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Boronic Acid Catalyzed Friedel−Crafts Reactions of Allylic Alcohols with Electron-Rich Arenes and Heteroarenes.

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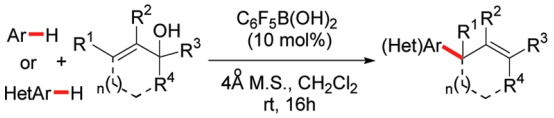
Received October 28, 2009



(Het)Ar−H: furan, indole, pyrrole, methoxyarenes, naphthol

Pentafluorophenylboronic acid catalyzes the regioselective coupling of structurally diverse allylic alcohols with a variety of electron-rich aromatic and heteroaromatic substrates under ambient conditions. The commercially available catalyst is recoverable and air and moisture stable, and the reaction produces water as the only byproduct.

Since its discovery over 130 years ago,[1] the Friedel−Crafts (FC) alkylation reaction has been established as a powerful and versatile method for C−C bond formation.[2] This is due primarily to its broad scope and ability to directly functionalize rings at a C−H bond.[3] Significant disadvantages of classical methods, primarily due to environmental concerns, have been addressed to some extent, namely their reliance on harsh reaction conditions, stoichiometric quantities of electrophile activators, and the resulting waste produced. From an environmental and atom-economical standpoint, the ideal FC process would be catalytic and employ hydroxide as a leaving group on the electrophile and, thus, generate only water as a byproduct of the reaction. This approach has so far been limited, primarily by the poor leaving group ability of the OH group, but has been achieved with some success in recent years with the use of π-activated alcohols as electrophiles.[4] Allylic, propargylic, and benzylic alcohols (or combinations thereof) lead to resonance-stabilized carbocations that can be generated under mild conditions. The products of these reactions have the added advantage of functionality that may be further elaborated.

Several classes of catalysts have been successfully applied to the FC reaction of allylic alcohols, including Bronstead acids,[5] conventional Lewis acids,[6] and transition metals.[7] So far, reaction scope in terms of allylic alcohols, particularly with respect to cyclic ones, remains limited. Given the nature of the proposed allylic carbocation intermediates, regioselectivity in terms of the sight of nucleophilic attack can be problematic. In several cases, a large excess of the nucleophile is required, and all of the methods reported require either strongly acidic or toxic and often expensive metal-based catalysts. Thus, an environmentally benign, mild, selective, and recoverable catalyst would be a useful alternative.

Diversely substituted arylboronic acids are widely available due primarily to their common use in Suzuki−Miyaura cross-coupling reactions.[8] In contrast to their use as reactants, there are only sporadic reports of their use as catalysts,[9] despite several attractive features, including the Lewis acidity of the boron atom, their ability to complex with

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(2) (a) Larock, R. C., *Comprehensive Organic Transformations*: VCH: New York, 1999; (b) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 293−339. (c) Roberts, R. M.; Khalaf, A. A. *Friedel−Crafts Alkylation Chemistry. A Century of Discovery*; Dekker: New York, 1984. (d) Olah, G. A. *Friedel−Crafts and Related Reactions*; Wiley- Interscience: New York, 1964; Vol. II, Part 1.

(3) For a concise review of FC reactions in the context of direct transformations of C−H bonds, see: Dyker, G. In *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 1, pp 137−142.

(4) For an excellent review, see: Bandini, M.; Tragni, M. *Org. Biomol. Chem.* **2009**, *7*, 1501.

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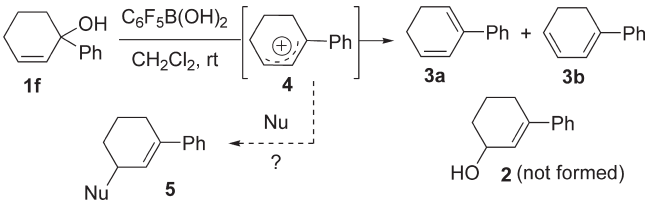
(7) Pd: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (c) Usui, I.; Schmidt, S.; Keller, M.; Breit, B. *Org. Lett.* **2008**, *10*, 1207. Ru: (d) Zaitsev, A. B.; Gruber, S.; Pregosin, P. S. *Chem. Commun.* **2007**, 4692. (e) Zaitsev, A. B.; Gruber, S.; Plüss, P. A.; Pregosin, P. S.; Veiros, L. F.; Wörle, M. *J. Am. Chem. Soc.* **2008**, *130*, 11604. (f) Onodera, G.; Imajima, H.; Yamanashi, M.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *Organometallics* **2004**, *23*, 5841. (g) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945. (h) Yokoyama, Y.; Takagi, N.; Hikawa, H.; Kaneko, S.; Tsubaki, N.; Okuno, H. *Adv. Synth. Catal.* **2007**, *349*, 662.

(8) For reviews, see: (a) *Metal Catalyzed Cross Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) Dedicated special issue of 30 years of cross-coupling: Tamao, K., Hiyama, T., Negishi, E.-i., Eds. *J. Organomet. Chem.* **2002**, 653. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.

(9) See, for example: (a) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876. (b) Tale, R. H.; Adude, R., N. *Tetrahedron Lett.* **2006**, *47*, 7263. (c) Rao, G.; Philipp, M. *J. Org. Chem.* **1991**, *56*, 1505. (d) Debache, A.; Boumold, B.; Amimour, M.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Tetrahedron Lett.* **2006**, *47*, 5697. (e) Debache, A.; Boulcina, R.; Belfaitah, A.; Rhouati, S.; Carboni, B. *Synlett* **2008**, 509. (f) Letsinger, R. L.; MacLean, D. B. *J. Am. Chem. Soc.* **1963**, *85*, 2230. (g) Maki, T.; Ishihara, H.; Yamamoto, H. *Synlett* **2004**, 1355. (h) Wipf, P.; Wang, X. *J. Comb. Chem.* **2002**, *4*, 656. (i) Tale, R. H.; Patil, K. M.; Dapurkar, S. E. *Tetrahedron Lett.* **2003**, 3427. (j) Tale, R. H.; Patil, K. M. *Tetrahedron Lett.* **2002**, *43*, 9715.

DOI: 10.1021/jo9023073 Published on Web 01/07/2010

SCHEME 1. Attempted Allylic Alcohol Rearrangement



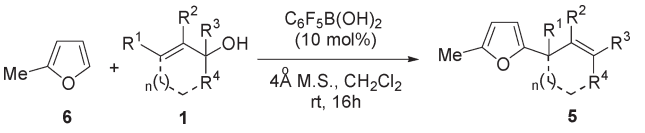
sterically hindered alcohols, solubility in organic solvents, and stability in the presence of air and moisture.[10] Furthermore, arylboronic acids are easily recovered from complex mixtures via basic extraction.[11]

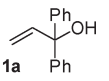
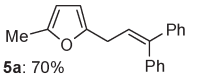
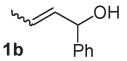
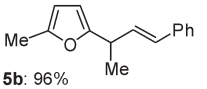
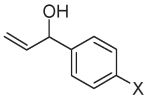
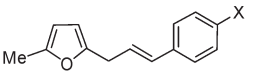
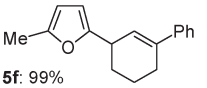
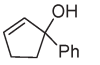
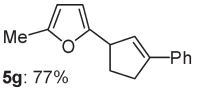
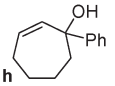
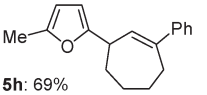
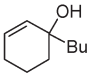
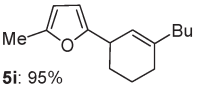
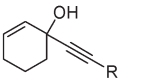
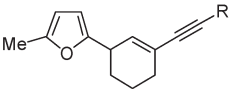
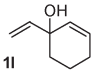
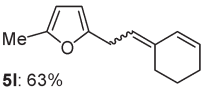
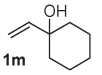
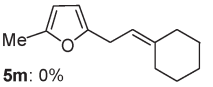
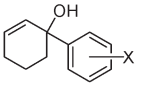
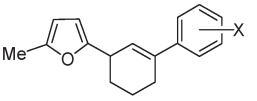
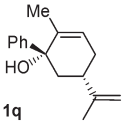
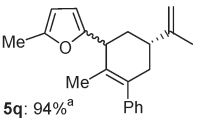
During the course of a study on boronic acid catalyzed rearrangement reactions of allylic alcohols (e.g., **1f** to **2**),[12] we noted the formation of dehydration byproducts (e.g., **3a** and **3b**), which suggested the possible intermediacy of a carbocation (**4**, Scheme 1). We reasoned that these intermediates could be trapped with nucleophiles to afford useful substitution products (**5**).

Indeed, treatment of a mixture of alcohol **1a**, 2-methylfuran (**6**), and 4 Å molecular sieves in CH_2Cl_2 with pentafluorophenylboronic acid at room temperature for 16 h afforded allylated methylfuran **5a** in good yield and excellent regioselectivity with respect to both the position of alkylation on the furan ring and the site of nucleophilic attack (Table 1, entry 1). Similarly, alcohol **1b** underwent addition regio- and stereoselectively to afford **5b** in near-quantitative yield, with only the *E* product observed (entry 2). Compound **1c**, with an unsubstituted phenyl substituent, failed to react under the specified conditions (entry 3), but upon modification with an electron-donating substituent in **1d**, the reaction proceeds in good yield, with excellent regio- and stereoselectivity. Similarly to **1c**, electron-poor derivative **1e** failed to react (entry 5). Endocyclic allylic alcohols are also effective substrates in the reaction. Phenyl-substituted, medium-sized ring substrates **1f**−**h** undergo reaction in good to near-quantitative yields, affording single regioisomers **5f**−**h**, respectively, as products (entries 6−8). Alkyl (**1i**) as well as alkynyl (**1j**,) substrates are well tolerated, albeit with the latter producing products in somewhat decreased yields (entries 9−11). Bis-allylic alcohol substrate **1l** undergoes substitution exclusively at the exocyclic site and exhibits low *E*/*Z* selectivity in the product (**5l**, entry 12). The related, semisaturated exocyclic-only derivative **1m** failed to undergo reaction under the specified conditions (entry 13).

Other aryl-substituted cyclic allylic alcohols (**1n**−**p**) are highly effective substrates for the reaction, regardless of electronic (entries 14 and 15) or steric (entry 16) factors,

TABLE 1. Allylation of 2-Methylfuran



entry	alcohol (**1**)	product (**5**): yield (%)
1	 **1a**	 **5a**: 70%
2	 **1b**	 **5b**: 96%
		
3	**1c**: X = H	**5c**: 0%
4	**1d**: X = OMe	**5d**: 82%
5	**1e**: X = F	**5e**: 0%
6	 **1f**	 **5f**: 99%
7	 **1g**	 **5g**: 77%
8	 **1h**	 **5h**: 69%
9	 **1i**	 **5i**: 95%
		
10	**1j**: R = Ph	**5j**: 74%
11	**1k**: R = TMS	**5k**: 63%
12	 **1l**	 **5l**: 63%
13	 **1m**	 **5m**: 0%
		
14	**1n**: X = 4-CF_3	**5n**: 99%
15	**1o**: X = 4-OMe	**5o**: 95%
16	**1p**: X = 2-Me	**5p**: 98%
17	 **1q**	 **5q**: 94%[a]

[a]The product is an inseparable 10:3 mixture of diastereomers.

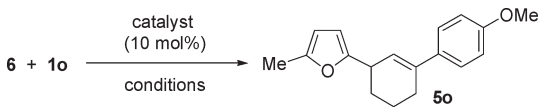
affording products **5n**−**p** in near-quantitative yields. Similarly, enantiomerically and diastereomerically pure carvone-derived

(10) *Boronic Acids—Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, 2005.

(11) Bhat, S.; Punachithaya, S.; Ganesh, S. Int. Patent 019229, **2005**. See also the Supporting Information

(12) McCubbin, J. A. Unpublished results. For related reactions, see: (a) Leleti, R. R.; Hu, B.; Prashad, M.; Repič, O. *Tetrahedron Lett*. **2007**, *48*, 8505. (b) Yoshihito, A.; Akio, O.; Hiroshi, I. *Chem. Pharm. Bull*. **1982**, *30*, 881. (c) Mukhopadhyay, M.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *J. Org. Chem*. **1995**, *60*, 2670. (d) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc*. **2005**, *127*, 2842. (e) Morrill, C.; Beutner, G.; Grubbs, R. H. *J. Org. Chem*. **2006**, *71*, 7813. (f) Ge, W.; Ampa, J.; Rudy, L. L. *Inorg. Chem. Acta* **2005**, *358*, 933. (g) Frank, R. F.; Rudy, L. L.; Ge, W. *Inorg. Chem. Commun*. **2002**, *5*, 384. (h) Schoop, T.; Roesky, H. W.; Noltermeyer, M.; Schmidt, H.-G. *Organometallics* **1993**, *12*, 571. (i) Jacob, J.; Espenson, J. H.; Jensen, J. H.; Gordon, M. S. *Organometallics* **1998**, *17*, 1835.

TABLE 2. Comparison with Other Catalysts



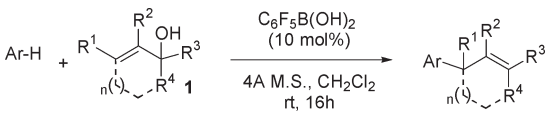
entry	catalyst	conditions	yield (%)
1	$C_6F_5B(OH)_2$	4 Å M.S. CH_2Cl_2, 16 h, rt	95
2	TsOH	CH_3CN, 16 h, rt	38
3	$BF_3 \cdot OEt_2$	CH_2Cl_2, 16 h, rt	81
4	$FeCl_3$	$MeNO_2$, 16 h, rt	52
5	$AuCl_3$	4 Å M.S. CH_2Cl_2, 16 h, rt	92

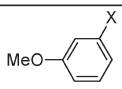
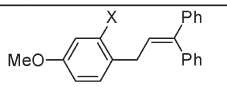
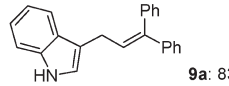
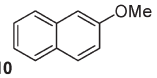
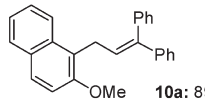
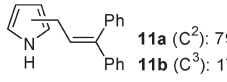
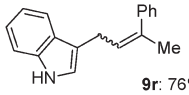
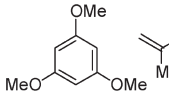
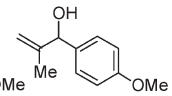
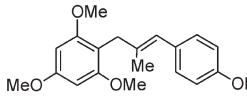
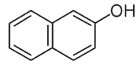
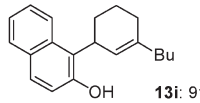
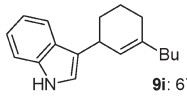
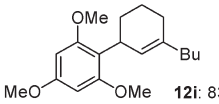
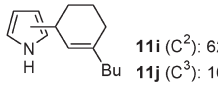
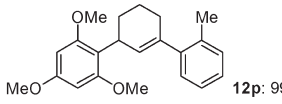
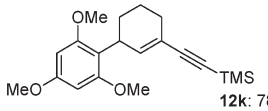
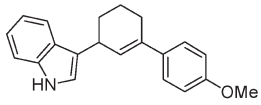
alcohol **1q** affords product **5q** in excellent yield, but as a 10:3 mixture of diastereomers.

In order to compare our method with established protocols for FC reactions of this type, we tested the reaction of cyclic substrate **1o** with **6** with a selection of known catalysts (Table 2). In each case, the literature method was adhered to with the exception of catalyst loading (10 mol % was used in each case), and the molar ratio of alcohol to aromatic substrate (a 1:1 ratio was used) so that results in terms of yield and purity could be compared directly.[13] As a protic acid, TsOH afforded the product in low yield (entry 2), with significant byproduct formation as illustrated by the NMR spectra of the crude reaction product **5o**. By comparison, BF_3 was effective, affording the product in moderate purity and good yield (entry 3).[14] $FeCl_3$, which has been shown to be very effective in FC reactions of benzylic alcohols,[15] afforded the product in modest yield and with significant impurities (entry 4). Of the four alternative catalysts tested, $AuCl_3$ performed the best (entry 5).[6d] These conditions afforded **5o** in comparable yield to ours (entry 1), with only very minor impurities evident by NMR. However, pentafluorophenylboronic acid is significantly less expensive than $AuCl_3$ on a per mole basis.

Having established the scope of the reaction with 2-methylfuran as the nucleophile, we began testing the efficacy of a variety of other electron-rich heterocycles in the reaction with a selection of our allylic alcohol substrates (Table 3). 1,3-Dimethoxybenzene (**7**), indole (**9**), 2-methoxynaphthalene (**10**), and pyrrole (**11**) all react with alcohol **1a** to afford the corresponding products (**7a**, **9a**−**11a**) in good to excellent yields, with excellent regioselectivity with respect to the site of allylic substitution (entries 1, 3−5). In the case of pyrrole, a ca. 5:1 mixture of C^2 and C^3 allylation products was observed (entry 5). In contrast, anisole (**8**) failed to react with **1a** (entry 2). Indole reacts with alcohol **1r** to afford the product **9r** in good yield, but with moderate *E*/*Z* selectivity as an inseparable mixture of stereoisomers (entry 6). 1,3,5-Trimethoxybenzene **12** is also an effective nucleophile, affording monoallylated product **12s** in moderate yield, along with a small amount of diallylated product **12t** (entry 7). Free 2-naphthol **13** alkylates selectively at C^1 upon treatment with

TABLE 3. Allylation of Other Nucleophiles



entry	Ar-H	1	product: yield (%)
			
1	**7**: X = OMe	**1a**	**7a**: 95%
2	**8**: X = H	**1a**	**8a**: 0%
3	 **9**	**1a**	 **9a**: 83%
4	 **10**	**1a**	 **10a:** 89%
5	 **11**	**1a**	 **11a** (C^2): 79% **11b** (C^3): 17%
6	**9**	 **1r**	 **9r**: 76%[a]
7	 **12**	 **1s**	 **12s**: 58%[b]
8	 **13**	**1i**	 **13i**: 91%
9	**9**	**1i**	 **9i**: 67%
10	**12**	**1i**	 **12i**: 83%
11	**11**	**1i**	 **11i** (C^2): 62% **11j** (C^3): 16%
12	**12**	**1p**	 **12p**: 99%
13	**12**	**1k**	 **12k**: 78%
14	**9**	**1o**	 **9o**: 95%

[a]Inseparable 4:1 mixture of *E*/*Z* isomers. [b]23% of disubstituted product (**12t**) was isolated.

cyclic alcohol **1i** to afford **13i** in high yield (entry 8). Compounds **9**, **12**, and **11** are also effective substrates for

(13) Purity of the products was compared qualitatively by comparison of the ^1H and ^{13}C NMR spectra of the reaction mixtures prior to chromatographic purification. See the Supporting Information.

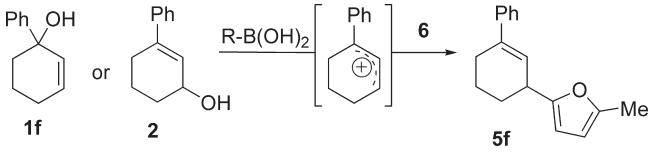
(14) Liu, J.; Muth, E.; Flörke, U.; Henkel, G.; Merz, K.; Sauvageau, J.; Schwake, E.; Dyker, E. *Adv. Synth. Catal.* **2006**, *348*, 456.

(15) Mertins, K.; Iovel, I.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 238.

coupling with cyclic derivative **1i**, affording the corresponding products **9i**, **12i**, and **11i** in good yields. Similarly to coupling with **1a** (entry 5), pyrrole (**11**), upon treatment with **1i**, affords a mixture of regioisomers with moderate selectivity (entry 11).

In contrast to the mixtures obtained upon reaction of **12** with acyclic alcohols (entry 7), reaction with aryl- or alkynyl-substituted cyclic derivates **1p** and **1k** affords monoallylated products exclusively (**12p** and **k**, entries 12 and 13). A second allylation in these cases may be precluded for steric reasons. Indole is an effective nucleophile for reaction with electron-rich aryl-substituted alcohol **1o** and affords the product **9o** in excellent yield (entry 14).

SCHEME 2. Mechanistic Study



In all examples of the coupling reaction studied thus far, only products attributable to a formal conjugate nucleophilic addition to the allylic alcohol have been observed, which suggests the possibility that an S_N2' mechanism is involved. On the other hand, the site of attack also consistently corresponds to the least hindered terminus of an allylic carbocation, which would be formed during the course an S_N1-type process. In order to determine which mechanism is operative, we prepared alcohol **2** and subjected it to the reaction conditions in the presence of **6**. We obtained in 96% isolated yield product **5f** (Scheme 2), a nearly identical result for the analogous reaction of **1e** (cf. Table 1, entry 6). This suggests formation of a delocalized carbocation followed by nucleophilic attack, where steric effects control the regioselectivity. Indeed, such a mechanism is consistent with the partial loss of stereochemical information in Table 1, entry 17, and the failure of substrates that would lead to poorly stabilized carbocations (e.g., **1e**,**m**) to undergo reaction.

In summary, we have developed a mild, catalytic method for the allylation of electron-rich aromatic and heteroaromatic rings. This method is amenable to a large array of cyclic and acyclic allylic substrates without the need for preactivation of the alcohol moiety. This protocol compares favorably to other methods in terms of yield and selectivity for the desired product. Initial studies suggest that a resonance-stabilized carbocation is involved and the observed high regioselectivity is due mainly to steric control. Further mechanistic studies and expansion of the scope of this reaction are ongoing in our laboratory.

Experimental Section

5a. To a vial containing **1a** (0.5 mmol) in CH_2Cl_2 (2.5 mL) were added freshly dried powdered 4 Å molecular sieves (500 mg), **6** (1.0 equiv), and pentafluorophenyl boronic acid (11 mg, 0.1 equiv). The vial was capped and the mixture allowed to stir for 16 h at room temperature. The suspension was filtered through a 1 in. plug of silica, eluting with CH_2Cl_2, and the eluent concentrated in vacuo. Purification of the residue by flash chromatography (0−2% EtOAc/Hex) afforded the desired product (**5a**) as a colorless oil (96 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.33 (m, 2H), 7.31−7.28 (m, 1H), 7.25−7.22 (m, 7H), 6.25−6.21 (t, J = 7.5 Hz, 1H), 5.90−5.89 (d, J = 3.0 Hz, 1H), 5.85−5.83 (d, J = 3.0 Hz, 1H), 3.41−3.39 (d, J = 7.5 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 150.6, 143.1, 142.3, 139.5, 129.8, 128.2, 128.1, 127.4, 127.14, 127.10, 124.4, 105.9, 105.8, 29.0, 13.5; FTIR (neat) υ 3057, 3027, 2921, 1953, 1889, 1661, 1494, 1445, 1020, 756 cm^{-1}; HRMS (m/z) calcd for $C_{20}H_{17}O$ 273.1280, found 273.1282.

Acknowledgment. Financial support of this work was provided by the University of Winnipeg in the form of a Major Research Grant (J.A.M) and the Natural Sciences and Engineering Research Council of Canada (O.V.K).

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.