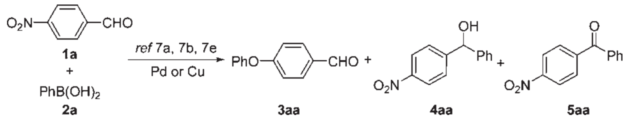
temperature. Therefore, we set out to search for alternative coupling partners and novel catalytic systems.

Organoboron reagents are highly regarded due to their advantages of stability to air and moisture as well as good functional group tolerance.[6] A continuation of our interest in the development of organoboron reactions led us to explore the potential reactions between organoboron reagents and aldehydes or aldimines.[7] Herein, we report a new method for the synthesis of unsymmetrical diaryl ethers for the first time by Rh-catalyzed coupling of arylboronic acids with nitroarenes. In many cases, direct use of ubiquitous arylboronic acids and nitroarenes in cross-coupling could be a synthetically ideal route that is environmentally friendly, avoiding the use of halides.

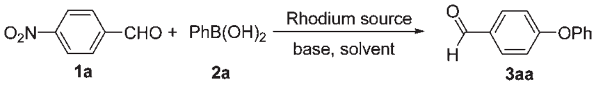
Scheme 1



We recently observed that 4-phenoxybenzaldehyde **3aa** occurred as a secondary product during the palladium- or copper-catalyzed synthesis of (4-nitrophenyl)(phenyl)-methanol **4aa**[7a,e] and (4-nitrophenyl)(phenyl)methanone **5aa**[7b] from the coupling of 4-nitrobenzaldehyde **1a** with phenylboronic acid **2a** (Scheme 1). This surprising development encouraged us to carefully adjust reaction parameters for the selective generation of **3aa** by a coupling reaction of arylboronic acids with nitroarene. First, we began our investigation by testing the model reaction of 4-nitrobenzaldehyde **1a** with phenylboronic acid **2a** in the presence of catalytic amounts of a palladium catalyst such as $Pd(OAc)_2$ and $PdCl_2$ under various reaction conditions. However, only trace amounts of the desired product **3aa** were obtained. To our delight, after the catalyst was switched to a rhodium catalyst such as $RhCl_3 \cdot 3H_2O$, the desired product **3aa** was isolated in 35% yield in DMF (Table 1, entry 5). $RhCl(PPh_3)_3$ exhibited the highest catalytic activity compared to other rhodium catalysts, affording a 78% yield (Table 1, entries 5−8). Among the solvents examined, only DMSO was found to be as effective as DMF (Table 1, entries 8−14). When the reaction was performed in various bases, the yield improved significantly, with Cs_2CO_3 being the best (Table 1, entries 8, 15−23). Shortening the reaction time decreased the yield (Table 1, entry 24), whereas a longer reaction time did not improve the yield (Table 1, entry 25). A trace product was obtained when the procedure was preformed under a nitrogen atmosphere (Table 1, entry 26). In addition, no reaction occurred when the procedure was carried out in the absence of catalyst (Table 1, entry 27). Finally, the use of an additional 0.5 equiv of Cs_2CO_3 increased the yield to 81% (Table 1, entry 28).

Under the optimized reaction conditions, the reaction of various arylboronic acids with nitrobenzenes was examined to explore the scope and generality of this coupling reaction (Table 2).

Table 1. Optimization of Reaction Conditions[a]



entry	Rh source	base	solvent	yield (%)[b]
1	$RhCl_3 \cdot 3H_2O$	Cs_2CO_3	toluene	<5
2	$RhCl_3 \cdot 3H_2O$	Cs_2CO_3	CH_3NO_2	<5
3	$RhCl_3 \cdot 3H_2O$	Cs_2CO_3	1,4-dioxane	<5
4	$RhCl_3 \cdot 3H_2O$	Cs_2CO_3	xylene	<5
5	$RhCl_3 \cdot 3H_2O$	Cs_2CO_3	DMF	35
6	$Rh_2(OAc)_2$	Cs_2CO_3	DMF	<5
7	$Rh(CO)H(PPh_3)_3$	Cs_2CO_3	DMF	65
8	$RhCl(PPh_3)_3$	Cs_2CO_3	DMF	78
9	$RhCl(PPh_3)_3$	Cs_2CO_3	CH_3NO_2	<5
10	$RhCl(PPh_3)_3$	Cs_2CO_3	toluene	<5
11	$RhCl(PPh_3)_3$	Cs_2CO_3	1,4-dioxane	<5
12	$RhCl(PPh_3)_3$	Cs_2CO_3	xylene	<5
13	$RhCl(PPh_3)_3$	Cs_2CO_3	DMSO	71
14	$RhCl(PPh_3)_3$	Cs_2CO_3	NMP	60
15	$RhCl(PPh_3)_3$	$NaHCO_3$	DMF	<5
16	$RhCl(PPh_3)_3$	K_2CO_3	DMF	62
17	$RhCl(PPh_3)_3$	Na_2CO_3	DMF	35
18	$RhCl(PPh_3)_3$	$KF \cdot 2H_2O$	DMF	<5
19	$RhCl(PPh_3)_3$	NEt_3	DMF	<5
20	$RhCl(PPh_3)_3$	LiF	DMF	21
21	$RhCl(PPh_3)_3$	CsF	DMF	29
22	$RhCl(PPh_3)_3$	TBAF	DMF	<5
23	$RhCl(PPh_3)_3$	tBuONa	DMF	<5
24[c]	$RhCl(PPh_3)_3$	Cs_2CO_3	DMF	58
25[d]	$RhCl(PPh_3)_3$	Cs_2CO_3	DMF	76
26[e]	$RhCl(PPh_3)_3$	Cs_2CO_3	DMF	<5
27[f]		Cs_2CO_3	DMF	0
28[g]	$RhCl(PPh_3)_3$	Cs_2CO_3	DMF	81

[a] Unless otherwise noted, the reaction conditions were as follows: **1a** (0.6 mmol), indicated rhodium source (1 mol %), **2a** (0.3 mmol), base (0.6 mmol), solvent (3 mL), 100 °C, 24 h, air. [b] Isolated yield. [c] For 12 h. [d] For 48 h. [e] Under N_2 atmosphere. [f] No rhodium source was added. [g] With 2.5 equiv of Cs_2CO_3.

Both electron-withdrawing and electron-donating substituted arylboronic acids were successfully coupled to nitroarenes (Table 2, entries 1−11). As shown in Table 2, the influence of a monosubstituent group at the *ortho*- and *para*-position for arylboronic acids (Table 2, entries 2−5) was investigated to examine the steric effect in our system. For example, **1a** proceeded with arylboronic acids

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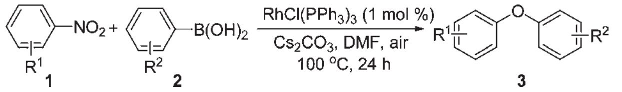
(6) (a) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(7) (a) Qin, C. M.; Wu, H. Y.; Cheng, J.; Chen, X. A.; Liu, M. C.; Zhang, W. W.; Su, W. K.; Ding, J. C. *J. Org. Chem.* **2007**, *72*, 4102. (b) Qin, M.; Chen, J.; Wu, H.; Cheng, J.; Zhang, Q.; Zuo, B.; Su, W.; Ding, J. *Tetrahedron Lett.* **2008**, *49*, 1884. (c) Zhang, Q.; Chen, J. X.; Liu, M. C.; Wu, H. Y.; Cheng, J.; Qin, C. M.; Su, W. K.; Ding, J. C. *Synlett* **2008**, *6*, 935. (d) Qin, C. M.; Wu, H. Y.; Chen, J. X.; Liu, M. C.; Cheng, J.; Su, W. K.; Ding, J. C. *Org. Lett.* **2008**, *10*, 1537. (e) Zheng, M.; Zhang, Q.; Chen, J.; Liu, M.; Cheng, S.; Ding, J.; Wu, H.; Su, W. *J. Org. Chem.* **2009**, *74*, 943.

Table 2. Substrate Scope in the Rhodium-Catalyzed Coupling of Arylboronic Acids with Nitroarenes[a]



entry	Ar^1 (**1**)	Ar^2 (**2**)	product	yield (%)[b]
1	*p*-(CHO)C_6H_4 (**1a**)	Ph (**2a**)	**3aa**	81
2	*p*-(CHO)C_6H_4 (**1a**)	*p*-(Me)C_6H_4 (**2b**)	**3ab**	76
3	*p*-(CHO)C_6H_4 (**1a**)	*o*-(Me)C_6H_4 (**2c**)	**3ac**	56
4	*p*-(CHO)C_6H_4 (**1a**)	*p*-(MeO)C_6H_4 (**2d**)	**3ad**	80
5	*p*-(CHO)C_6H_4 (**1a**)	*o*-(MeO)C_6H_4 (**2e**)	**3ae**	58
6	*p*-(CHO)C_6H_4 (**1a**)	*m*-(MeO)C_6H_4 (**2f**)	**3af**	48
7	*p*-(CHO)C_6H_4 (**1a**)	*p*-(F)C_6H_4 (**2g**)	**3ag**	52
8	*p*-(CHO)C_6H_4 (**1a**)	*p*-(Cl)C_6H_4 (**2h**)	**3ah**	71
9	*p*-(CHO)C_6H_4 (**1a**)	*p*-(Br)C_6H_4 (**2i**)	**3ai**	36
10	*p*-(CHO)C_6H_4 (**1a**)	*p*-(CF_3)C_6H_4 (**2j**)	**3aj**	31
11	*p*-(CHO)C_6H_4 (**1a**)	2-naphthyl (**2k**)	**3ak**	61
12	*o*-(CHO)C_6H_4 (**1b**)	Ph (**2a**)	**3ba**	52
13	*o*-(CHO)C_6H_4 (**1b**)	*p*-(Me)C_6H_4 (**2b**)	**3bb**	55
14	*o*-(CHO)C_6H_4 (**1b**)	*o*-(Me)C_6H_4 (**2c**)	**3bc**	32
15	*o*-(CHO)C_6H_4 (**1b**)	*p*-(MeO)C_6H_4 (**2d**)	**3bd**	35
16	*o*-(CHO)C_6H_4 (**1b**)	*p*-(F)C_6H_4 (**2g**)	**3bg**	29
17	*o*-(CHO)C_6H_4 (**1b**)	*p*-(Cl)C_6H_4 (**2h**)	**3bh**	47
18	*o*-(CHO)C_6H_4 (**1b**)	*p*-(Br)C_6H_4 (**2i**)	**3bi**	31
19	*p*-(MeC=O)C_6H_4 (**1c**)	Ph (**2a**)	**3ca**	62
20	*p*-(MeC=O)C_6H_4 (**1c**)	*p*-(Me)C_6H_4 (**2b**)	**3cb**	61
21	*p*-(MeC=O)C_6H_4 (**1c**)	*o*-(Me)C_6H_4 (**2c**)	**3cc**	58
22	*p*-(MeC=O)C_6H_4 (**1c**)	*p*-(F)C_6H_4 (**2g**)	**3cg**	41
23	*p*-(MeC=O)C_6H_4 (**1c**)	*p*-(Cl)C_6H_4 (**2h**)	**3ch**	54
24	*p*-(MeC=O)C_6H_4 (**1c**)	*p*-(Br)C_6H_4 (**2i**)	**3ci**	32
25	*p*-(PhC=O)C_6H_4 (**1d**)	Ph (**2a**)	**3da**	<5
26	*p*-($PhOSO_2$)C_6H_4 (**1e**)	Ph (**2a**)	**3ea**	35
27	*p*-(MeO_2C)C_6H_4 (**1f**)	Ph (**2a**)	**3fa**	0
28	*p*-(CN)C_6H_4 (**1g**)	*p*-(Me)C_6H_4 (**2b**)	**3gb**	34
29	*m*-(CHO)C_6H_4 (**1h**)	Ph (**2a**)	**3ha**	0

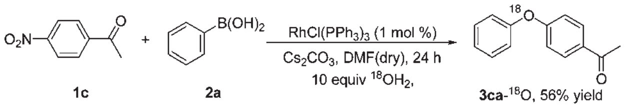
[a] Unless otherwise noted, the reactions conditions were as follows: **1** (0.6 mmol), $RhCl(PPh_3)_3$ (1 mol %), 2 (0.3 mmol), Cs_2CO_3 (0.75 mmol), DMF (3 mL), 100 °C, 24 h, air. [b] Isolated yield.

(**2b** and **2c**) efficiently, affording the corresponding products **3ad**−**3af** in 76% and 56% yields, respectively (Table 2, entries 2−3). Electron-rich aromatic arylboronic acids with a methoxy group at the *ortho*-, *para*-, or *meta*-position proved to be good substrates for this transformation, affording the corresponding products **3ad**−**3af** in impressive yields (Table 2, entries 4−6). Notably, the fluoro, chloro, and bromo moieties (commonly used for cross-coupling reactions) in phenylboronic acids **2g**, **2h**, and **2i** (Table 2, entries 7−9, 16−18, and 22−24) were all tolerated under this novel coupling and afforded the targeted products in poor to good yields, making further elaborations of the corresponding biaryl products possible. Nevertheless, the reaction became sluggish by using arylboronic acid with electron-withdrawing groups such as a trifluoromethyl substituent at the *para*-position (**2j**) (Table 2, entry 10). It is noteworthy that **3aj** is difficult to prepare from the corresponding aryl halides and phenols via an Ullmann coupling reaction since the electron-withdrawing groups on the aryl will decrease its migratory rate. Moreover, naphthalen-2-ylboronic acid (**2k**) was found to couple with **1a** efficiently and afforded the desired product in 61% yield (Table 2, entry 11).

On the other hand, different electron-deficient groups on the phenyl ring in the nitroarenes was also examined. Not only a formyl group but also other electron-withdrawing groups such as acetyl, phenyl sulpho, and cyano groups deliver the desired product in poor to good yields under the standard reaction conditions (Table 2, entries 1, 19, 26, and 28). However, the reaction of (4-nitrophenyl)(phenyl)-methanone (**1d**) and methyl 4-nitrobenzoate (**1f**) with **2a** failed to afford the corresponding product (Table 2, entries 25 and 27). Nitrobenzene itself and 3-nitrobenzaldehyde (**1h**) resisted the coupling etherification under the same conditions (Table 2, entry 29).

According to relevant reports in the literature,[8] we suggest that the oxygen atom of **3ca** might be derived from water present in the solvent and in the ambient environment. To clarify the source of the oxygen in this reaction, we carried out the Rh-catalyzed reaction of 1-(4-nitrophenyl)ethanone (**1c**) with phenylboronic acid (**2a**) in the presence of $^{18}OH_2$ in dry DMF (Scheme 2).[9] As a result, we found that **3ca**-^{18}O was formed in 56% yield,[10] its ^{18}O content being 40%[11] (see Supporting Information). From this result we can conclude that the oxygen atom is derived from the ambient water during the reaction.

Scheme 2. Isotope Labeling Studies



The mechanism of this coupling reaction remains uncertain at this time. Nevertheless, given this isotope labeling result, two possible pathways can be considered (Scheme 3). In pathway A, nucleophilic attack of nitroarene **1** by a water molecule would generate the phenoxide intermediate **4**.[12] This intermediate could be further coupled with arylboronic acid **2** to produce product **3**. Alternatively in pathway B, oxidative hydroxylation of

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(8) (a) Simon, J.; Salzbrunn, S.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2001**, *66*, 633. (b) Xu, J.; Wang, X.; Shao, C.; Su, D.; Cheng, G.; Hu, Y. *Org. Lett.* **2010**, *12*, 1964.

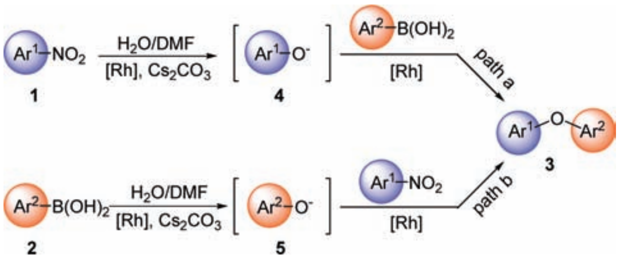
(9) $^{18}OH_2$ was purchased from Aldrich Co. The ^{18}O content in the product was determined by high resolution mass spectrometry (HRMS). We found the relative abundance of 212.0845 (ionic flux: 1020) and 214.0885 (ionic flux: 689) by HRMS. From this result we confirmed by calculation that the ^{18}O content is 40.3%, which greatly exceeds the natural ^{18}O content in **3ca**.

(10) We suppose that the low ^{18}O content is due to scrambling of the oxygen atom ^{16}O by ambient water ($^{16}OH_2$) during the reaction.

(11) The lower yield in relation to that shown in Table 2, entry 19 may be caused by the primary or secondary isotope effect. (a) Wiberg, K. B. *Chem. Rev.* **1955**, *55*, 713. (b) For a review of secondary isotope effects, see: Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.

(12) (a) Marquet, J.; Cayon, E.; Martin, X.; Casado, F.; Gallardo, I.; Moreno, M.; Lluch, J. M. *J. Org. Chem.* **1995**, *60*, 3814. (b) Kobayashi, N.; Higashi, R.; Tomura, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2693.

Scheme 3. Plausible Mechanism



arylboronic acid **2** in water would generate the phenoxide intermediate **5**,[8] which could be converted to product **3** by nucleophile displacement of a nitro group.

In summary, an unprecedented rhodium-catalyzed coupling of arylboronic acids with electron-deficient nitroarenes was developed. This new method provides a simple way to synthesize unsymmetrical diaryl ethers with yields ranging from poor to good. Ongoing work seeks to gain further insights into the mechanism of this reaction and to expand the scope of the coupling of unactivated nitroarenes.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 21072153) and Science and Technology Department of Zhejiang Province (No. 2009R50002) for financial support.

Supporting Information Available. Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.