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Phosphine-Free Palladium-Catalyzed C−H Bond Arylation of Free (N−H)-Indoles and Pyrroles

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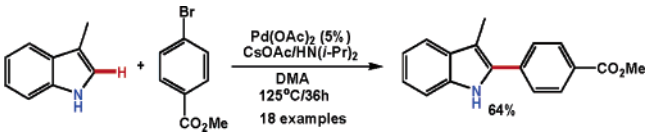

This paper describes a phosphine-free palladium-catalyzed method for direct *C*-arylation of free (N−H)-indoles and pyrroles with iodo- and bromoarene donors. Employing commercially available materials, this new and operationally simple procedure provides a rapid entry to a wide range of *C*-arylated (N−H)-indoles including derivatives of tryptamine. In the course of this study, a profound halide effect was uncovered, affecting both the efficiency and regioselectivity of indole arylation.

Many natural products and pharmaceuticals contain *C*-arylated azole core structures. Although palladium-catalyzed cross-coupling reactions provide an efficient entry to these compounds, such protocols require the preparation of functionalized heteroarenes (e.g., boronates and halides).[1] For this reason, considerable effort has been directed toward the development of *C*-arylation reactions of azole and related heteroarenes via direct C−H bond functionalization of the parent heteroarenes.[2] Despite significant progress in this area, *C*-arylation of free (N−H)-indoles and pyrroles with haloarene donors remains an unsolved problem. One approach relies on the protection of the amine functionality prior to the palladium-catalyzed arylation step, either by formation of azole magnesium[3,4] or azole zinc salts,[5] or by installing the SEM protecting group [SEM = 2-(trimethylsilyl)-ethoxymethyl].[6] Direct *C*-arylation of free indoles and pyrroles has recently been described with a rhodium catalyst and a mild base.[7] However, this system did not tolerate hindered substrates containing a substituent in the 3-position of indole or in the 2-position of the haloarene donor.[8−10] As part of our continuing efforts in the broad area of C−H bond functionalization,[11] we herein describe the development of a simple phosphine-free palladium catalytic system for the direct *C*-arylation of free indoles and pyrroles. This protocol not only obviates the protection of the N−H function, but also accommodates both ortho-substituted aryl donors and 3-substituted indoles, including tryptamine derivatives. On a strategic level, this method (as well as other catalytic C−H functionalization reactions) provides new approaches to complex heteroarenes, advantages of which are particulalry apparent in the context of preparation of a series of compounds, wherein established multistep methods become inefficient.[11]

We have previously reported a catalytic system [$Pd(OAc)_2$/PPh_3/CsOAc] for selective *C*-arylation of *N*-alkyl indoles with iodoarene donors.[2e] Although this method performed poorly with free (N−H)-indoles, closer examination revealed that the efficiency could be improved by increasing the substrate concentration. Specifically, the yield was nearly tripled, from 6% to 16% of 2-phenylindole, when the indole concentration was increased from 1.25 to 5.0 M (Table 1, entries 1 and 2). In addition to this concentration effect, we also found that phosphine ligands inhibited the reaction.[12] A representative collection of phosphine and carbene ligands, frequently used in arylation coupling chemistry, was examined (Table 1, entries 3−7). While the presence of the IPr carbene ligand had a small effect, PPh_3 exhibited strong inhibition, as clearly demonstrated by a dramatic increase in the reaction yield and selectivity when the amount of PPh_3 was decreased.

Thus $Pd(OAc)_2$ as the catalyst and CsOAc as the base provided the highest yield of 2-phenylindole. Specifically, a concentrated mixture of indole (5.0 M), PhI, and CsOAc in DMA, when heating at 125 °C for 24 h, afforded 75% GC yield of *C*-arylated indoles in 15:1 regioisomeric ratio favoring 2-phenylindole (Table 1). We were pleased that no *N*-phenylindole was observed under these simple conditions, which is consistent with the requirement for bulky σ-donor ligands at the palladium metal for the *N*-arylation to proceed.[13] Also, the importance of CsOAc base should be noted—it is too weak to

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(7) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996−4997.

(8) A recent report described C-2 arylation of free and *N*-methyl indoles with $[Ar_2I]BF_4$ as the arene donor, see: Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973.

(9) New methods for arylation of the electron-deficient C-2 position of imidazole substrates, see: (a) Lewis, J. C.; Wu, J. Y.; Bergman, R. G.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1589−1591. (b) Bellina, F.; Cauteruccio, S.; Rossi, R. *Eur. J. Org. Chem.* **2006**, 1379−1382.

(10) For recent advances in catalytic C−H arylation of arenes, see: (a) Campeau, L. C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581−590. (b) Daugulis, O.; Zaitsev, V. G. *Angew. Chem., Int. Ed*. **2005**, *44*, 4046−4048. For a recent application of direct coupling in total synthesis, see: (c) Bowie, A. L.; Hughes, C. C.; Trauner, D. *Org. Lett*. **2005**, *7*, 5207−5209.

(11) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72.

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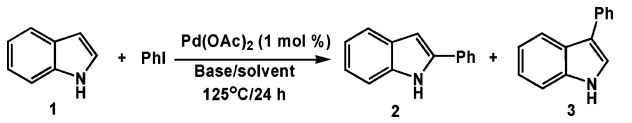
TABLE 1. Ligand Effect on Palladium-Catalyzed Arylation of Indole with PhI[a]



entry	ligand (mol %)	base	yield (%)[b]	ratio (**2**/**3**)[c]
1[d]	PPh_3 (4%)	CsOAc	6	5:1
2	PPh_3 (4%)	CsOAc	16	9:1
3	PPh_3 (2%)	CsOAc	23	9:1
4	PPh_3 (1%)	CsOAc	68	15:1
5	IPr (2%)	CsOAc	70	15:1
6	$HPCy_3BF_4$ (2%)	CsOAc	54	14:1
7	2-[di-(*tert*-butyl)phosphino]-biphenyl (2%)	CsOAc	3	
8	no ligand	CsOAc	75	15:1

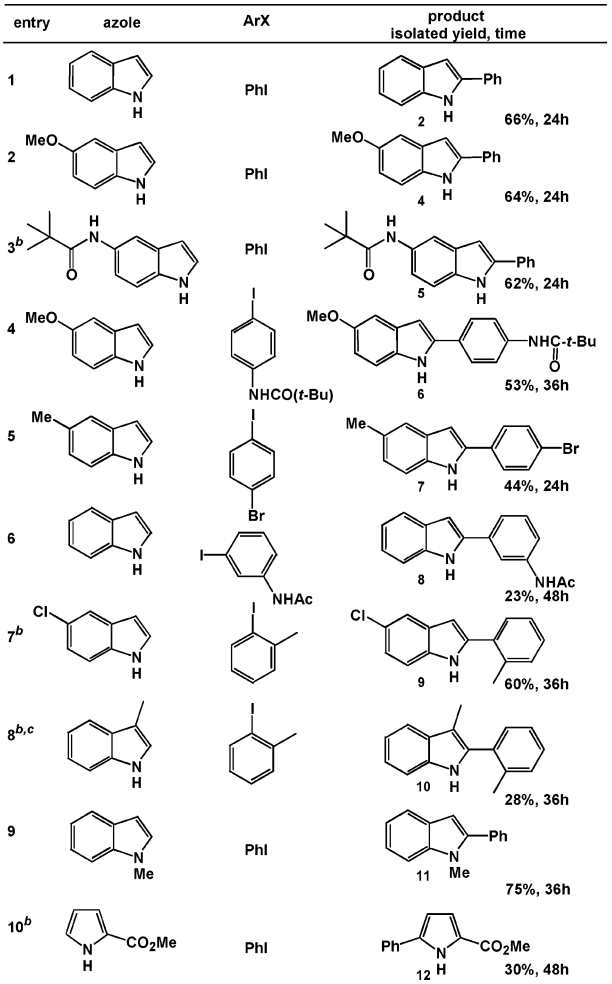
[a] Conditions: indole (5.0 M), PhI (1.2 equiv), CsOAc (2.8 equiv), DMA, 125 °C/24 h. [b] GC yield calibrated against an internal standard. [c] Product ratio in a crude reaction mixture was determined by GC analysis. [d] Indole (1.25 M) used.

deprotonate the indole N−H bond or other protic substituents, while it seems to facilitate the palladation step.

In contrast to the previous methods that require protection of the azole amine as *N*-Mg or *N*-Zn salts,[3,5] this direct protocol displayed low air/moisture sensitivity. It also showed good functional group scope, tolerating amido, methoxy, bromo, and chloro substituents (Table 2, entries 1−7). Moreover, coupling of sterically demanding arene donors was feasible, as exemplified by the reaction of 2-iodotoluene with 5-chloroindole to afford biaryl product **9** in 60% isolated yield (Table 2, entry 7). This catalytic system also enabled the arylation of sterically hindered indoles. To push the limits of this method, the reaction between two sterically demanding substrates, namely 3-methylindole and 2-iodotoluene was examined; it did proceed, affording the sterically congested biaryl product **10** in 28% isolated yield (Table 2, entry 8). In the context of this difficult coupling, the beneficial effect of amine base, in this case *t*-$BuNH_2$, was discovered (vide infra).[14] The presence of strong electron-withdrawing groups led to lower efficiency (Table 1, entry 10), which is consistent with the electrophilic palladation mechanistic hypothesis.[3] Although the efficiency of the arylation is modest with challenging substrates, this method still offers a significant practical value as desirable compounds can be obtained in one step from readily available materials under operationally simple conditions.

Bromoarene donors were less efficient than iodoarenes, giving lower conversion and poor C-2/C-3 selectivity under similar conditions. The former problem was significantly improved by addition of the stoichiometric amount of $(i\text{-Pr})_2NH$. For example, the yield of palladium-catalyzed formation of 3-methyl-2-phenylindole, from 3-methylindole and PhBr, increased from 28% to 63% yield by the addition of 1 equiv of $(i\text{-Pr})_2NH$ (Table 3, entry 1). Among a number of amines investigated, $(i\text{-Pr})_2NH$ gave the best results. Although the role of the amine is not clear at this stage, we reasoned that it may facilitate both the reduction

TABLE 2. Phosphine-Free Palladium-Catalyzed Direct Arylation of Free Indoles and Pyrroles with Iodoarenes[a]



[a] Conditions: $Pd(OAc)_2$ (1 mol %), CsOAc (2.8 equiv), indole (5.0 M), iodoarene (1.4−2 equiv), DMA, 125 °C, isolated yield for average of two runs. [b] $Pd(OAc)_2$ (5 mol %) and PhI (2 equiv) were employed. [c] *t*-BuNH2 (1 equiv) was added.

of Pd(II) and the subsequent oxidative addition of PhBr to Pd(0).[15] Amine bases have previously been used as both ligands and bases in palladium-catalyzed coupling processes.[16]

This new protocol is suited for sterically hindered indoles and substituted pyrroles. It is also tolerant of a range of functional groups including esters, ketones, and amides (Table 3, entries 2−5). Tryptamine derivatives were also arylation substrates, affording corresponding *C*-arylation products in moderate yields (Table 3, entries 4 and 5).[17] Sensitivity to the basic sp^2 nitrogen (e.g., pyridine and imidazole) is a notable shortcoming of this method, most likely responsible for the low yield in the arylation of protected tryptamine with 4-bromopy-

(13) For Pd-catalyzed *N*-arylation of indoles, see: (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827−828. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403−1406. (c) Grasa, G. A.; Viciu, M. S; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729−7737.

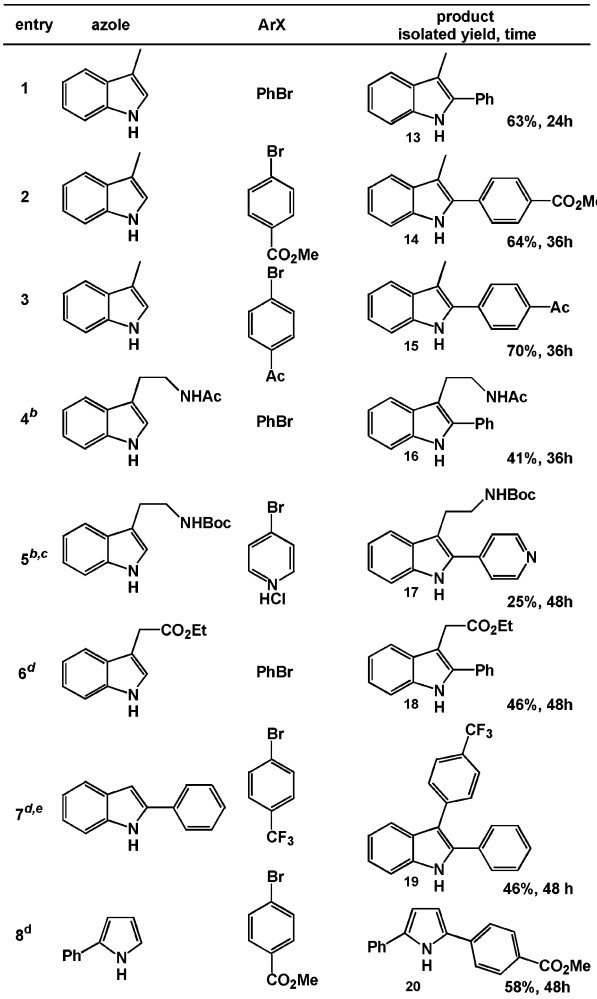
(14) One equivalent of *t*-$BuNH_2$ was required, presumably to facilitate the oxidative addition of sterically hindered arene donor.

(15) Addition of $(i\text{-Pr})_2NH$ also increased formation of biphenyl, a strong indication of the higher concentration of the PhPdX species.

(16) (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320−2322. (b) Tao, B.; Boykin, D. W. *J. Org. Chem.* **2004**, *69*, 4330−4335. (c) Tundel, R. E.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2006**, *71*, 430−433.

(17) Free tryptamine was also a good substrate, affording the 2-arylated product in ∼50% yield. However, partial acetylation of the primary amine occurred under the reaction conditions.

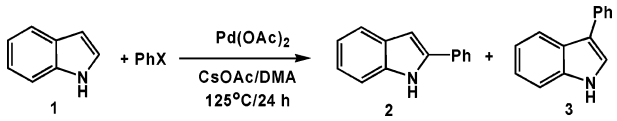
TABLE 3. Palladium-Catalyzed *C*-Arylation of Substituted Indoles and Pyrroles with Bromoarenes[a]



[a] Conditions: $Pd(OAc)_2$ (1 mol %), CsOAc (2.8 equiv), indole (5.0 M), bromoarene (1.4 equiv), $HN(i\text{-}Pr)_2$ (1 equiv), DMA, 125 °C, isolated yield for average of two runs. [b] $Pd(OAc)_2$ (5 mol %), bromoarene (2 equiv). [c] $HN(i\text{-}Pr)_2$ (3 equiv) used. [d] $Pd(OAc)_2$ (2 mol %). [e] NBu_4Cl (1 equiv) and bromoarene (3 equiv) were used.

ridine (Table 3, entry 5). Nevertheless, an interesting structure can be accessed in a rapid manner from common building units.[18,19] Furthermore, 2-substituted indoles were also substrates as exemplified by the arylation of 2-phenylindole (Table 3, entry 7). This is a particularly unreactive substrate, requiring the presence of a stoichiometric amount of Bu_4NCl, presumably to stabilize the Pd(0) species.[20] Under these conditions, 2,3-diarylated indole **19** was obtained in 46% isolated yield. Thus, the sequential arylation is feasible, enabling the synthesis of 2,3-diarylindoles from the parent indole core in two steps. Similarly, 2,5-diarylpyrroles may now be prepared in two steps (Table 3, entry 8). Combined with the established *N*-arylation or *N*-alkylation of the pyrrole amine functionality, a series of

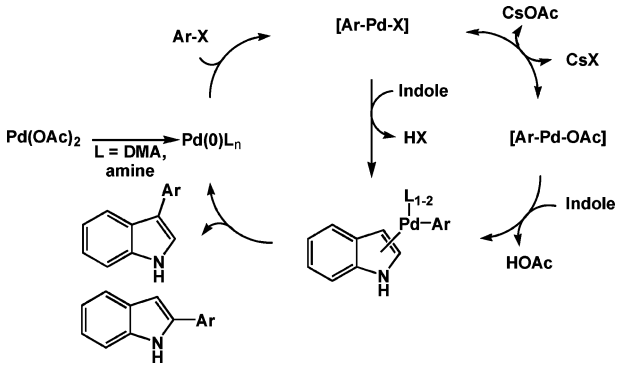
TABLE 4. Halide Effect in Pd-Catalyzed *C*-Arylation of Indole[a]



entry	X	additive	yield (%)[b]	ratio (**2**/**3**)[c]
1	I		75	15:1
2	I	CsBr	76	14:1
3	I	CsI	78	15:1
4	Br		28	2:1
5	Br	CsCl	25	2:1
6	Br	CsBr	26	2:1
7	Br	CsI	<2	

[a] Conditions: $Pd(OAc)_2$ (1 mol %), CsOAc (2.8 equiv), indole (5.0 M), cesium salt additive (0.2 equiv), haloarene (1.4 equiv), DMA, 125 °C/24 h. [b] GC yield calibrated with an internal standard. [c] Ratio in a crude reaction mixture was determined by GC analysis.

SCHEME 1



complex pyrrole and indole structures are readily accessible from common starting materials ("structural core diversification").[11]

As noted earlier, bromoarenes and iodoarenes showed distinctly different reactivity in the palladium-catalyzed *C*-arylation of indoles and pyrroles. Specifically, Pd-catalyzed reaction of indole with PhI afforded a 15:1 mixture of 2-phenylindole and 3-phenylindole in 75% yield, whereas an analogous process with PhBr gave a 2:1 mixture of the same products in 28% yield [$(i\text{-}Pr)_2NH$ improved the yield but did not affect the regioselectivity of the latter reaction].

Intrigued by these results, we examined the potential effect of halide counter ions on both the reactivity and regioselectivity of the arylation reactions by adding cesium halides to the reaction mixture. We found that CsI or CsBr had no significant effect on the arylation with PhI (Table 4, entries 1−3). In contrast, CsI strongly inhibited the reaction with PhBr (Table 4, entries 4−6), while CsBr and CsCl had no effect.[21] These observations suggest, assuming a Pd(0)/Pd(II) catalytic cycle (Scheme 1), that iodide ion inhibits the oxidative addition of bromobenzene to a Pd(0) species and/or the indole palladation step with a Ar−Pd−X species.[22] Also, these results imply that the nature of the anionic ligand at the palladium center (i.e., X = bromide, iodide, or acetate) affects the mechanism of the arylation process.

(18) Preliminary experiments show that similar yields can be obtained in a significantly shorter time (<1 h) in a microwave reactor.

(19) For arylation of imidazoles, the method developed for SEM-protected azoles is recommended; see ref 6.

(20) Phase-transfer reagents were used in the ligand-free Heck reactions, see: Jeffery, T. *Tetrahedron* **1996,** *52*, 10113−10130. The beneficial effect of this additive was not seen with 3-substituted indole substrates.

(21) During the course of our study, similar inhibition by iodide salts was reported in the palladium-catalyzed intramolecular arylation of arenes; ref 10a.

(22) For an alternative Pd(0)/Pd(II) mechanism, see: Cardenas, D. J.; Martin-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc*. **2006**, *128*, 5033−5040.

In summary, we have developed a phosphine-free palladium system for direct *C*-arylation of free (NH)-indoles and pyrroles with iodo- and bromoarenes. This simple catalytic system will enable rapid access to a variety of azole products.

Experiemental Section

Typical Procedure for Arylation of Free (N−H)-Indole with Iodoarenes (Procedure A): On benchtop, CsOAc (260 mg, 1.35 mmol) was placed in a vial containing indole (58.5 mg, 0.50 mmol). The vial was capped with a Teflon septum cap, evacuated, and refilled with argon via a needle through the septum. The evacuation/refill procedure was repeated twice before PhI (143 mg, 0.70 mmol) and a solution of $Pd(OAc)_2$ (100 μL, 11.0 mg/mL in DMA) were added sequentially via syringe. Under an argon purge provided by a needle, the septum cap was replaced with a FTFE-faced Kimble phenolic cap. The reaction mixture was then stirred at 125 °C, at which point the base melted and reaction mixture became homogeneous. The resulting solution was heated for 24 h while white precipitate (CsI) started to form. The reaction mixture was then cooled to room temperature, diluted with EtOAc (5 mL), stirred for 1 min, passed through a short plug of silica gel, and eluted with EtOAc (15 mL). The resulting solution was concentrated, absorbed on silica gel (∼2 g), dry-loaded to a column, and chromatographed (SiO_2, 15:1 hexanes:EtOAc) to afford 2-phenylindole[23] (64 mg, 66%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.6 (s, 1 H), 7.87 (dd, J = 1.2, 8.4 Hz, 2 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.41 (dd, J = 0.8, 8,0 Hz, 1 H), 7.29−7.33 (m, 1 H), 7.08−7.13 (m, 1 H), 7.00 (dt, J = 0.8, 8.0 Hz, 1 H), 6.90 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 137.6, 137.1, 132.2, 128.8, 128.6, 127.3, 124.9, 121.5, 120.0, 119.3, 111.3, 98.6.

Typical Procedure for Arylation of C-3 Substituted Indole with Bromoarenes (Procedure B): CsOAc (260 mg, 1.35 mmol) was placed in a vial containing 3-methylindole (65.5 mg, 0.50 mmol). The vial was capped with a Teflon septum cap, evacuated, and refilled with argon via a needle through the septum. The evacuation/refill procedure was repeated twice. PhBr (110 mg, 0.7 mmol), diisopropylamine (50 mg, 0.50 mmol), and a solution of $Pd(OAc)_2$ (100 μL, 11.0 mg/mL in DMA) were added sequentially via syringe. Under an argon purge provided by a needle, the septum cap was replaced with a FTFE-faced Kimble phenolic cap. The solid mixture was then heated at 125 °C, at which point the base melted and reaction mixture became homogeneous. The reaction mixture was heated for 24 h before being cooled to room temperature. After addition of EtOAc (5 mL), the reaction mixture was stirred for 1 min, passed through a short plug of silica gel, and eluted with EtOAc (15 mL). The resulting solution was concentrated, absorbed on silica gel (∼2 g), dry-loaded to a column, and chromatographed (SiO_2, 20:1 hexanes:EtOAc) to afford 3-methyl-2-phenylindole[24] (65 mg, 63%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (bs, 1 H), 7.56−7.61 (m, 3 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.33−7.37 (m, 2 H), 7.20 (td, J = 1.3, 7.5 Hz, 1 H), 7.14 (tm, J = 7.3 Hz, 1 H), 2.46 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 133.9, 133.2, 129.9, 128.7, 127.7, 127.2, 122.2, 119.5, 118.9, 110.7, 108.6, 9.6.

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

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