ChemInform Abstract: Rapid Nickel-Catalyzed Suzuki-Miyaura Cross-Couplings of Aryl Carbamates and Sulfamates Utilizing Microwave Heating.

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Rapid Nickel-Catalyzed Suzuki−Miyaura Cross-Couplings of Aryl Carbamates and Sulfamates Utilizing Microwave Heating

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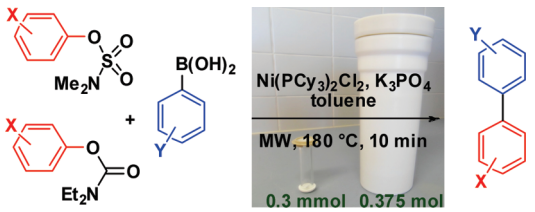
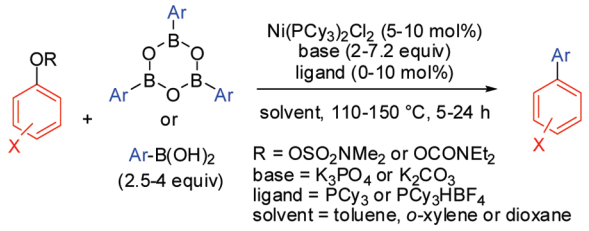


High-speed and scalable nickel-catalyzed cross-coupling of arylboronic acids with aryl carbamates and sulfamates is achieved by using sealed-vessel microwave processing.

In recent years Ni-catalyzed carbon−carbon cross-coupling transformations involving phenol derivatives as electrophiles have attracted a substantial amount of interest.[1] In contrast to the more commonly used aryl halides, phenol derivatives originate from different precursors and therefore represent a valuable extension of the spectrum of electrophilic cross-coupling partners. Of equal importance, replacement of the traditionally used Pd with less expensive Ni-based catalyst systems can significantly lower costs for cross-couplings of this type when performed on scale. Aryl triflates[2] and related sulfonates[3] have frequently been investigated even at the early stages of Ni-catalyzed cross-coupling chemistry, but their high cost and/or instability has so far limited their use. To address this concern, other types of phenol derivatives such as ethers,[4] phosphoramides,[5] carboxylates,[6] phenolate,[7] and sulfate[8] derivatives have been intensely investigated in the past few years in a variety of Ni-catalyzed cross-coupling reactions.

SCHEME 1. Nickel-Catalyzed Suzuki−Miyaura Cross-Couplings of Aryl Carbamates and Sulfamates with Aryl Boronic Acids[9−11]



Recently, the groups of Garg,[9] Snieckus,[10] and Shi[11] have independently introduced the use of aryl carbamates and/or sulfamates as electrophilic coupling partners for Ni-catalyzed Suzuki−Miyaura cross-coupling reactions (Scheme 1). The ready availability, pronounced stability under a variety of reaction conditions, and ease of preparation of these phenolic substrates makes these coupling protocols highly attractive from the synthetic point of view. In all three reports the commercially available and air/moisture stable $Ni(PCy_3)_2Cl_2$ catalyst was employed.[9−11]

While Garg[9] used standard aryl boronic acids as nucleophilic coupling partners for carbamates and sulfamates, the work of Snieckus[10] and Shi[11] described the use of aryl boroxines for cross-couplings with carbamates. Despite the advantages of these novel Suzuki−Miyaura protocols, the coupling efficiency with aryl boronic acids in most of these transformations (except for aryl sulfamates) is only moderate for nonfused aromatic aryl substrates, even in the presence of a large excess of the boronic acid (Scheme 1).[9−11] Most importantly, these methods suffer from exceedingly long reaction times at an elevated temperature regime (typically 5−24 h at 110−150 °C) and the necessity to employ

(1) For reviews, see: (a) Rosen, B. M.; Quasdorf, K W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* DOI: 10.1021/cr100259t. Published Online: Dec 6, 2010. (b) Yu, D.-G.; Li, B.-J; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.

(2) (a) Quesnelle, C. A.; Familoni, O. B.; Snieckus, V. *Synlett* **1994**, 349. (b) Han, J. W.; Tokunaga, N.; Hayashi, T. *Synlett* **2002**, 871. (c) Melzig, L.; Gavryushin, A.; Knochel, P. *Org. Lett.* **2007**, *9*, 5529. (d) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (e) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733.

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(6) (a) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (b) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (c) Li, B.-J.; Li, Y.-Z.; Lu, X.-Y.; Liu, J.; Guan, B.-T.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 10124. (d) Sun, C.-L.; Wang, Y.; Zhou, X.; Wu, Z.-H.; Li, B.-J.; Guan, B.-T.; Shi, Z.-J. *Chem.—Eur. J.* **2010**, *16*, 5844. (e) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 2929.

(7) Yu, D.-G.; Li, B.-J.; Zheng, S.-F.; Guan, B.-T.; Wang, B.-Q.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4566.

(8) Guan, B.-T.; Lu, X.-Y.; Zheng, Y.; Yu, D.-G.; Wu, T.; Li, K.-L.; Li, B.-J.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 396.

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(10) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.

(11) Xu, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884.

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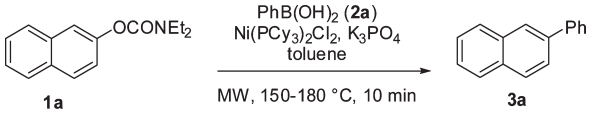
TABLE 1. Optimization Studies for Microwave-Assisted Cross-Coupling of 2-Naphthyl Carbamate 1a with $PhB(OH)_2$ (2a)[a]



entry	**2a** (equiv)	catalyst (mol %)	K_3PO_4 (equiv)	T (°C)	time (min)	conv (%)[b]
1	4	10	7	180	10	94
2	4	10	4	180	10	75
3	2.5	10	7	180	10	94
4	2.5	5	7	180	10	95 (87)[c]
5	2.5	5	7	150	10	78
6	2.5	2	7	180	10	89
7	2	5	7	180	10	85
8[d]	2.5	5	7	180	10	93 (86)[c]

[a]Reactions were performed with sealed vessel single-mode microwave heating (Monowave 300) with internal fiber-optic temperature control and magnetic stirring on a 0.3 mmol scale of **1a**, using 2 mL of toluene as solvent. [b]Conversions were determined via peak area integration of the obtained GC-MS spectra. [c]Isolated yield. [d]Performed in a SiC reaction vessel.

additional quantitites of phosphine ligand to achieve high conversions for difficult substrates.[10,11]

Employing controlled sealed-vessel microwave heating we herewith report an improved protocol that allows the execution of these intriguing coupling reactions in only 10 min with use of standard aryl boronic acids as coupling partners. Our method avoids the use of additional phosphine ligands[10,11] and—in several cases—utilizes lower catalyst loadings and reduced boronic acid stoichiometry. We also demonstrate the scalability of these new microwave protocols up to a 0.375 mol scale in the context of the preparation of 2-(4-tolyl)benzonitrile, a key intermediate in the synthesis of the angiotensin II receptor antagonist losartan.

Using the conditions reported by Garg[9] as an initial reference point (5−10 mol % of $Ni(PCy_3)_2Cl_2$, 2.5−4 equiv of boronic acid, and 4−7.2 equiv of K_3PO_4), a series of coupling experiments involving 2-naphthyl carbamate **1a** and phenylboronic acid (**2a**) were performed in a single-mode microwave reactor with accurate internal temperature monitoring.[12] After considerable experimentation varying reaction times and temperatures we discovered that nearly full conversion in this cross-coupling reaction could be obtained in toluene at 180 °C within <1 h. Fine-tuning of the reaction parameters ultimately led to conditions that utilized 5 mol % of the Ni catalyst and 2.5 equiv of boronic acid at 180 °C for 10 min, resulting in a 87% isolated yield of desired biaryl product **3a** (Table 1, entry 4). This outcome is comparable to the yields reported by Garg,[9] Snieckus,[10] and Shi[11] for similar substrates, albeit requiring reaction times of 20−24 h. Control experiments employing a reaction vial made out of strongly microwave absorbing silicon carbide (SiC)[13] demonstrated that the improvements in reaction rate are the result of a purely thermal effect (Table 1, entry 8).

To explore the scope and limitations of this microwave-assisted cross-coupling protocol a series of aryl carbamate and sulfamate substrates **1** were reacted with arylboronic acids **2a**−**e** utilizing the optimized reaction conditions shown in Table 1. Gratifyingly, although the coupling reaction of nonfused aryl carbamates has been reported to be challenging and sensitive to electronic factors,[9,10] we find that in addition to the naphthyl derivatives (Table 2, entries 1−4) also nonfused aryl derivatives display a high reactivity under these conditions and lead to the corresponding cross-coupled biaryl products **3e**−**n** in high yields (Table 2, entries 5−15).

In agreement with Snieckus[10] we find that for simple aryl substrates, electron-withdrawing group substituted systems show somewhat higher reactivity (entries 5, 6, and 10) compared to those having electron-donating groups (entries 7, 8, 9, 12, and 13). However, under controlled microwave conditions at 180 °C the yields for these more challenging substrates are significantly higher compared to experiments performed with conventional heating.[9,10] Furthermore, heteroaromatic carbamates (entries 14 and 15) as well as a sterically highly congested 2,6-disubstituted substrate (entry 12) also participate successfully in the desired cross-coupling process with arylboronic acids. The optimized microwave conditions thus provide high conversions also for aryl carbamates which have been previously reported as low-reactive electrophiles in these Suzuki−Miyaura cross-coupling reactions.[9,10] In the case of aryl sulfamate substrates, the reported yields using conventional heating (110 °C, 24 h) by Garg[9] are similar to the yields obtained with microwave heating (Table 2) under otherwise more or less identical reaction conditions. Therefore, the main advantage here is a reduction of the required reaction time. Apart from different aryl carbamates and sulfamates, arylboronic acids coupling partners bearing electron-withdrawing (entries 2 and 3) and electron-donating groups are also tolerated (entries 6, 7, 9, 13, and 15).

An example involving the preparation of 2-aminobiphenyl derivatives **8** via the Ni-catalyzed Suzuki−Miyaura route is highlighted in Scheme 2. To prevent *N* versus *O* selectivity problems encountered during classical *N*-acetyl protection, the amino group in 2-aminophenol (**4**) was protected with succinic anhydride.[14,15] In the next step, aryl sulfamate **6** was prepared, which was subsequently subjected to the optimized microwave-assisted Suzuki−Miyaura cross-coupling protocol (Table 2), providing—despite severe steric hindrance—the desired biaryl substrates **7** in high yield. Finally, basic

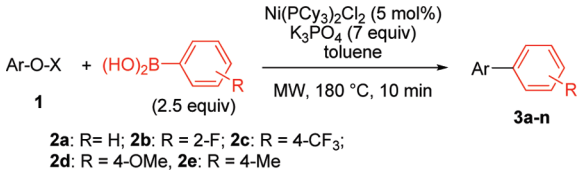
(12) For the importance of internal temperature measurement in microwave chemistry and a description of the microwave reactor, see: Obermayer, D.; Kappe, C. O. *Org. Biomol. Chem.* **2010**, *8*, 114 and references cited therein. See also ref 13.

(13) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321.

(14) Caulfield, M. J.; Looney, M. G.; Pittard, R. A.; Solomon, D. H. *Polymer* **1998**, *39*, 6541.

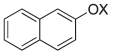
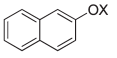
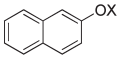
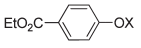
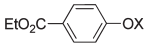
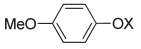
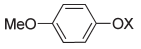
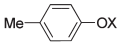
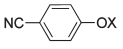
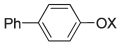
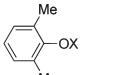
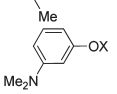
(15) Attempts to perform cross-coupling experiments with the cyclic carbamate derivative of 2-hydroxyaniline were unsuccessful.

TABLE 2. Aryl Carbamates and Sulfamates in Microwave-Assisted Suzuki−Miyaura Cross-Coupling Reactions[a]



1 3a-n

2a: R= H; **2b**: R = 2-F; **2c**: R = 4-CF_3;
2d: R = 4-OMe, **2e**: R = 4-Me

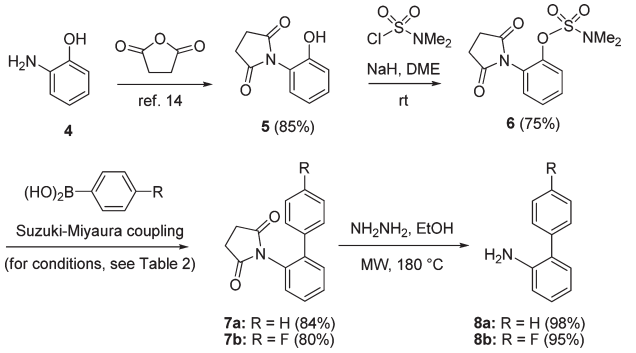
entry	1	X	2	3 (yield%)
1		X = $CONEt_2$ (**1a**) X = SO_2NMe_2 (**1A**)	**2a**	**3a** (87) **3a** (90)
2		X = $CONEt_2$ (**1a**) X = SO_2NMe_2 (**1A**)	**2b**	**3b** (90) **3b** (93)
3		X = $CONEt_2$ (**1a**) X = SO_2NMe_2 (**1A**)	**2c**	**3c** (74) **3c** (80)
4		X = $CONEt_2$ (**1b**) X = SO_2NMe_2 (**1B**)	**2a**	**3d** (85) **3d** (87)
5		X = $CONEt_2$ (**1c**) X = SO_2NMe_2 (**1C**)	**2a**	**3e** (80) **3e** (80)
6		X = $CONEt_2$ (**1c**) X = SO_2NMe_2 (**1C**)	**2d**	**3f** (93) **3f** (93)
7		X = $CONEt_2$ (**1d**) X = SO_2NMe_2 (**1D**)	**2e**	**3g** (72) **3g** (75)
8		X = $CONEt_2$ (**1d**) X = SO_2NMe_2 (**1D**)	**2a**	**3h** (67) **3h** (70)
9		X = $CONEt_2$ (**1e**) X = SO_2NMe_2 (**1E**)	**2d**	**3g** (82) **3g** (85)
10		X = $CONEt_2$ (**1f**) X = SO_2NMe_2 (**1F**)	**2a**	**3i** (80) **3i** (83)
11		X = $CONEt_2$ (**1g**) X = SO_2NMe_2 (**1G**)	**2a**	**3j** (82) **3j** (85)
12		X = $CONEt_2$(**1h**) X = SO_2NMe_2(**1H**)	**2a**	**3k** (57) **3k** (60)
13		X = $CONEt_2$(**1i**) X = SO_2NMe_2(**1I**)	**2d**	**3l** (60) **3l** (62)
14		X = $CONEt_2$(**1j**)	**2a**	**3m** (84)
15		X = $CONEt_2$(**1j**)	**2d**	**3n** (92)

[a]Reaction conditions: sealed vessel single-mode microwave heating (Monowave 300) with internal fiber-optic temperature control and magnetic stirring; 0.3 mmol of **1**, 0.75 mmol of **2**, 0.015 mmol of $Ni(PCy_3)_2Cl_2$, 2.1 mmol of K_3PO_4 in 2 mL of toluene; 180 °C for 10 min.

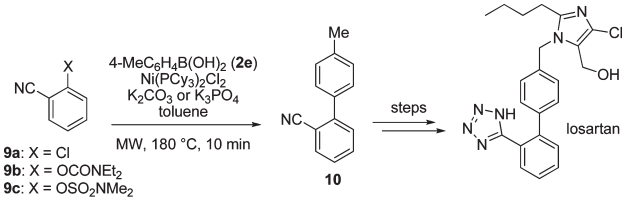
deprotection of the imide[16] furnished the corresponding 2-aminobiphenyl derivatives **8a**,**b** in 52% overall yield.

In an attempt to apply the above method for the preparation of 2-amino-4′-chlorobiphenyl (**8c**: R = Cl), a key intermediate in the industrial synthesis of the fungicide Boscalid,[17]

SCHEME 2. Preparation of 2-Aminobiphenyl Derivatives 8 via Nickel-Catalyzed Suzuki−Miyaura Cross-Coupling



SCHEME 3. Preparation of the Sartan Precursor 2-(4-Tolyl)-benzonitrile (10)



for **9a**: 1.5 equiv **2e**, 2 mol% Ni catalyst, 2 equiv K_2CO_3; yield 87%
for **9b**: 2.5 equiv **2e**, 5 mol% Ni catalyst, 7 equiv K_3PO_4; yield 85%
for **9c**: 2.5 equiv **2e**, 5 mol% Ni catalyst, 7 equiv K_3PO_4; yield 90%

a limitation of these cross-coupling reactions involving C−O bond activation in phenolic substrates became evident. Using 4-chloroboronic acid as nucleophilic substrate in the coupling step (**6** → **7**) resulted in a complex mixture of products, including polymeric materials. Since aryl chlorides are known to undergo Suzuki−Miyaura cross-coupling with boronic acids in the presence of Ni catalysts, this is not surprising.[18] Competition experiments have demonstrated that aryl chlorides are far more reactive compared to the corresponding carbamates and sulfamates, and that very efficient cross-couplings of a diverse range of aryl chloride substrates with boronic acids could be achieved by using only slightly modified microwave reaction conditions (see the Supporting Information, including Table S1, for details).

Finally, in order to highlight the synthetic usefulness of these high-speed microwave protocols and to investigate the scalability of these reactions, the preparation of 2-(4-tolyl)-benzonitrile (**10**), a key intermediate in the synthesis of the angiotensin II receptor antagonist losartan (and related compounds), was performed (Scheme 3).[19] Using both types of electrophilic coupling precursors (aryl chloride **9a** and aryl carbamate/sulfamate **9b**,**c**) high yields (85−90%) of the corresponding ortho-substiuted biaryl derivative **10** were

(16) Martin, S. F.; Limberakis, C. *Tetrahedron Lett.* **1997**, *38*, 2617.
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obtained applying the appropriate cross-coupling conditions (Scheme 3).

All cross-coupling transformations described herein were initially performed on a 0.3 mmol scale with 2 mL of solvent in a single-mode microwave reactor employing a 10 mL Pyrex reaction vial. Since microwave-assisted transformations are not always easy to scale,[20] the cross-coupling of the chloro and carbamate precursors (**9a** and **9b**) with 4-tolylboronic acid (**2e**) was additionally evaluated on a 10 times higher scale employing the same microwave instrument (Monowave 300), albeit with a larger vessel.[12] In the event, nearly identical yields compared to the small scale experiment were obtained. To obtain sufficient quantities of 2-(4-tolyl)benzonitrile (**10**) for further chemical manipulation, the coupling of aryl chloride **9a** with 4-tolylboronic acid (**2e**) was ultimately performed in a recently developed multimode benchtop microwave reactor (Masterwave) that allows batch processing of up 700 mL volume in a 1 L PTFE reactor.[21] Gratifyingly, performing this cross-coupling reaction on a 0.375 mol scale (~700 mL volume) provided very similar results in terms of yield and product purity as in the smaller scale experiments (see the Supporting Information for further details).

In conclusion, a rapid and highly efficient microwaveassisted procedure for the Ni-catalyzed Suzuki−Miyaura cross-coupling of aryl carbamates and sulfamates with boronic acids was developed. Compared to the originally published methods by Garg,[9] Snieckus,[10] and Shi,[11] this improved protocol features coupling times of only 10 min, and in a number of instances allows a reduction in catalyst loading and boronic acid stoichiometry, while retaining high coupling efficiency. The improved conditions presented herein make these intriguing carbon−carbon cross-coupling transformations involving phenol derivatives as electrophiles significantly more practical, and will stimulate the further development of this area. We have also established that the microwave conditions work exceedingly well with aryl chlorides as electrophilic cross-coupling partners, and have additionally demonstrated the scalability of the coupling process up to 700 mL scale.

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Experimental Section

General Procedure for the Cross-Coupling Reaction of Aryl Carbamate and/or Aryl Sulfamates with Aryl Boronic Acids (Table 2). Aryl carbamate and/or aryl sulfamate (0.3 mmol), arylboronic acid (0.75 mmol, 2.5 equiv), potassium phosphate (2.1 mmol, 450 mg, 7 equiv), and bis(tricyclohexylphosphine)-nickel(II) chloride (10.3 mg, 0.015 mmol, 5 mol %) were added to a 10 mL flame-dried microwave vial containing a Teflon-coated stir bar. After the vial was sealed dry toluene (2 mL) was transferred to the vial and the mixture was purged with Ar for 2 min. The mixture was subsequently placed in the microwave cavity and irradiated for 10 min at 180 °C (hold time). After cooling, ethyl acetate (10 mL) was added and the crude reaction mixture was subsequently washed with 25% aqueous ammonia (2 × 10 mL). The aqueous ammonium layer was extracted again with ethyl acetate (2 × 10 mL). The combined organic phases were dried over $MgSO_4$ and the residue after evaporation purified by flash chromatography by using a mixture of petroleum ether and ethyl acetate as eluent solvent. All compounds are literature known and NMR data are in good agreement with published data.

2-Phenylnaphthalene (3a):[9]**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.48 (m, 1H), 7.53−7.60 (m, 4H), 7.78−7.83 (m, 3H), 7.91−7.99 (m, 3H), 8.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 138.6, 133.7, 132.6, 128.9, 128.4, 128.2, 127.7, 127.5, 127.4, 126.3, 126.0, 125.8, 125.6.

3-Phenylpyridine (3m):[10]**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.52 (m, 4H), 7.57−7.61 (m, 2H), 7.89 (dt, J = 7.5, 1.8 Hz, 1H), 8.60 (dd, J = 4.8, 1.8 Hz, 1H), 8.87 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 148.2, 137.8, 136.6, 134.4, 129.1, 128.1, 127.1, 123.5.

3-(4-Methoxyphenyl)pyridine (3n):[10]**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.03 (d, J = 8.7 Hz, 2H), 7.32−7.37 (m, 1H), 7.53 (d, J = 9 Hz, 2H), 7.82−7.86 (m, 1H), 8.56 (dd, J = 4.8, 1.5 Hz, 1H), 8.83 (d, J = 1.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 148.0, 147.8, 136.2, 133.8, 130.2, 128.2, 123.5, 114.5, 55.4.

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