JOC Article
pubs.acs.org/joc

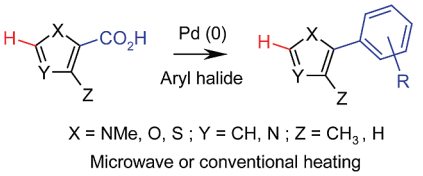
Palladium-Catalyzed Decarboxylative Cross-Coupling Reaction Between Heteroaromatic Carboxylic Acids and Aryl Halides

François Bilodeau,* Marie-Christine Brochu, Nicolas Guimond, Kris H. Thesen, and Pat Forgione*

Boehringer Ingelheim (Canada) Ltd. Research and Development, 2100 rue Cunard, Laval (Québec), Canada H7S 2G5

francois.bilodeau@boehringer-ingelheim.com

Received November 20, 2009



A full overview of the decarboxylative cross-coupling reaction between heteroaromatic carboxylic acids and aryl halides is described. This transformation employs palladium catalysts with short reaction times providing facile synthesis of aryl-substituted heteroaromatics. The effect of each reaction parameter including solvent, base, and additive employed as well as the full substrate scope of this transformation are reported. Mechanistic evidence is also disclosed that sheds light on possible reaction pathways.

Introduction

Much effort has been devoted in the last decades toward new methods to form carbon−carbon bonds. Notably, metal-catalyzed cross-coupling reactions have found great utility in synthetic chemistry and are now valuable tools that are routinely employed.[1] As a result, palladium-catalyzed reactions,[2] such as Suzuki−Miyaura[3] or Stille−Migita[4] couplings, can often be found as common synthetic steps in numerous total syntheses. However, drawbacks still exist, including the limited commercial availability of some coupling partners or their tedious preparation. In recent years, alternative methods that attempt to address these issues have begun to emerge. Direct functionalization through C−H activation methods[5] is an elegant example of atom economy as well as synthetic efficiency since it precludes the need of prefunctionalization. However, despite recent advances, a key challenge that persists is regioselective C−H activation.

The metal-catalyzed decarboxylative cross-coupling strategy has been recently highlighted[6] as a new synthetically useful tool. This stems from the observation that common carboxylic acids can be employed as coupling partners in palladium-catalyzed cross-coupling reactions. Pioneering work in this field was reported by Myers[7] which demonstrated the use of a highly electrophilic palladium source to generate, from electron-rich benzoic acids, the requisite Pd(II) species that subsequently underwent a Mirozoki−Heck coupling reaction (Scheme 1).

(1) (a) *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004. (c) *Handbook of Functionalized Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, 2005; Vols. 1&2. (d) *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Vols. 1 and 2. (e) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (f) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.

(2) (a) *Palladium Reagents in Organic Synthesis*; Heck, R. F., Ed.; Academic Press: New York, 1985. (b) *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J., Eds.; Wiley & Sons: New York, 1995. (c) Beller, M.; Zapf, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: New York, 2002; Vol. 1, p 1209. (d) Tamao, K.; Hiyama, T.; Negishi, E.-I. *J. Organomet. Chem.* **2002**, *653*, 1.

(3) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.

(4) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

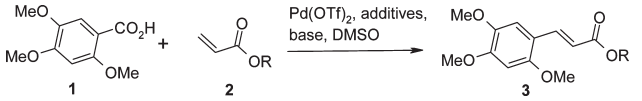
(5) (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Proch, S.; Kempe, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 3135. (c) Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 11904. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (e) Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172. (f) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7996.

(6) (a) Baudoin, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 2. (b) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100. (c) Moon, J.; Jang, M.; Lee, S. *J. Org. Chem.* **2009**, *74*, 1403.

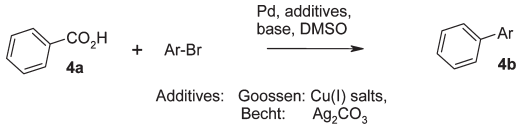
(7) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.*, **2005**, *127*, 10323 and references therein.

Published on Web 02/08/2010 DOI: 10.1021/jo9022793

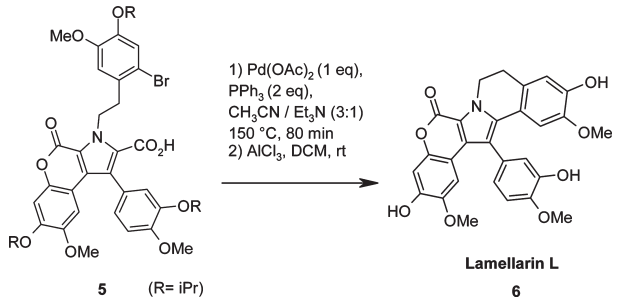
SCHEME 1



SCHEME 2



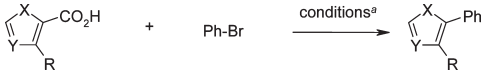
SCHEME 3

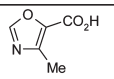
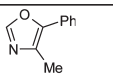
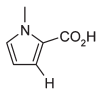
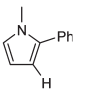
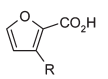
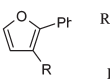
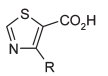
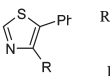
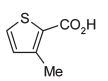
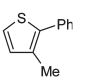
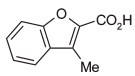
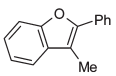
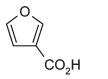
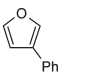
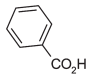
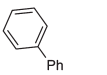


More recently, two groups have reported the use of the decarboxylative coupling concept using benzoic acids (Scheme 2). Employing copper(I) salts, Goossen et al.[8] were able to generate the nucleophilic partner from benzoic acids for the synthesis of biaryl motifs using palladium catalysts. Additionally, Becht et al.[9] reported a strategy in which they were able to perform a decarboxylative cross-coupling reaction between a benzoic acid and an aryl halide using palladium catalyst with silver carbonate as the additive (Scheme 2). Steglich and co-workers reported an intramolecular Heck-like coupling between an aryl bromide and a tetrasubstituted pyrrole carboxylic acid in their synthesis of lamellarin L employing a stoichiometric amount of palladium (Scheme 3).[11] Subsequently, many reports have appeared in the literature expanding the use of carboxylic acids and related moieties in metal catalyzed cross-couplings.[10]

Previously, we reported the intermolecular coupling reaction between heteroaromatic carboxylic acids and aryl halides employing catalytic palladium.[12] This transformation differs from both the Myers couplings and the Goosen/Becht couplings of carboxylic acids. In the Myers case, the carboxylic acid is employed to generate the electrophilic coupling partner that undergoes subsequent coupling, in an oxidative Heck-type mechanism, with a nucleophilic alkene. In the Goosen/Becht examples, decarboxylation is promoted by the presence of a second metal (Cu or Ag, respectively) which generates the nucleophilic coupling partner from the carboxylic acid, thus permitting the catalytic cycle to be operative, in these cases with aryl halides as coupling partners. In the present system, and similarly to the known reactivity of 5-membered heteroaromatic, the nucleophilicity of the heteroaromatic partner stems from the delocalization of the lone pair of electrons of the heteroatom into the ring, which then undergoes reaction with the electrophilic, in situ generated, Ar−Pd(X)(L) species. Another distinction to be made is that because of the different intrinsic nature of the carboxylic acid partner (aryl vs heteroaryl) it is likely that, although similar, such transformations would follow different mechanistic pathways. Recently, seminal work by Liu shed light on Pd-catalyzed decarboxylative coupling of carboxylic acids with olefins.[13]

TABLE 1. Pd-Catalyzed Arylation of Various Heteroaromatic Carboxylic Acids with PhBr



Entry	Substrate		Product		Yield (%)
1		**9a**		**9b**	53[b]
2		**7a**		**7b**	88
3		R=Me, **10a**		R=Me, **10b**	86
4		R=H, **11a**		R=H, **11b**	41
5		R=Me, **12a**		R=Me, **12b**	74
6		R=H, **13a**		R=H, **13b**	23
7		**14a**		**14b**	63
8		**15a**		**15b**	86
9		**16a**		**16b**	0[c]
10		**4a**		**4b**	0[c]

[a]Reaction conditions: heterocycle (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), $n\text{-}Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), Cs_2CO_3 (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min. [b]Yield without additive (yield with $n\text{-}Bu_4NCl\cdot H_2O$ = 74% (contains 10 mol % of 1-methyl-2-pyrrole-*n*-butylcarboxylic ester by ^1H NMR)). [c]No trace of product by HPLC.

(8) (a) Goossen, L. J.; Deng, G; Levy, L. M. *Science* **2006**, *313*, 662. (b) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *127*, 4824. (c) Goossen, L. J.; Rodriguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248. (d) Goossen, L. J.; Zimmermann, B.; Knauber, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 7103.

(9) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. *Org. Lett.* **2007**, *9*, 1781.

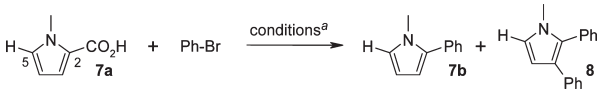
(10) (a) Maehara, A.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1159. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *127*, 3510. (c) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194. (d) Miyasaka, M.; Fukushima, A.; Satoh, T.; Hirano, K.; Miura, M. *Chem.—Eur. J.* **2009**, *15*, 3674. (e) Voutchkova, A.; Coplin, A.; Leadbeater, N. E.; Crabtree, R. H. *Chem. Commun.* **2008**, 6312. (f) Use of silanolate was reported: Denmark, S. E.; Baird, J. D.; Regens, C. S. *J. Org. Chem.* **2008**, *73*, 1440.

(11) Peschko, C.; Winklhofer, C.; Steglich, W. *Chem.—Eur. J.* **2000**, *6*, 1147.

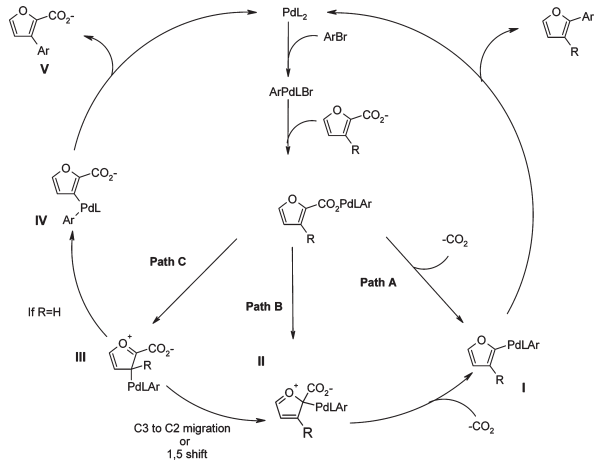
(12) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *126*, 11350.

(13) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638 and references cited therein.

SCHEME 4



SCHEME 5. Postulated Mechanism



Additionally, in contrast to the intramolecular Heck-like coupling of a pyrrole that is stoichiometric in palladium as reported by Steglich, our communication demonstrated a catalytic, intermolecular decarboxylative coupling in the presence of reactive C−H groups for a variety of heteroaromatics to generate the desired products in modest to good yields (Table 1). Despite the variety of examples demonstrated in our initial report, some limitations were observed, such as the effect on the yield of some substituents present on the heteroaromatic partner (for example, entry 3 vs 4). We demonstrated that the reduction in yield was in fact due to the formation of 2,3-diarylated heteroaromatic products (Scheme 4), which could be reduced by appropriate selection of the additive. Despite this beneficial effect we still could observe, in the case of entry 4, a 5:1 ratio of mono- and diarylated product, respectively.

The reaction was also found to be limited by the specificity of the position of the acid on the hereoaromatic ring (Table 1, entry 9). In order to ensure that this reactivity was specific to 5-membered heteroaromatics, we also submitted benzoic acid to the reaction conditions (entry 10) where, similarly to 3-furoic acid, no coupling product was observed.

In an attempt to provide a rationale for the formation of the 2,3-diarylated side products, we presented in our initial report a mechanism invoking C3 electrophilic palladation. (Scheme 5, path C). Effectively, this mechanistic pathway accounts for the production of both 2-arylated and 2,3-diarylated products. Similar observations were reported by Miura's group for the palladium-catalyzed multiple arylation of thiophenes.[14] Moreover, it highlights the difference between our findings and those from the groups studying couplings employing benzoic acids where additives and/or cocatalysts are required to promote decarboxylation. This last point is important, since it explains why our method cannot be extended to benzoic acids. More detailed mechanistic considerations will be given later in this account; the first section will provide an exhaustive study on the effect of various reaction parameters as well as the scope of the reaction.

(14) Okazawa; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

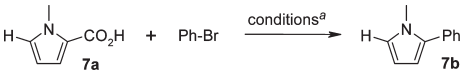
Results and Discussion

Base Effect. We first investigated the effect of the base on the reaction outcome. Numerous bases were successfully employed to promote the transformation (Table 2). Carbonates (entries 1−3), fluorides (entries 5 and 6), and potassium acetate (entry 8) all afforded the desired product in good yields. However, the use of both lithium carbonate (entry 4) and lithium fluoride as bases (entry 7) provided the desired product in poor yields. This supports the hypothesis that a precomplexation step between a carboxylate anion and a Pd(II) species is pivotal to the reaction course. Both potassium bicarbonate (entry 9) and potassium phosphate (entry 10) were found to give incomplete conversions (72% and 78%, respectively). Finally, complete conversion was observed when triethylamine (entry 11) was used, but it was found to be unsuitable for this transformation, giving a complex mixture of products.

Solvent Effect. A similar study was undertaken to determine if solvent polarity played a significant role in the reaction outcome (Table 3). We were pleased to observe that the reaction could be efficiently conducted in a number of solvents, ranging from highly polar (DMF, NMP and DMA, entries 1−3) to nonpolar solvents such as xylenes (entry 8). Moreover, the presence of protic solvents, such as water and ethanol (entry 4 and 9), in DMF was tolerated and resulted in only slightly lower yields (entries 4 and 9).

Catalyst Effect. Next, we examined the range of catalysts that could be employed by evaluating different palladium sources as well as varying the ligands and/or ligand stoichiometry (Table 4). Rewardingly, only a minor difference was observed when comparing reference conditions (entry 1) to conditions where the catalyst is formed in situ (entry 2). Further, since it has been previously demonstrated that the active palladium species for this system could be a monophosphine species,[15] the experiment was conducted with a 1:1 ligand to catalyst ratio. Reduction of the ligand ratio led to the desired product in comparable yield (entry 3 vs entry 2). The use of a Pd(0) catalyst stabilized with an NHC ligand was found not to be suitable for this transformation (entry 5). Lastly, other commercially available palladium catalysts

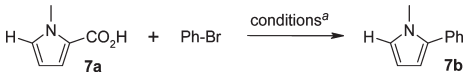
TABLE 2. Base Effect



entry	base	yield (%)	entry	base	yield (%)
1	Cs_2CO_3	88	7	LiF	4
2	K_2CO_3	81	8	KOAc	84
3	Na_2CO_3	88	9	$KHCO_3$	50[b]
4	Li_2CO_3	14	10	K_3PO_4	56[b]
5	CsF	81	11	Et_3N	36[c]
6	KF	75			

[a]Reaction conditions: *n*-$Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), base (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min [b]Incomplete reaction. [c]Complex mixture was obtained

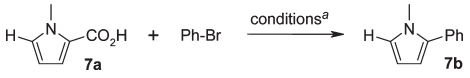
TABLE 3. Solvent Effect



entry	solvent	yield (%)	entry	solvent	yield (%)
1	DMF	88	6	THF	86
2	NMP	85	7	MeCN	74
3	DMA	81	8	xylenes	74
4	DMF/H_2O[b]	71	9	DMF/EtOH[b]	74
5	DMF/H_2O[c]	0			

[a]Reaction conditions: *n*-$Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %), Cs_2CO_3 (0.60 mmol, 1.5 equiv), solvent (4 mL), microwave, 170 °C, 8 min. [b]19:1 mixture. [c]1:1 mixture.

TABLE 4. Catalyst Effect



entry	catalyst	yield (%)
1	Pd[P(*t*-Bu)$_3$]$_2$	88
2	$PdCl_2$ + P(*t*-Bu)$_3$ (10%)	80
3	$PdCl_2$ + P(*t*-Bu)$_3$ (5%)	79
4	$PdCl_2$ + PMe(*t*-Bu)$_2$-BF_4 (5%)	81
5	PEPPSI-*i*-Pr[b]	0[c]
6	Pd[P(Ph)$_3$]$_4$	43
7	$PdCl_2$[P(Ph)$_3$]$_2$	76
8	$PdCl_2$ + P(Ph)$_3$ (10%)	70
9	Pd(OAc)$_2$ + P(Ph)$_3$ (5%)	62
10	$PdCl_2$[1,2-C_2H_4(P(Ph)$_2$)$_2$]	52

[a]Reaction conditions: *n*-$Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), catalyst (5 mol %), Cs_2CO_3 (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min. [b]PEPPSI-*i*-Pr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride. [c]A complex mixture was obtained.

(entries 6, 7, and 10) were also employed, and all gave modest to good yields.

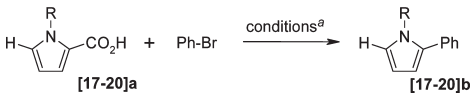
Reaction with *N*-Arylated Pyrroles. The decarboxylative coupling was examined to determine whether the electronic effects on the heteroaromatic acids would affect the reaction course. Toward this aim, various *N*-substituted pyrroles were prepared[16] and submitted to the reaction conditions (Table 5). Interestingly, all of the four analogues gave the desired products in modest to good yields. Moreover, it appears that a trend is observed where better yields are obtained with more electron-rich heteroaromatics.

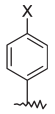
Intramolecular Arylation. Steglich and co-workers reported previously an intramolecular decarboxylative coupling where the C2- position on a pyrrole contained a carboxylic acid and all other positions were substituted. In order to determine if decarboxylative cross-coupling would occur preferentially over competitive C−H activation, we examined an intramolecular version of this transformation. Results from Table 6 show that the yields obtained are lower than in the intermolecular case (Table 1, entry 2, 88%). However, it is interesting that in both cases no products resulting from intermolecular reaction were

(15) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944.

(16) Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578.

TABLE 5. Pd-Catalyzed Arylation of *N*-Substituted Pyrrole-2-carboxylic Acid with PhBr



Entry	Substrate	R group	Product	Yield (%)
1	X=OMe, **17a**		X=OMe, **17b**	66
2	X=H, **18a**		X=H, **18b**	58
3	X=CF_3, **19a**		X=CF_3, **19b**	44
4	X=NO_2, **20a**		X=NO_2, **20b**	44

[a]Reaction conditions: *n*-$Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), heterocycle (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %), Cs_2CO_3 (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min.

TABLE 6. Intramolecular Pd-Catalyzed Arylation of *N*-Substituted Pyrrole-2-carboxylic Acid

entry	substrate	product	yield (%)
1	*n* = 1, **21a**	**21b**	60
2	*n* = 2, **22a**	**22b**	69

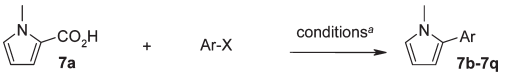
[a]Reaction conditions: *n*-$Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), heterocycle (0.80 mmol, 2.0 equiv), Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %), cesium carbonate (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min.

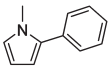
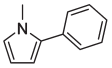
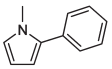
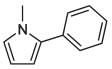
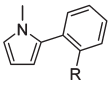
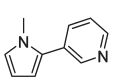
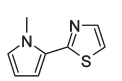
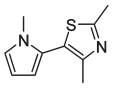
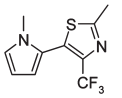
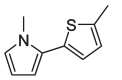
observed and that the decarboxylative coupling product prevailed over the C−H activation product.

Scope of the Reaction: Aryl Halide. In order to assess the full scope of the aryl halide coupling partner, we undertook a systematic study employing the pyrrole-2-carboxylic acid scaffold to evaluate coupling with various aryl halides (Table 7). Iodides, bromides, triflates, as well as chlorides (entries 1−4) were all found to give the desired product in good yields. The reaction is tolerant to substituents present on the aryl ring, affording the desired product in good yields, regardless of whether the substituents are electron-donating (entries 5, 9, 11 and 12) or -withdrawing (entries 7, 8, 10, 13, and 14). In only one case, namely 2-bromoanisole (entry 6), was the reaction completely shut down; however, the corresponding phenol (entry 9) and 4-bromoanisole (entry 12) both produced the desired product in good yield.

Heteroaromatic bromides can also be employed as shown in entries 15, 17, and 19. The low yield obtained with 2-bromothiazole (entry 16) may be due to competing C5-H activation as a side reaction. In addition, the 2,4-dimethylthiazole (entry 17) undergoes the requisite transformation, but no desired products were obtained using the more electron-deficient 5-bromo-4-trifluoromethyl-2-methyl-1,3-thiazole (entry 18) as the coupling partner. However, the examples from Table 7 exemplify this palladium-catalyzed decarboxylative coupling employing heteroaromatic carboxylic acids as an efficient transformation. Rewardingly, it is also clear that the reaction outcome is mostly unaffected by steric and/or electronic effects.

TABLE 7. Pd-Catalyzed Arylation of 1-Methyl 2-Pyrrolecarboxylic Acid with Various Aryl Halides



Entry	Aryl Halide		Product		Yield (%)
1		**23**		**7b**	78
2		**24**		**7b**	88
3		**25**		**7b**	86
4		**26**		**7b**	68
5		R=Me, **27**		**7c**	76
6		R=MeO, **28**		**7d**	0[b]
7		R=CF_3, **29**		**7e**	80
8		R=NO_2, **30**		**7f**	62
9		R=OH, **31**		**7g**	68
10		R=CO_2Et, **32**		**7h**	71
11		R=Me, **33**		**7i**	78
12		R=MeO, **34**		**7j**	77
13		R=CF_3, **35**		**7k**	78
14		R=NO_2, **36**		**7l**	66
15		**37**		**7m**	85
16		**38**		**7n**	18
17		**39**		**7o**	71
18		**40**		**7p**	0[c]
19		**41**		**7q**	78

[a]Reaction conditions: 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 equiv), aryl halide (0.40 mmol, 1 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), $n\text{-}Bu_4NCl\cdot H_2O$ (0.40 mmol, 1 equiv), Cs_2CO_3 (0.60 mmol, 1.5 equiv), DMF (4 mL), microwave, 170 °C, 8 min. [b]Messy reaction. [c]No reaction.

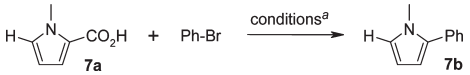
Thermal Conditions. All previous examples for this decarboxylative cross-coupling reaction were performed by microwave heating. As part of this extended study, we wished to ensure this transformation could also be performed under thermal conditions and evaluated the reaction of pyrrole 2-carboxylic acid with phenyl bromide (Table 8). We were pleased to observe that the reaction could be performed under thermal conditions, although a decrease in yields was observed (entries 1−4). The reaction time was remarkably fast, however, as in most solvents the reaction was complete within 2 h. A small quantity of water was again tolerated (entry 4), although accompanied with a decrease in yields (entry 1 vs 4). However, in contrast to microwave heating, significantly lowered yields were observed when the nonpolar solvent xylenes was employed (entry 5).

Mechanistic Considerations. In our initial communication, we proposed a mechanism based on our preliminary empirical observations, namely that an important byproduct of this process was C3-arylation. We also postulated that the carboxylate moiety could first attack the electrophilic X−PdLAr complex formed from the oxidative addition of the Pd(0) species into the C−X bond of the coupling partner (Scheme 5). This postulated chelation is based on Myers' report and is supported by our observation that lithium inorganic bases are not suitable for this transformation, presumably due to the poor nucleophilicity of the lithium carboxylate (see Table 2). Once this occurs, direct decarboxylation, or potentially a concerted palladation−decarboxylation, could occur to generate intermediate **I** (path A) which, after reductive elimination, would provide the observed product. However, this mechanistic pathway does not rationalize the formation of the 2,3-diarylation products. Moreover, the observation that there is no need for an additive specifically to promote decarboxylation (i.e., Ag or Cu salts) in the case of heteroaromatic carboxylic acids contradicts this proposal.

Due to these incongruities, we suggested in our earlier communication that the reaction could follow a C3-electrophilic palladation pathway (path C) to form the intermediate **III**. Despite the fact that this type of reactivity has only occasionally been invoked,[17] it provided a rationale for most

(17) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (b) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972. (c) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528.

TABLE 8. Pd-Catalyzed Arylation of 1-Methyl 2-Pyrrolecarboxylic Acid with PhBr under Thermal Conditions



entry	solvent	time (h)	yield (%)
1	DMF	1	57
2	NMP	1	66
3	DMA	1	63
4	DMF/H_2O[b]	2	45
5	xylenes	5	23

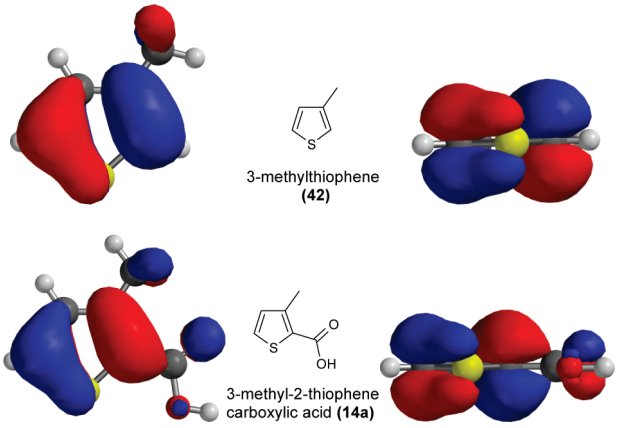
[a]Reaction conditions: *n*-$Bu_4NCl \cdot H_2O$ (0.40 mmol, 1 equiv), 1-methyl-2-pyrrolecarboxylic acid (0.80 mmol, 2.0 equiv), phenyl bromide (0.40 mmol, 1 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), cesium carbonate (0.60 mmol, 1.5 equiv), solvent (4 mL), 140 °C, 8 min. [b]19:1 mixture.

of our key observations. Effectively, we hypothesized that after the C3 electrophilic palladation a C3 to C2 palladium migration[18] could occur with concomitant or stepwise decarboxylation to generate intermediate **I**. Our rationalization of the formation of 2,3-diarylated compound was based on the observation that intermediates such as **III**, when R = H, could undergo a competing deprotonation reaction to generate intermediate **IV**. Reductive elimination of the latter would give intermediate **V** that could re-enter the catalytic cycle to ultimately yield the corresponding 2,3-diarylated compound.

Previously, we favored this mechanism since it provided a rationale for the pivotal role of the carboxylic acid moiety while accounting for the formation of 2,3-diarylated products through a competing deprotonation pathway (Scheme 5, **III** to **IV**). However, this proposal minimized the propensity of 5-membered heteroaromatics to undergo electrophilic aromatic substitution at the C2 position. This behavior was nicely exemplified in the study of the electrophilic iodination of pyrroles,[19] as well as in the recent publications reporting metal catalyzed C−H activation on 5- membered heteroaromatics. The Fagnou group has made seminal contributions demonstrating such CMD-type mechanisms to account for these related transformations.[20] These observations suggest that another plausible explanation for the formation 2-arylated and 2,3-diarylated products could be a competition between C2 and C3 electrophilic palladations (paths B and C). This implies that the conversion of intermediate **III** to **II** may not occur, and thus, the ratio of 2-arylated and 2,3-diarylated products could be explained by the differences in the rates of C2 vs C3 electrophilic palladations, respectively.

Acknowledging that these two pathways are plausible, we attempted to gain additional knowledge to differentiate these mechanistic possibilities. Toward this end, molecular orbital analysis was performed to determine the role of the carboxylic acid on the π-bond reactivity as well as the C2/C5 selectivity.[21] Since π-nucleophilicity has been postulated to contribute to reactivity and site selectivity,[22] the HOMOs were calculated for key heteroaromatics (Scheme 6).

SCHEME 6. Molecular Orbital Analysis on Key Heteroaromatics



Previously, we reported that C−H activation of 3-methylthiophene produces a 3:1 mixture of C2:C5 arylation. This is supported by the slight increase in the contribution to the HOMO of C2 vs C5. Interestingly, the HOMO for 3-methyl-2-thiophenecarboxylic acid is essentially identical to 3-methylthiophene; however, it yields exclusively the C2-arylated product. This suggests the carboxylic acid group is acting primarily as a directing group and does not significantly change the π-character of the HOMO of the heteroaromatics.

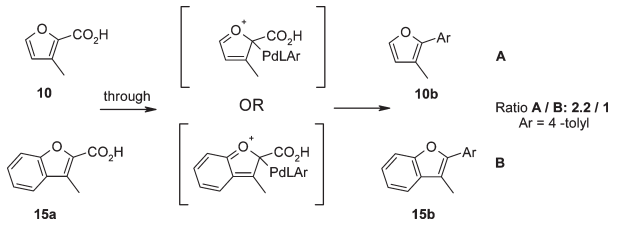
Further, we designed competition experiments to shed light on the mechanism. First, we reasoned that a competition experiment between 3-methyl-2-furoic acid and 3-methylbenzofuran-2-carboxylic acid would provide information on the comparative rates of C2 vs C3 electrophilic palladation. Effectively, the C2-electrophilic palladation should be of higher activation energy in the case of 3-methylbenzofuran-2-carboxylic acid due to the fact that the aromaticity of the phenyl group would be broken (Scheme 7).

Since both substrates underwent the reaction with similar yields, the rates were estimated through product distribution after a competition experiment. We observed a 2.2:1 ratio favoring the product resulting from the coupling with 3-methyl-2-furancarboxylic acid. This result seems to support the C2 electrophilic palladation pathway, since if the C3 pathway was favored, it could be expected that the product resulting from the benzofuran analogue would have predominated due to the lower aromatic character of the reacting double bond.

Further, an additional competition experiment was designed to evaluate electronic factors that could differentiate between the proposed mechanisms. In this regard, two analogues were synthesized and subjected to the reaction conditions (Scheme 8). In the event, a 1.8:1 ratio in favor of the electronic-rich substrate was obtained. This again lends support to the C2 electrophilic palladation pathway (path B). Namely, the electrophilic C3 pathway followed by a migration from C3 to C2 to yield the desired product should not be affected by electronic factors at this position while the C2 electrophilic pathway should be affected.

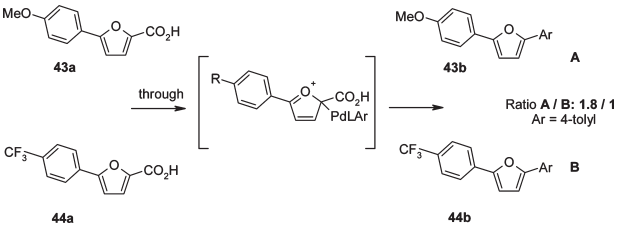
(18) Hamel, P. *J. Org. Chem.* **2002**, *67*, 2854.
(19) Doak, K. W.; Corwin, A. H. *J. Am. Chem. Soc.* **1949**, *71*, 159.
(20) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826.
(21) DFT calculations of compounds **42** and **14a** were performed to obtain the equilibrium geometries from the ground states using the B3LYP-(2) exchange correlation functional with the 6-311++G** basis set for all atoms.
(22) Campeau, L.-C.; Bertrand-Laperle, M.; Leclerc, J.-P.; Villemure, E.; Gorelsky, S.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3276.

SCHEME 7. Pd-Catalyzed Arylation of Benzofuran-3-methyl-2-carboxylic Acid[a]



[a]Conditions: 4-tolylBr, DMF, *n*-Bu_4NCl hydrate, $Pd[P(t\text{-}Bu)_3]_2$, microwave, 170 °C, 8 min.

SCHEME 8. Pd-Catalyzed Arylation of 5-Arylfuran-2-carboxylic Acid Analogues[a]



[a]Conditions: 4-tolylBr, DMF, *n*-Bu_4NCl hydrate, $Pd[P(t\text{-}Bu)_3]_2$, microwave, 170 °C, 8 min.

These results lead us to postulate that a mixed mechanism is a distinct possibility depending on the structure of the heteroaromatic scaffold employed (nature of substituents and/or heteroatoms forming the ring). There is only the formation of 2,3-diarylated products that constitutes an unequivocal observation of one of the three pathways (path C, Scheme 5); further studies are required that could shed more light on the other mechanistic possibilities.

Conclusion

We have demonstrated that the decarboxylative cross-coupling reaction between heteroaromatic carboxylic acids and aryl halides can be performed with a large range of aryl halides. This is a valuable new route to compounds that are commonly found in drug candidates. We have also shown that the base and the solvent can be varied with only minor impact on the reaction outcome. More importantly, the transformation could be performed using catalysts that are either preformed or formed in situ, both yielding similar results. Efforts were also made to further understand the operative mechanism for this intermolecular decarboxylative cross-coupling. Effectively, our observations lead us to postulate that the electrophilic palladation pathways, over direct decarboxylation, better accounts for the reactivity of the 5-membered heteroaromatic carboxylic acids. This is in contrast with what has been reported on related reactivity using benzoic acids as metal surrogates.

Experimental Section

Preparation of Aryl-Substituted Heteroaromatic by Palladium-Catalyzed Decarboxylative Coupling. General Procedure. Unless otherwise noted, each reaction was performed using the following procedure. In a microwave vial (2 to 5 mL), opened to air, were added aryl halide (0.40 mmol, 1 equiv), heterocyclic carboxylic acid (0.80 mmol, 2 equiv), tetra-*n*-butylammonium chloride hydrate (0.40 mmol, 1 equiv), base (0.60 mmol, 1.5 equiv), and catalyst (0.020 mmol, 0.05 equiv). Anhydrous DMF (4 mL) was then added after which the mixture was stirred for 30 s and submitted to the microwave conditions (170 °C, 8 min, high absorption level). The reaction mixture was then diluted with ethyl acetate (50 mL), and the organic layer was washed with brine (3×), saturated $NaHCO_3$ solution (2×), water (1×), and again with brine (1×). The organic layer was dried over $MgSO_4$ and filtered, and solvent evaporation over silica afforded a solid residue that was purified using normal-phase silica gel.

2-(2-Tolyl)-1-methylpyrrole (7c; Table 7, Entry 5). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a colorless oil (52.1 mg, 0.304 mmol, 76%): HPLC (220 nm) 98.5%; ^1H NMR (400 MHz, DMSO-d_6) δ 7.18−7.31 (m, 4H), 6.80 (s, 1H), 6.06 (s, 1H), 5.95 (s, 1H), 3.35 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.3, 132.7, 132.2, 130.8, 130.0, 127.8, 125.5, 108.2, 106.9, 33.8, 19.9; HRMS (EI) calcd for $C_{12}H_{13}N$ ($M^{+\bullet}$) 171.1048, found 171.1051.

2-(2-(Trifluoromethyl)phenyl)-1-methylpyrrole (7e; Table 7, Entry 7). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as an off-yellow oil (72.1 mg, 0.320 mmol, 80%): HPLC (220 nm) 97.8%; ^1H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 7.8 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 6.84 (br s, 1H), 6.06 (br s, 1H), 6.01 (br s, 1H) 3.33 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 133.4, 132.0, 128.8, 128.6, 126.1, 125.3, 122.8, 122.6, 109.7, 106.9, 33.9; HRMS (EI) calcd for $C_{12}H_{10}F_3N$ ($M^{+\bullet}$) 225.0765, found 225.0767.

2-(2-Nitrophenyl)-1-methylpyrrole (7f; Table 7, Entry 8). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a brown oil (50.0 mg, 0.247 mmol, 62%): HPLC (220 nm) 100%; ^1H NMR (400 MHz, DMSO-d_6) δ 7.97 (d, J = 8.2 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 6.89 (br s, 1H), 6.05 (br s, 1H), 6.00 (br s, 1H) 3.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 149.8, 132.9, 132.5, 129.1, 127.2, 126.4, 124.2, 123.7, 109.2, 107.6, 34.0; HRMS (EI) calcd for $C_{11}H_{10}N_2O_2$ ($M^{+\bullet}$) 202.0742, found 202.0745.[23]

2-(2-Hydroxyphenyl)-1-methylpyrrole (7g; Table 7, Entry 9). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a colorless oil (47.1 mg, 0.272 mmol, 68%): ^1H NMR (400 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.12−7.16 (m, 1H), 7.10 (d, J = 1.6 Hz, 1H), 6.91 (d, J = 7.1 Hz, 1H), 6.80−6.84 (m, 1H), 6.75−6.76 (m, 1H), 6.01 (d, J = 3.5, 1H), 5.93 (d, J = 3.5, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.1, 131.8, 131.2, 128.8, 122.3, 120.6, 118.9, 115.6, 108.3, 106.9, 34.2; HRMS (EI) calcd for $C_{11}H_{12}NO$ ($M^{+\bullet}$) 173.0843, found 173.0841.

2-(2-(Ethyl carboxylic ester)phenyl)-1-methylpyrrole (7h; Table 7, Entry 10). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a colorless oil (65.4 mg, 0.285 mmol, 71%): HPLC (220 nm) >99%; ^1H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 7.8 Hz, 1H), 7.58−7.62 (m, 1H), 7.49−7.53 (m, 1H), 7.40 (d, J = 7.4 Hz, 1H), 6.79−6.81 (m, 1H), 6.01−6.03 (m, 1H), 5.89−5.90 (m, 1H), 4.04 (q, J = 7.0 Hz, 2H), 3.36 (s, 3H), 1.03 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.7, 132.6, 131.8, 131.2, 129.0, 127.8, 122.6, 108.3, 107.0, 60.5, 33.8, 13.7; HRMS (EI) calcd for $C_{14}H_{15}NO_2$ ($M^{+\bullet}$) 229.1109, found 229.1103.

(23) Gryko, D. T.; Vakaliuk, O.; Gryko, D.; Beata, K. *J. Org. Chem.* **2009**, *74*, 9517.

2-(4-Tolyl)-1-methylpyrrole (7i; Table 7, Entry 11). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a colorless oil (53.6 mg, 0.313 mmol, 78%): HPLC (220 nm) 99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.31 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 7.8 Hz, 1H), 6.80 (s, 1H), 6.09 (s, 1H), 6.03 (s, 1H), 3.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 135.7, 133.5, 130.2, 129.1, 127.9, 108.0, 107.3, 34.8, 20.7; HRMS (EI) calcd for $C_{12}H_{13}N$ ($M^{+\bullet}$) 171.1048, found 171.1051.[24]

2-(4-Methoxyphenyl)-1-methylpyrrole (7j; Table 7, Entry 12). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a very pale yellow oil (57.7 mg, 0.308 mmol, 77%): HPLC (220 nm) 99.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 6.77−6.78 (m, 1H), 6.01−6.05 (m, 2H), 3.78 (s, 3H), 3.59 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.1, 133.3, 129.3, 125.5, 123.4, 113.9, 107.6, 107.1, 55.1, 34.7.[23]

2-(4-Trifluoromethyl)phenyl-1-methylpyrrole (7k; Table 7, Entry 13). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A (R_f = 0.3 in 2:98 EtOAc/hexanes) to yield the title compound as a white solid (70 mg, 0.312 mmol, 78%): HPLC (220 nm) >99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (d, J = 8.2 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 6.93 (m, 1H), 6.33 (m, 1H), 6.12 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 136.9, 131.9, 128.0, 125.9, 125.4, 110.1, 107.8, 35.2; HRMS (EI) calcd for $C_{12}H_{10}F_3N$ ($M^{+\bullet}$) 225.210, found 225.0760.[25]

2-(4-Nitrophenyl)-1-methylpyrrole (7l; Table 7, Entry 14). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a yellow solid (54 mg, 0.267 mmol, 66%): HPLC (220 nm) >99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.23 (d, J = 9.1 Hz, 2H), 7.74 (d, J = 9.1 Hz, 2H), 6.99−7.01 (m, 1H), 6.47−6.49 (m, 1H), 6.14−6.16 (m, 1H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.1, 139.4, 131.3, 127.7, 127.4, 123.9, 111.5, 108.3, 35.6.[23,26]

2-(3-Pyridyl)-1-methylpyrrole (7m; Table 7, Entry 15). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a pale yellow solid (53.5 mg, 0.338 mmol, 85%): HPLC (220 nm) 96.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65−8.66 (m, 1H), 8.47−8.48 (m, 1H), 7.85−7.87 (m, 1H), 7.42−7.45 (m, 1H), 6.90−6.91 (m, 1H), 6.27−6.28 (m, 1H), 6.09−6.11 (m, 1H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 148.4, 147.4, 135.0, 130.0, 129.0, 125.5, 123.7, 109.6, 107.8, 35.0.[27]

2-(2-Thiazolyl)-1-methylpyrrole (7n; Table 7, Entry 16). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A (except that the temperature is 190 °C) to yield the title compound as a yellow oil (12.1 mg, 0.074 mmol, 18%): HPLC (220 nm) 96.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 4.0 Hz, 1H), 7.58 (d, J = 3.4 Hz, 1H), 6.97 (s, 1H), 6.64 (t, J = 1.7 Hz, 1H), 6.10 (t, J = 3.1 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.3, 142.9, 127.1, 125.9, 117.6, 112.2, 108.1, 36.3; HRMS (EI) calcd for $C_8H_8N_2S$ ($M^{+\bullet}$) 164.0408, found 164.0404.

2-(2,4-Dimethyl-5-thiazole)-1-methylpyrrole (7o; Table 7, Entry 17). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as a colorless oil (52.6 mg, 0.274 mmol, 71%): HPLC (220 nm) >99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.89 (s, 1H), 6.13 (s, 1H), 6.08 (s, 1H), 3.48 (s, 3H), 2.61 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.7, 149.7, 124.2, 122.0, 121.3, 111.1, 107.5, 34.2, 18.8, 15.7; HRMS (EI) calcd for $C_{10}H_{12}N_2S$ ($M^{+\bullet}$) 192.0721, found 192.0724.

2-(5-Thiophene)-1-methylpyrrole (7q; Table 7, Entry 19). Starting from 1-methyl-2-pyrrolecarboxylic acid, the compound was prepared and purified according to general procedure A to yield the title compound as an colorless oil (57.4 mg, 0.0.324 mmol, 78%): HPLC (220 nm) >99%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.90 (s, 1H), 6.82 (s, 1H), 6.81 (s, 1H), 6.14 (s, 1H), 6.01 (s, 1H), 3.66 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 137.9, 132.3, 126.5, 126.0, 124.3, 124.2, 108.9, 107.4, 34.9, 14.8; HRMS (EI) calcd for $C_{10}H_{11}NS$ ($M^{+\cdot}$) 177.0612, found 177.0609.[26]

1-(4-Methoxyphenyl)-2-phenylpyrrole (17b; Table 5, Entry 1). Starting from compound **17a**, the compound was prepared according to general procedure A and purified by preparative HPLC to yield the title compound as a pale orange solid (66 mg, 0.265 mmol, 66%). HPLC (220 nm): 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.23 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.5 Hz, 1H), 7.09 (m, 4H), 6.98 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.39 (m, 1H), 6.27 (m, 1H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 157.9, 133.1, 132.9, 132.7, 128.2, 127.6, 126.9, 126.6, 125.0, 114.3, 110.2, 108.9, 55.3; HRMS (EI) calcd for $C_{17}H_{15}NO$ ($M^{+\bullet}$) 249.307 found 229.1159.[28]

1-Phenyl-2-phenylpyrrole (18b; Table 5, Entry 2). Starting from compound **18a**, the compound was prepared according to general procedure A and purified by preparative HPLC to yield the title compound as a white solid (51 mg, 0.233 mmol, 58%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (t, J = 7.5 Hz, 2H), 7.33 (m, 1H), 7.23 (t, J = 7.4 Hz, 2H), 7.17 (m, 3H), 7.08 (m, 3H), 6.42 (m, 1H), 6.31 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 140.0, 132.6, 129.2, 128.2, 127.7, 126.8, 126.3, 125.5, 124.9, 110.8, 109.4; HRMS (EI) calcd for $C_{16}H_{13}N$ ($M^{+\bullet}$) 219.281, found 219.1052.[28]

1-(4-Trifluoromethylphenyl)-2-phenylpyrrole (19b; Table 5, Entry 3). Starting from compound **19a**, the compound was prepared according to general procedure A and purified by preparative HPLC to yield the title compound as a white solid (50 mg, 0.174 mmol, 44%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.21 (t, J = 7.6 Hz, 2H), 7.10 (d, J = 7.1 Hz, 2H), 6.47 (m, 1H), 6.37 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 143.2, 132.9, 132.2, 128.5, 127.9, 126.7, 126.4, 125.8, 124.9, 111.9, 110.2; HRMS (EI) calcd for $C_{17}H_{12}F_3N$ ($M^{+\bullet}$) 287.279, found 287.0927.

1-(4-Nitrophenyl)-2-phenylpyrrole (20b; Table 5, Entry 4). Starting fom compound **20a**, the compound was prepared according to general procedure A and purified by preparative HPLC to yield the title compound as a yellow solid (46 mg, 0.176 mmol, 44%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 9.0 Hz, 2H), 7.28 (m, 4H), 7.12 (d, J = 7.1 Hz, 2H), 6.50 (m, 1H), 6.41 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.1, 133.1, 132.0, 128.6, 128.0, 126.9, 125.8, 125.0, 124.8, 112.7, 110.7; HRMS (EI) calcd for $C_{17}H_{12}N_2O_2$ ($M^{+\bullet}$) 264.279, found 264.0904.

Compound 21b (Table 6, Entry 1). Starting from compound **21a**, the compound was prepared and purified according to general procedure A (R_f = 0.35 in 5:95 EtOAc/hexanes) to yield

(24) Drichkov, V. N.; Sobenina, L.; Vakul'skaya, T. I.; Ushakov, I.; Mikhaleva, A. I.; Trofimov, B. A. *Synthesis* **2008**, *16*, 2631.

(25) Maekawa, T.; Kunitomo, J.; Odaka, H.; Kimura, H. *PCT Int. Appl.* **2003**, 114 pp .

(26) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bildeau, F. *J. Am. Chem. Soc.* **2006**, *126*, 11350.

(27) Woodward, C. F.; Badgett, C. O.; Haines, P. G. Oxidation of nicotine to 1-methyl-2-(3-pyridyl)pyrrole. US 2432642 19471216, 1947; CAN 42:12012 AN 1948:12012 .

(28) Shibata, I.; Kato, H.; Yasuda, M.; Baba, A. *J. Organomet. Chem.* **2007**, *16*, 604.

the title compound as an off-white solid (37 mg, 0.240 mmol, 60%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 7.07 (m, 1H), 6.22 (m, 2H), 5.00 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 140.6, 137.3, 133.2, 127.8, 124.8, 123.5, 118.1, 117.1, 112.2, 98.0, 50.0.[29]

Compound 22b (Table 6, Entry 2). Starting from compound **22a** (0.196 mmol) (quantity of other reagents adjusted accordingly), the compound was prepared and purified according to general procedure A (R_f = 0.34 in 5:95 EtOAc/hexanes) to yield the title compound as a gray-blue solid (23 mg, 0.136 mmol, 69%): HPLC (220 nm): 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.51 (d, J = 7.4 Hz, 1H), 7.21 (m, 2H), 7.08 (t, J = 7.4 Hz, 1H), 6.82 (s, 1H), 6.49 (m, 1H), 6.09 (m, 1H), 4.05 (t, J = 6.5 Hz, 2H), 3.00 (t, J = 6.5 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 130.4, 129.2, 128.7, 128.1, 126.9, 125.3, 121.9, 121.3, 108.2, 103.7, 43.3, 28.7.[30]

General Procedure for *N*-Alkylation of 1*H*-2-Pyrrole Methyl Ester. Unless otherwise noted, each reaction was performed using the following procedure. To a solution of the alkylating agent (4.62 mmol) and 1*H*-2-pyrrole methyl ester (6.47 mmol, 1.4 equiv) in anhyd DMF (25 mL) at rt was added cesium carbonate (18.47 mmol, 4 equiv). The mixture was stirred for 16 h, after which it was diluted with ethyl acetate (150 mL), the organic layer was washed with brine (4×), dried over $MgSO_4$, and filtered, and solvent evaporation over silica afforded a solid residue that was purified using normal-phase silica gel. Using 2-bromobenzyl bromide as the alkylating agent, the compound **21a** methyl ester was prepared and purified according to general procedure B (R_f = 0.34 in 5:95 EtOAc/hexanes) to yield the *N*-alkylated compound as a white solid (1.24 g, 4.23 mmol, 92%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (d, J = 7.8 Hz, 1H), 7.27 (m, 2H), 7.21 (td, J = 7.7 Hz and J = 1.3 Hz, 1H), 6.99 (m, 1H), 6.26 (m, 1H), 6.22 (d, J = 7.3 Hz, 1H), 5.59 (s, 2H), 3.64 (s, 3H).

Using 2-bromophenethyl bromide as the alkylating agent (see below for preparation), the compound **22a** methyl ester was prepared and purified according to general procedure B (R_f = 0.24 in 5:95 EtOAc/hexanes) to yield the desired *N*-alkylated compound as a yellow oil (66 mg, 0.214 mmol, 5%): HPLC (220 nm) 97.4%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, J = 8.0 Hz, 1H), 7.27 (td, J = 7.7 Hz and J = 1.3 Hz, 1H), 7.15 (m, 2H), 6.94 (m, 1H), 6.85 (m, 1H), 6.06 (m, 1H), 4.52 (t, J = 7.1 Hz, 2H), 3.72 (s, 3H), 3.11 (t, J = 7.1 Hz, 2H).

Preparation of 2-Bromophenethyl Bromide. To a solution of 2-bromophenethyl alcohol (1 g, 4.97 mmol) and triphenylphosphine (5.97 mmol, 1.2 equiv) in anhydrous dichloromethane (50 mL) at 23 °C was added carbon tetrabromide (5.97 mmol, 1.2 equiv). The resulting mixture was stirred at 23 °C for 16 h, after which time silica gel was added. Solvent evaporation afforded the mixture that was purified using normal-phase silica gel (R_f = 0.54 in 2:98 EtOAc/hexanes) to afford the desired product as a colorless oil (1.22 g, 4.62 mmol, 93%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.61 (d, J = 7.8 Hz, 1H), 7.43 (dd, J = 7.5 Hz and J = 1.5 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.21 (td, J = 7.5 Hz and J = 1.5 Hz, 1H), 3.71 (t, J = 7.4 Hz, 2H), 3.25 (t, J = 7.4 Hz, 2H).

General Procedure for Saponification of *N*-Alkylated-2-pyrrole Methyl Esters. Unless otherwise noted, each reaction was performed using the following procedure. To a solution of the ester in THF (4 mL) and methanol (2 mL) at 23 °C was added 1 N aqueous NaOH solution. The resulting solution was stirred to 50 °C for 4 h, after which time the solution was allowed to cool to 23 °C before being acidified using 1 N aqueous HCl. The aqueous layer was extracted with EtOAc (3×), and the organic layer was dried over anhyd $MgSO_4$. Filtration and solvent evaporation afforded the desired products that were used without further purification for the next step.

***N*-(2-Bromobenzyl)-2-pyrrolecarboxylic Acid (21a; Table 6, Entry 1):** pale brown solid (1.17 g, 4.177 mmol, 99%); HPLC (220 nm) 98.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (s, 1H), 7.62 (d, J = 7.0 Hz, 1H), 7.27 (m, 1H), 7.20 (m, 2H), 6.94 (m, 1H), 6.22 (m, 2H), 5.58 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.6, 138.6, 132.3, 129.9, 128.9, 128.1, 126.5, 122.4, 121.0, 118.1, 108.4, 51.7.

***N*-(2-Bromophenethyl)-2-pyrrolecarboxylic Acid (22a: Table 6, Entry 2):** off-white solid (58 mg, 0.196, 96%); HPLC (220 nm) 96.6%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (s, 1H), 7.58 (d, J = 7.2 Hz, 1H), 7.28 (m, 1H), 7.16 (m, 2H), 6.87 (m, 1H), 6.80 (m, 1H), 6.01 (m, 1H), 4.51 (t, J = 7.2 Hz, 2H), 3.11 (t, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 137.6, 132.5, 130.9, 129.0, 128.7, 127.8, 124.0, 122, 117.8, 107.5, 47.9, 37.4.

General Procedure for *N*-Arylation of 1*H*-2-Pyrrole Methyl Ester. Unless otherwise noted, each reaction was performed using the following procedure. In a microwave vial (2 to 5 mL), opened to air, were added 1-methyl-2-pyrrole methyl ester (400 mg, 3.197 mmol), aryl halide (3.836 mmol, 1.2 equiv), copper iodide (0.639 mmol, 0.2 equiv), potassium phosphate tribasic (6.713 mmol, 2.1 equiv), and *N,N*-dimethylethylenediamine (1.279 mmol, 0.4 equiv). Anhydrous toluene (4 mL) was then added, and the reaction mixture was put under argon atmosphere, capped, and heated at 110 °C for 16 h. The reaction mixture was cooled to 23 °C and diluted with ethyl acetate (100 mL), and the organic layer was washed with water (1×) and 1 N HCl (2×). The organic layer was dried over $MgSO_4$ and filtered, and solvent evaporation over silica afforded a solid residue that was purified using normal-phase silica gel.

1-(4-Nitrophenyl)-2-pyrrole Methyl Ester. Using 4-nitroiodobenzene as aryl halide, the compound was prepared and purified according to general procedure D (R_f = 0.20 in 1:9 EtOAc/hexanes) to yield the title compound as an off-white solid (354 mg, 1.436 mmol, 45%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (d, J = 8.9 Hz, 2H), 7.66 (d, J = 8.9 Hz, 2H), 7.40 (m, 1H), 7.13 (m, 1H), 6.41 (m, 1H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 146.2, 145.0, 130.6, 127.0, 124.0, 122.6, 120.2, 110.4, 51.3. [31]

1-(4-Methoxyphenyl)-2-pyrrole Methyl Ester. Using 4-iodoanisole as aryl halide, the compound was prepared and purified according to general procedure D (R_f = 0.17 in 1:9 EtOAc/hexanes) to yield the title compound as a white solid (665 mg, 2.877 mmol, 90%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, J = 8.8 Hz, 2H), 7.16 (m, 1H), 7.00 (m, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.28 (m, 1H), 3.80 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 158.5, 132.9, 130.7, 127.3, 122.5, 118.5, 113.7, 109.0, 55.4, 50.9.[32]

1-(4-Trifluoromethylphenyl)-2-pyrrole Methyl Ester. Starting with 200 mg (1.598 mmol) of the pyrrole ester and using 4-(trifluoromethyl)iodobenzene as aryl halide (quantity of other reagents adjusted accordingly), the compound was prepared and purified according to general procedure D (R_f = 0.39 in 1:9 EtOAc/hexanes) to yield the title compound as a white solid (385 mg, 1.428 mmol, 89%). HPLC (220 nm): 99.5%; ^{1}H NMR

(29) Antonio, Y.; De la Cruz, M. E.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15.

(30) Crigg, R.; Myers, P.; Somasunderam, A.; Sridharan, V. *Tetrahedron* **1992**, *48*, 9735.

(31) Auvin, S.; Harnett, J.; Bigg, D.; Chabrier De Lassauniere, P.-E.PCT Int. Appl. **1998**, 134 pp

(32) Fogassy, K.; Kovacs, K.; Keseru, G. M.; Toke, L.; Faigl, F. *J. Chem. Soc., Perkin Trans. 1* **2001**, *9*, 1039.

(400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.35 (s, 1H), 7.09 (m, 1H), 6.38 (m, 1H), 3.65 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 143.1, 130.6, 128.0, 126.9, 125.8, 125.4, 122.4, 119.6, 110.0, 51.2.33.[33]

1-Phenyl-2-pyrrole Methyl Ester. Using iodobenzene as aryl halide, the compound was prepared and purified according to general procedure D (R_f = 0.34 in 1:9 EtOAc/hexanes) to yield the title compound as a white solid (596 mg, 2.963 mmol, 93%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.43 (m, 3H), 7.38 (d, J = 6.8 Hz, 2H), 7.24 (m, 1H), 7.04 (m, 1H), 6.32 (m, 1H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 139.9, 130.6, 128.6, 127.6, 126.0, 122.4, 118.9, 109.3, 51.0.[34]

General Procedure for Saponification of *N*-Arylated 2-Pyrrole Methyl Esters. Unless otherwise noted, each reaction was performed using the following procedure. To a solution of the ester in THF (4 mL) and methanol (2 mL) at 23 °C was added 1 N aqueous NaOH solution. The resulting solution was stirred to 50 °C for 4 h, after which time the solution was cooled to 23 °C and acidified using 1 N aqueous HCl. The aqueous layer was extracted with EtOAc (3×), and the combined organic layer was dried over anhydrous $MgSO_4$. Filtration and solvent evaporation afforded the desired products that were used without further purification.

1-(4-Methoxyphenyl)-2-pyrrolecarboxylic Acid (17a; Table 5, Entry 1). Starting from the corresponding ester, the acid was prepared according to general procedure E to yield the title compound as a pale pink solid (614 mg, 2.828 mmol, 98%): HPLC (220 nm) 99.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 7.23 (d, J = 8.8 Hz, 2H), 7.10 (m, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.94 (m, 1H), 6.25 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.0, 158.3, 133.3, 130.2, 127.2, 123.6, 118.4, 113.6, 108.7, 55.4.

1-Phenyl-2-pyrrolecarboxylic Acid (18a; Table 5, Entry 2). Starting from the corresponding ester, the acid was prepared according to general procedure E to yield the title compound as a white solid (514 mg, 2.745 mmol, 93%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.2 (s, 1H), 7.3 (m, 5H), 7.16 (s, 1H), 6.99 (s, 1H), 6.28 (s, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.0, 140.2, 130.1, 128.5, 127.4, 126.0, 123.6, 118.8, 109.0.

1-(4-Trifluoromethylphenyl)-2-pyrrolecarboxylic Acid (19a; Table 5, Entry 3). Starting from the corresponding ester, the acid was prepared according to general procedure E to yield the title compound as a white solid (328 mg, 1.286 mmol, 90%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.3 (s, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.28 (s, 1H), 7.04 (m, 1H), 6.34 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.1, 143.4, 130.2, 127.8, 127.5, 126.8, 125.7, 123.7, 119.6, 109.7.

1-(4-Nitrophenyl)-2-pyrrolecarboxylic Acid (20a; Table 5, Entry 4). Starting from the corresponding ester, the acid was prepared according to general procedure E to yield the title compound as an off-white solid (320 mg, 1.379 mmol, 96%): HPLC (220 nm) 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.5 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.33 (s, 1H), 7.08 (m, 1H), 6.37 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.0, 146.0, 145.3, 130.1, 126.9, 124.0, 120.1, 110.1.

Competition Experiments. 1. 3-Methylfuroic acid (10) vs 3-methylbenzofurancarboxylic Acid (15a). Using general procedure A (but using 4-bromotoluene as the aryl bromide), both 3-methyl-2-furoic acid (0.4 mmol, 1 equiv) and 3-methylbenzofuran-2-carboxylic acid (0.4 mmol, 1 equiv) were submitted to the cross-coupling conditions. HPLC analysis of the crude mixture revealed that both coupling products and *n*-butyl ester products of the acids (through reaction with tetra-*n*-butyl ammonium chloride hydrate) were formed. The crude mixture was then submitted to the saponification conditions (see general procedure E, stirred for 18 h), which after workup gave the mixture of cross-coupling products. ^{1}H NMR analysis of the crude mixture demonstrated that the ratio of 2-arylated products was of 2.2:1 favoring the 2-(4-tolyl)-3-methylfuran.

2-(4-Tolyl)-3-methylfuran (10b). Starting from 3-methyl-2-furoic acid and using the 4-bromotoluene as aryl bromide, the compound was prepared and purified according to general procedure A (R_f = 0.88 in 1:9 EtOAc/ hexanes) to yield the title compound as a pale yellow oil (57 mg, 0.331 mmol, 83%): HPLC (220 nm) 97.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 1.8 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 6.44 (d, J = 1.8 Hz, 1H), 2.32 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.8, 141.1, 136.2, 129.3, 128.5, 124.8, 115.5, 115.4, 20.8, 11.5.

2-(4-Tolyl)-3-methylbenzofuran (15b). Starting from 3-methyl-2-benzofurancarboxylic acid and using 4-bromotoluene as the aryl bromide, the compound was prepared and purified according to general procedure A (R_f = 0.71 in 5:95 EtOAcb/ hexanes) to yield the title compound as a white solid (76 mg, 0.341 mmol, 85%): HPLC (220 nm) 98.8%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 7.1 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.29 (m, 2H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.0, 150.1, 137.8, 130.7, 129.5, 127.8, 126.3, 124.5, 122.6, 119.5, 110.8, 110.6, 20.9, 9.1.

2. 5-(4-Methoxyphenyl)-2-furoic Acid (43a) vs 5-(4-Trifluoromethylphenyl)-2-furoic Acid (443a). Using general procedure A (but using 4-bromotoluene as the aryl bromide), both 5-(4-methoxyphenyl)-2-furoic acid (0.4 mmol, 1 equiv) and 5-(4-trifluoromethylphenyl)-2-furoic acid (0.4 mmol, 1 equiv) (see syntheses for both analogues below) were submitted to the cross-coupling conditions. HPLC analysis of the crude mixture revealed that both coupling products and *n*-butyl ester products of the acids (through reaction with tetra-*n*-butyl ammonium chloride hydrate) were formed. The crude mixture was then submitted to the saponification conditions (see general procedure E, stirred for 18 h) which after workup gave the mixture of cross-coupling products. ^{1}H NMR analysis of the crude mixture clearly demonstrated that the ratio of 2-arylated products was of 1.8: 1 favoring the 2-(4-tolyl)-3-methylfuran.

5-(4-Methoxyphenyl)-2-(4-tolyl)furan (43b). Starting from 5-(4-methoxyphenyl)-2-furoic acid and using 4-bromotoluene as the aryl bromide, the compound was prepared according to general procedure A (purified using a semipreparative HPLC) which yielded the desired product contaminated with *n*-butyl ester derivative (resulting from the reaction with tetra-*n*-butyl ammonium chloride hydrate). This mixture was then submitted to the saponification conditions (see general procedure E) which after appropriate workup gave the title compound as an off-white solid (32 mg, 0.121 mmol, 30%): HPLC (220 nm) 96.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (d, J = 8.6 Hz, 2H), 7.67 (d, J = 8.2 Hz, 2H), 7.25 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 3.5 Hz, 1H), 6.89 (d, J = 3.5 Hz, 1H), 3.80 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8, 152.4, 152.1, 136.6, 129.5, 127.6, 124.9, 123.2, 123.1, 114.4, 107.3, 106.3, 55.2, 20.8.[35]

Synthesis of 5-(4-Methoxyphenyl)-2-methylfuroic Acid (43a). In a microwave vial (10−20 mL), opened to air, were added 2-bromo-5-methylfuroate ester (4.88 mmol, 1 equiv), 4-methoxyphenyl boronic acid (5.85 mmol, 1.2 equiv), potassium

(33) Faigl, F.; Fogassy, K.; Szucs, E.; Kovacs, K.; Keseru, G. M.; Harmat, V.; Bocskeri, Z.; Toke, L. *Tetrahedron* **1999**, *55*, 7881.

(34) Cartoon, M. E. K.; Cheeseman, G. W. H. *J. Organomet. Chem.* **1982**, *2*, 123.

(35) Rees, C. W.; Yue, T.-Y, *J. Chem. Soc., Perkin Trans. 1* **1997**, *15*, 2247.

carbonate (9.76 mmol, 2 equiv), and palladium(0) tetrakis-triphenylphosphine (0.49 mmol, 0.10 equiv), and DMF (12 mL) followed by water (3 mL), after which the mixture was stirred for 30 s and submitted to the microwave conditions (130 °C, 12 min, high absorption level). The reaction mixture was then diluted with ethyl acetate (100 mL), the organic layer was washed with brine (3×), saturated $NaHCO_3$ solution (2×), water (1×), and again with brine (1×). The organic layer was finally dried over $MgSO_4$ and filtered, and solvent evaporation over silica afforded a solid residue that was purified using normal-phase silica gel (R_f = 0.23 in 1:9 EtOAc/hexanes) to yield the title compound as a white crystalline solid (544 mg, 2.34 mmol, 48%). *This is an unoptimized yield; much saponification was observed* (*which material was not recovered*): HPLC (220 nm) 98.7%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 3.8 Hz, 1H), 7.04 (m, 3H), 3.83 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.0, 158.3, 157.1, 142.3, 126.2, 121.7, 120.8, 114.6, 106.5, 55.3, 51.7.

This intermediate was then submitted to the saponification conditions (see general procedure E), which after appropriate workup gave the title compound as an off-white solid (469 mg, 2.15 mmol, 97%) that was used without further purification: HPLC (220 nm) 98.9%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.0 (s, 1H), 7.74 (d, J = 9.0 Hz, 2H), 7.29 (d, J = 3.7 Hz, 1H), 7.05 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 3.7 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.8, 159.3, 156.5, 143.4, 126.0, 122.0, 120.0, 114.5, 106.3, 55.3.[36]

5-(4-Trifluoromethylphenyl)-2-(4-tolyl)furan (44b). Starting with 78 mg (0.304 mmol) of 5-(4-trifluoromethylphenyl)-2-furoic acid and using 4-bromotoluene as the aryl bromide (quantity of other reagents adjusted accordingly), the compound was prepared according to general procedure A. The crude mixture contained the desired product together with the *n*-butyl ester derivative (resulting from the reaction with tetra-*n*-butylammonium chloride hydrate). It was then submitted to the saponifications conditions (see general procedure E) which after appropriate workup gave the mixture that was purified according to general procedure A to yield the title compound as a white solid (22 mg, 0.073 mmol, 48%): HPLC (220 nm) 99.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.29 (m, 3H), 7.08 (d, J = 3.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.0, 150.6, 137.5, 133.7, 129.5, 127.1, 125.9, 123.7, 110.8, 107.8, 20.9.[37]

Synthesis of 5-(4-Trifluoromethylphenyl)-2-methylfuroic Acid (44a). In a microwave vial (10 to 20 mL), opened to air, were added 2-bromo-5-methylfuroate ester (4.88 mmol, 1 equiv), 4-trifluoromethylphenyl boronic acid (5.85 mmol, 1.2 equiv), potassium carbonate (9.76 mmol, 2 equiv), palladium(0) tetrakis-triphenylphosphine (0.49 mmol, 0.10 equiv), and DMF (12 mL) followed by water (3 mL), after which the mixture was stirred for 30 s and submitted to the microwave conditions (130 °C, 12 min, high absorption level). The reaction mixture was then diluted with ethyl acetate (100 mL), and the organic layer was washed with brine (3×), saturated $NaHCO_3$ solution (2×), water (1×), and again with brine (1×). The organic layer was dried over $MgSO_4$ and filtered, and solvent evaporation over silica afforded a solid residue that was purified using normal-phase silica gel (R_f = 0.32 in 1:9 EtOAc/hexanes) to yield the title compound as a white crystalline solid (214 mg, 0.792 mmol, 16%). *This is an unoptimized yield, much saponification was observed* (*which material was not recovered*): HPLC (220 nm) 99.5%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 8.3 Hz, 2H), 7.47 (d, J = 3.5 Hz, 1H), 7.39 (d, J = 3.5 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 158.2, 154.9, 143.9, 132.5, 126.1, 125.1, 120.5, 110.3, 52.0.

This intermediate was then submitted to the saponification conditions (see general procedure E), which after appropriate workup gave the title compound as a white solid (189 mg, 0.738 mmol, 93%) that was used without further purification for the cross-coupling reaction: HPLC (220 nm) 99.3%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.3 (s, 1H), 8.02 (d, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.36 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.2, 154.4, 145.1, 132.8, 126.1, 126.0, 124.9, 119.8, 110.2.[38]

Acknowledgment. This paper is dedicated to the memory of Professor Keith Fagnou, an inspiring scientist and wonderful individual who provided valuable insights on this work. We wish also to thank Professor A. B. Charette for valuable discussions concerning this work and our colleagues, especially Dr. L. Morency, Dr. B. Moreau, and Dr. O. Lepage, at Boehringer Ingelheim (Canada) Ltd., R&D, for their support and useful suggestions during the preparation of this manuscript. We also acknowledge Professor S. K. Collins for suggestions concerning the manuscript and Professor X. Ottenwaelder for his assistance with the molecular orbital analysis.

Note Added after ASAP Publication. In the version published ASAP on February 8, 2010, in the full paragraph under Table 8, the expression S_EAr-type was changed to CMD-type; the corrected version posted on February 10, 2010.

Supporting Information Available: Experimental procedures, NMR spectra, and HRMS data for compounds **7c**,**e**−**o**, **q**, **10b**, **15b**, **17**−**22**, **43a**,**43b**, **44a**, and **44b** and details on the molecular orbital analysis of **42** and **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(36) Prasad, D. J.; Ashok, M.; Karegoudar, P.; Poojary, B.; Holla, B. S.; Kumari, N. S. *Eur. J. Med. Chem.* **2009**, *2*, 551.

(37) Iwai, T.; Fujihara, T.; Terao, J.; Tsuji, Y. *J. am. Chem. Soc.* **2009**, *131*, 6668.

(38) Carter, P. H.; Cherney, R. J.; Batt, D. G.; Dunica, J. V.; Gardner, D. S.; Ko, S. S.; Srivastava, A. S.; Yang, M. G. PCT Int. Appl. **2005**, 437 pp.