ORGANIC LETTERS
2013
Vol. 15, No. 2
362–365

Microwave-Assisted Synthesis of 3-Nitroindoles from *N*-Aryl Enamines via Intramolecular Arene–Alkene Coupling

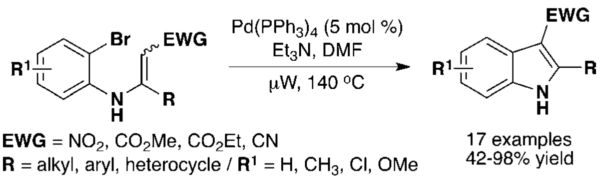
Huy H. Nguyen and Mark J. Kurth*

Department of Chemistry, University of California, One Shields Avenue, Davis, California 95616, United States

mjkurth@ucdavis.edu

Received December 3, 2012

ABSTRACT



A variety of *N*-aryl β-nitroenamines were effectively transformed into 3-nitroindoles in good yields and with complete regioselectivity via a rapid microwave (μW) assisted intramolecular arene–alkene coupling reaction. This report further demonstrates the versatility of this method by constructing 3-carboalkoxy- and 3-cyanoindoles. Optimization data, substrate scope, and applications are discussed.

The indole scaffold, a ubiquitous core structure present in numerous natural products and synthetic pharmaceuticals, has been found to present antitumor, anticancer, antimicrobial, antibacterial, and anti-inflammatory activities,[1] and dozens of methods for the construction of indoles have been developed.[2] Belonging to this privileged heterocyclic class, substituted nitroindoles are versatile intermediates in the synthesis of important biologically active molecules. For example, 3-nitroindoles are useful precursors in the syntheses of the novel antidiabetic agent *N*-(1*H*-indol-3-yl)-guanidine[3] (**1**) as well as the cruciferous phytoalexins isocyalexin A (**2**) and rapalexin A (**3**) (naturally occurring isocyanide and isothiocyanate indoles, respectively; see Figure 1).[4] A 3-nitroindole is also the key building block in the synthesis of a 3-acylamino-2-aminopropionic acid derivative (**4**),[5] which has proven to be a potent ligand for the glycine coagonist site on the *N*-methyl-D-aspartate (NMDA) receptor involved in memory and developmental processes.

---

(1) (a) Wu, S.; Wang, L.; Guo, W.; Liu, X.; Liu, J.; Wei, X.; Fang, B. *J. Med. Chem.* **2011**, *54*, 2668–79. (b) Robinson, M. W.; Overmeyer, J. H.; Young, A. M.; Erhardt, P. W.; Maltese, W. A. *J. Med. Chem.* **2012**, *55*, 1940–56. (c) Haug, B. E.; Stensen, W.; Kalaaji, M.; Rekdal, O.; Svendsen, J. S. *J. Med. Chem.* **2008**, *51*, 4306–14. (d) Hossein nia, R.; Mamaghani, M.; Tabatabaeian, K.; Shirini, F.; Rassa, M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5956–60. (e) Elmegeed, G. A.; Baiuomy, A. R.; Abdel-Salam, O. M. E. *Eur. J. Med. Chem.* **2007**, *42*, 1285–92.

(2) (a) Fischer, E.; Jourdan, F. *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2241–5. (b) Fischer, E.; Hess, O. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559–68. (c) Bartoli, G.; Leardini, R.; Medici, A.; Rosini, G. *J. Chem. Soc.* **1978**, 692–6. (d) Bartoli, G.; Palmieri, F.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129–32. (e) Bartoli, G.; Bosco, M.; Dalpozzo, R. *J. Chem. Soc.* **1991**, 2757–61. (f) Madelung, W. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 1128–34. (g) Nenitzescu, C. D. *Bull. Soc. Chem. Romania* **1929**, *11*, 37–43. (h) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–90. (i) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jorgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 888–90. (j) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403–6. (k) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem., Int. Ed.* **2004**, *43*, 4526–8. (l) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676–7. (m) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2010**, *132*, 11416–7. (n) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–34. (o) Fang, Y.; Lautens, M. *Org. Lett.* **2005**, *7*, 3549–52. (p) Fayol, A.; Fang, Y.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203–6. (q) Edmondson, S. D.; Mastracchio, A.; Parmee, E. M. *Org. Lett.* **2000**, *2*, 1100–12. (r) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251–63. (s) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220–2. (t) Wei, Y.; Deb, I.; Yoshikai, W. *J. Am. Chem. Soc.* **2012**, *134*, 9098–101.

(3) Bahekar, R. H.; Jain, M. R.; Goel, A.; Patel, D. N.; Prajapati, V. M.; Gupta, A. A.; Jadav, P. A.; Patel, P. R. *Bioorg. Med. Chem.* **2007**, *15*, 3248–65.

(4) Soledade, M.; Pedras, C.; Yaya, E. E. *Org. Biomol. Chem.* **2012**, *10*, 3613–16.

(5) Urwyler, S.; Floersheim, P.; Roy, B. L.; Koller, M. *J. Med. Chem.* **2009**, *52*, 5093–107.

10.1021/ol303314x

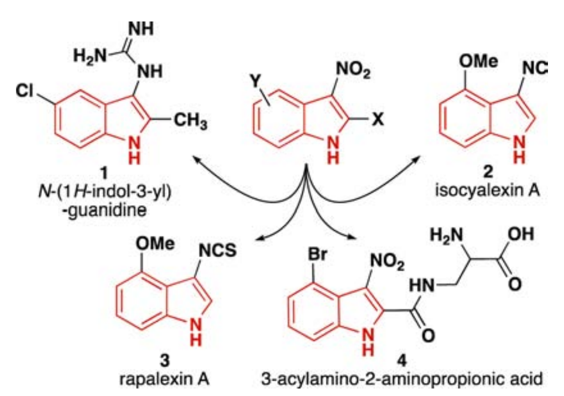


Figure 1. Bioactive compounds containing indole scaffold.

The synthetic utility of 3-nitroindoles creates a demand for reliable and versatile routes to these heterocycles from inexpensive precursors. Classic indole nitration methods, utilizing strongly acidic conditions,[6a] nitrous acid,[6b] or benzoyl nitrate[6c] (generated *in situ* from benzoyl chloride and silver nitrate), can be effective, but their harsh conditions generally result in low functional group tolerance, low yield, and/or lack of regioselectivity.[6]

Experimentally, we observed that the benzoyl nitrate method leads to the formation of significant quantities of tarry side products, reducing the reaction yield and complicating purification. This method also requires stoichiometric silver nitrate, which creates heavy metal waste disposal issues. These shortcomings, in conjunction with the inherent limitations of direct nitration, prompted our investigation into more effective routes to 3-nitroindoles.

In the past several years, the emergence of numerous methods for indole synthesis utilizing organometallic catalyzed cross-coupling or metal-free oxidative coupling C−N/C−C bond formation has attracted considerable attention.[2j−m,7,8] In that context, Nazaré's methodology is particularly interesting, as it represents an effective route to substituted indoles from *o*-chloroanilines and ketones.[2k] Driver et al. reported a route to 3-nitroindoles from β-nitro styryl azides by Rh_2(II)-catalyzed nitro-group migration,[9] which is an effective method, but it is somewhat limited by its use of the expensive $Rh_2(esp)_2$ catalyst as well as the multiple synthetic steps required to prepare the precursor nitro styryl azides. 3-Nitroindoles prepared by this method were unfunctionalized at the 2-position. To the best of our knowledge, there has been only one report of a substituted 3-nitroindole synthesized by C−H activation cyclization (a modest yield of 62% was reported).[10]

Building on our recently reported multicomponent method for indole synthesis utilizing coupled palladium-catalyzed coupling reactions,[11] we believed an appropriate methodology could be developed to construct substituted 3-nitroindoles. Herein, we report the versatile palladium-catalyzed cyclization of *N*-aryl β-nitroenamines as a route to functionalized 3-nitroindoles, a method also applicable (*vide infra*) to the synthesis of indoles bearing other electron-withdrawing groups ($-CO_2R$/$-CN$) at C3.

Since its first introduction in the mid-1980s, microwave (μW) irradiation has been widely employed as an effective reaction acceleration protocol, resulting in rapid, clean, and high-yielding transformations.[12] Indeed, there is ample literature precedent proving microwave irradiation can mediate, for example, the Heck reaction.[13] It is also well established that elevated pressure also assists a Pd-mediated coupling reaction by accelerating oxidative addition and improving the catalyst lifetime and turnover by enhancing ligand association−dissociation.[14]

Our initial studies focused on the intramolecular arene−alkene coupling of enamine **5a** [(*Z*)-2-bromo-*N*-(1-nitroprop-1-en-2-yl)aniline; Table 1], which is available from the condensation of *o*-bromoaniline with 1-nitropropan-2-one.[15] This *o*-bromoaniline-based enamine was chosen as a model substrate since bromoarenes are known to undergo palladium cross-coupling reaction faster than, for example, chloroarenes; in addition, *o*-bromoaniline derivatives are more readily available than iodoanilines. As illustrated in Table 1, we began by assessing the catalytic activities of various sources of palladium(0) (entries 1−3).

While $Pd_2(dba)_3$/DPPF/Cs_2CO_3/toluene/130 °C/48 h (Table 1, entry 1) and $Pd(PPh_3)_4$/CuI/Et_3N/toluene/130 °C/18 h (entry 2) systems did not promote product formation, 5 mol % $Pd(PPh_3)_4$/Et_3N/pyridine/140 °C/48 h (entry 3) did effect the desired transformation. However,

---

(6) (a) Noland, W. E.; Smith, L. R.; Rush, K. R. *J. Org. Chem.* **1965**, *30*, 3457–69. (b) Colonna, M.; Greci, L.; Poloni, M. *J. Chem. Soc., Perkin Trans. 2* **1984**, 165–9. (c) Berti, G.; Da Settimo, A.; Nannipieri, E. *J. Chem. Soc. C* **1968**, 2145–51.

(7) (a) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160–65. (b) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844–50. (c) Hiroya, K.; Itoh, S.; Sakamoto, T. *Tetrahedron* **2005**, *61*, 10958–64. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279–81. (e) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919–22.

(8) For the cyclization of *o*-haloanilino enamines, see: (a) Kasahara, A.; Izumi, T.; Murakami, S.; Yanai, H.; Takatori, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 927–8. (b) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215–8. (c) Michael, J. P.; Chang, S.-F.; Wilson, C. *Tetrahedron Lett.* **1993**, *34*, 8365–8. (d) Chen, L.-C.; Yang, S.-C.; Wang, H.-M. *Synthesis* **1995**, 385–6. (e) Blache, Y.; Sinibaldi-Troin, M.-E.; Voldoire, A.; Chavignon, O.; Gramain, J.-C.; Teulade, J.-C.; Chapat, J.-P. *J. Org. Chem.* **1997**, *62*, 8553–6. (f) Edmonson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109–12. (g) Dajka-Halasz, B.; Monsieurs, K.; Elias, O.; Karolyhazy, L.; Tapolcsanyi, P.; Maes, B. U. W.; Riedl, Z.; Hajos, G.; Dommisse, R. A.; Lemiere, G. L. F.; Kosmrlj, J.; Matyus, P. *Tetrahedron* **2004**, *60*, 2283–91. (h) Maruyama, J.; Yamashita, H.; Watanabe, T.; Arai, S.; Nishida, A. *Tetrahedron* **2009**, *65*, 1327–35. (i) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J. Org. Chem.* **2003**, *68*, 6011–19. (j) Yamazaki, K.; Kondo, Y. *J. Comb. Chem.* **2002**, *4*, 191–2. (k) Yamazaki, K.; Kondo, Y. *Chem. Commun.* **2002**, 210–1.

(9) Stokes, B. J.; Liu, S.; Driver, T. G. *J. Am. Chem. Soc.* **2011**, *133*, 4702–5.

(10) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417–20.

(11) Knapp, J. M.; Zhu, J. S.; Tantillo, D. J.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 10588–91.

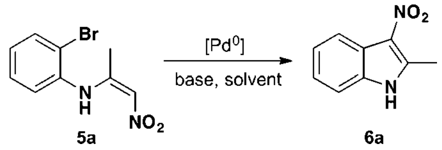
(12) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–83.

(13) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–66.

(14) (a) De Meijere, A.; Braese, S. In *Transition Metal Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999. (b) Hillers, S.; Sartori, S.; Reiser, O. *J. Am. Chem. Soc.* **1996**, *118*, 2087–88.

(15) Tietze, L. F.; Böhnke, N.; Dietz, S. *Org. Lett.* **2009**, *11*, 2948–50.

Table 1. Condition Optimization: Synthesis of **6a** from **5a**[a]



entry	catalyst	base	solvent	*t* (°C)	time (h)	yield[b] (%)
1[c]	$Pd_2(dba)_3$/DPPF	Cs_2CO_3	toluene	130	48	0
2[c]	$Pd(PPh_3)_4$/CuI	Et_3N	toluene	130	18	0
3[c]	$Pd(PPh_3)_4$	Et_3N	pyridine	140	48	25
4[d]	$Pd(PPh_3)_4$	Et_3N	pyridine	140	1.5	57
5[d]	$Pd(PPh_3)_4$	Et_3N	DMF	140	1.5	81
6[d]	$Pd(PPh_3)_4$	DIPEA	DMF	140	1.5	81
7[d]	$Pd(OAc)_2$/P(*o*-tol)$_3$	Et_3N	DMF	140	1.5	82
8[d]	$Pd(OAc)_2$/P(*n*-Bu)$_3$	Et_3N	DMF	140	1.5	48
9[d]	$Pd(OAc)_2$/P(*t*-Bu)$_3$	Et_3N	DMF	140	1.5	83
10[d]	$Pd(OAc)_2$/*t*BuXPhos	Et_3N	DMF	140	1.5	83

[a] Optimal reaction condition: **5a** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), Et_3N (5 equiv), DMF (0.1 M), *μ*W at 140 °C, 90 min. [b] Isolated yields. [c] Conventional oil bath heating. [d] Microwave irradiated. dba = dibenzylideneacetone, DPPF = 1,1′-bis(diphenylphosphanyl)-ferrocene. DIPEA = *N*,*N*-diisopropylethylamine. *t*BuXPhos = 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl.

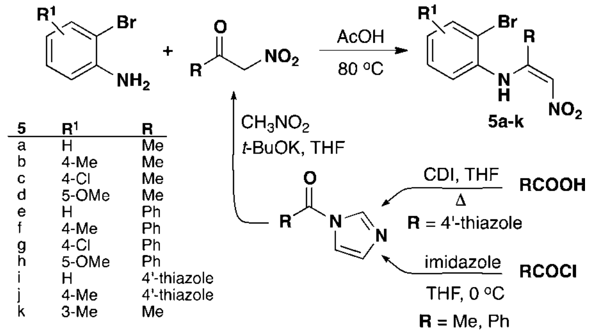
the interconversion proceeded slowly and in low yield (25%) under conventional oil bath heating conditions.

Under microwave irradiation at the same bulk temperature, the transformation went to completion in 90 min and in significantly improved yield (57%; entry 4). As illustrated in Table 1/entry 5, switching to DMF, another highly polarizable solvent that, like pyridine, responds well to microwave irradiation, further improved the 3-nitroindole yield (57→81%). Finally, DIPEA and Et_3N were both similarly effective, affording product **6a** in 81% yield (Table 1, entries 5 and 6). A combination of $Pd(OAc)_2$ (4 mol %) and PPh_3 (8 mol %) gave the same results as $Pd(PPh_3)_4$ (5 mol %). We also screened more active *σ*-donor monodentate phosphine ligands (entries 7−10); while P(*o*-tol)$_3$, P(*t*-Bu)$_3$, and *t*BuXPhos gave slightly higher yields, these ligands were not utilized in this work due to their air sensitivity and higher costs compared to $Pd(PPh_3)_4$.

With optimized conditions for **5a** → **6a** in hand (Table 1), we set out to more generally explore methodology for converting *o*-bromoanilines and α-nitroketones into the requisite 2-bromo-*N*-(1-nitroprop-1-en-2-yl)- and 2-bromo-*N*-(2-nitro-1-arylvinyl)aniline derivatives (**5a**−**k**; Scheme 1). These enamine substrates were synthesized in 30−88% yield by an acid-catalyzed condensation reaction between commercially available *o*-bromoanilines and α-nitroketones, in turn available by the C-acylation of nitromethane with *N*-acylimidazoles[15] [prepared *in situ* by the reaction of carboxylic acids with 1,1′-carbonyldiimidazole (CDI) or acid chlorides with imidazole (Scheme 1)].[16] Substrates **5a**−**k** were obtained only as the *Z*-isomers, which presumably is a consequence of hydrogen bonding between the NH group and an oxygen on the nitro moiety.[17]

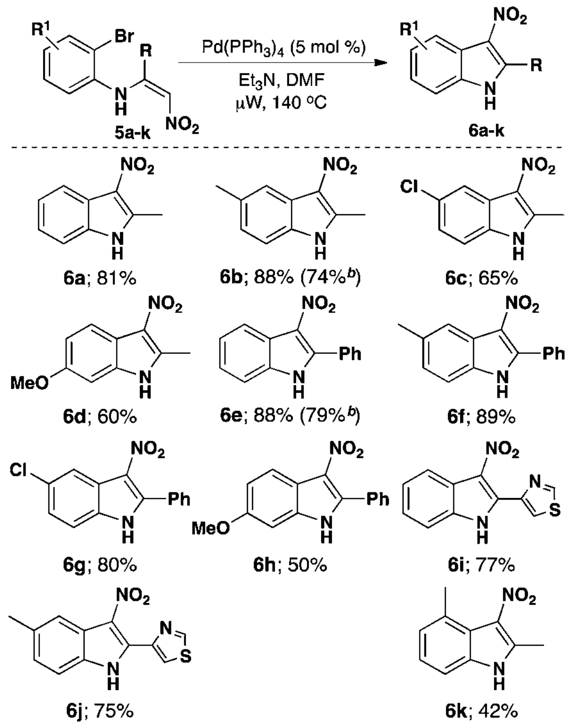
Under our optimized conditions, enamines **5a**−**k** were successfully transformed into the corresponding 3-nitroindoles (**6a**−**k**) in moderate to good yields (Scheme 2). Substrates with electron-donating or -neutral substituents were converted to the desired indoles in higher yields than those with electron-withdrawing groups. Microwave heating provided better indole yields than conventional oil bath heating (**6b**,**e**). The presence of an electron-donating 5-OMe group in substrates **5d** and **5h** lowered the yields

Scheme 1. Synthesis of *β*-Nitroenamines **5** from *o*-Bromoanilines and α-Nitroketones



5	R1	R
a	H	Me
b	4-Me	Me
c	4-Cl	Me
d	5-OMe	Me
e	H	Ph
f	4-Me	Ph
g	4-Cl	Ph
h	5-OMe	Ph
i	H	4'-thiazole
j	4-Me	4'-thiazole
k	3-Me	Me

Scheme 2. Examples of Substituted 3-Nitroindoles[a]



[a] Optimal reaction condition: **5** (1 equiv), $Pd(PPh_3)_4$ (5 mol %), Et_3N (5 equiv), DMF (0.1 M), *μ*W at 140 °C, 90 min. Isolated yields. Products characterized by ^1H, ^{13}C NMR, IR, and HRMS. [b] Oil bath heating yields.

---

(16) Staab, H. A. *Angew. Chem., Int. Ed.* **1962**, *1*, 351–67.

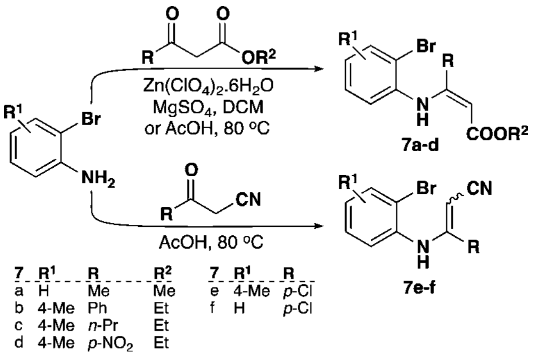
(17) Casarrubios, L.; Perez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358–59.

of the corresponding indoles. Aryl enamines (**5e**–**g**) led to slightly higher indole yields than did aliphatic enamines. Substitution at C4 (see **6k**) is also tolerated, but the yield is diminished (42% vs 81% for **6a**).

In the case of heterocyclic (4′-thiazole, **5i**–**j**) enamines, the yields were slightly lower, which could be due to poisoning of the catalyst. A chloro substituent on the aryl part of the enamine (**5c,g**) is tolerated in this transformation. We did not observe the formation of intermolecular coupling products with chloro-substituted aryl enamines. We also verified that this reaction does not involve the formation of soluble palladium nanoparticles as the catalytically active species by adding Hg(0); this poisoning test on substrate **5b** was negative.[18] Finally, microwave irradiation provided such clean reaction mixtures that the isolation/purification protocol consisted of subjecting the crude reaction mixture to silica gel chromatography without the need for an aqueous workup.

With these encouraging results in hand, we decided to further probe the reaction scope by employing other enamine substrates bearing electron-withdrawing substituents, such as cyano or carboalkoxy groups. *N*-Arylenamine carboxylate and *N*-arylaminoacrylonitrile substrates were obtained in good yields from the acid catalyzed condensation of *o*-bromoanilines with *β*-ketoesters or 3-oxo-3-aryl-propionitrile, respectively (Scheme 3).

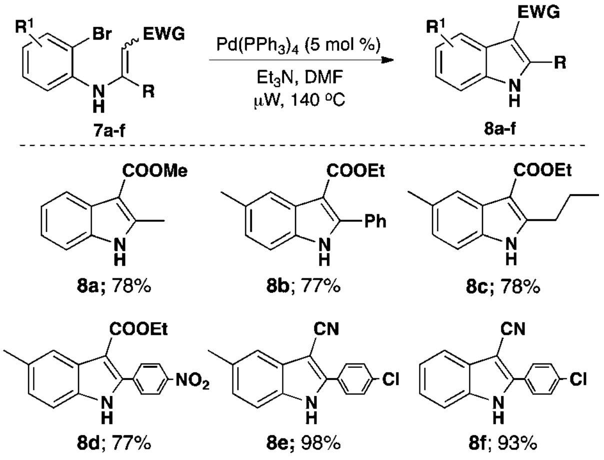
Scheme 3. Preparation of *N*-Aryl Enamine Carboxylates and 3-Arylaminoacrylonitriles



7	R¹	R	R²
a	H	Me	Me
b	4-Me	Ph	Et
c	4-Me	*n*-Pr	Et
d	4-Me	*p*-NO₂	Et

7	R¹	R
e	4-Me	*p*-Cl
f	H	*p*-Cl

Scheme 4. Extending the Scope of Reaction[a]



[a] Reaction condition: **7** (1 equiv), Pd(PPh$_3$)$_4$ (5 mol %), Et$_3$N (3 equiv), DMF (0.1 M), *μ*W at 140 °C, 50 min. Isolated yields. Products characterized by ^{1}H, ^{13}C NMR, IR, and HRMS.

Employing these enamines in our optimized reaction delivered the desired 3-carboalkoxy indoles and 3-cyanoindoles (Scheme 4) with a shorter irradiation time. Our yields of 3-carboalkoxy indoles were comparable to similar examples synthesized by the C–H activation method reported by Glorius et al.[19] With our *o*-bromoaniline protocol, we did not observe any nonselective formation of regioisomers, an issue with the Glorius method. *N*-Arylaminoacrylonitriles were rapidly converted to 3-cyanoindoles (**8e,f**) in excellent yield and modest catalyst loading. We note that 3-cyanation methods[20] on preformed indoles utilize stoichiometric amounts of toxic cyanating agents.

Finally, we note that the aryl chloride moieties in **6c**/**g** and **8e**/**f** can be exploited in subsequent synthetic modification. For example, Suzuki–Miyaura cross-coupling reactions can enable further diversification.[21]

In summary, we have developed a rapid and effective microwave mediated route to 3-nitroindoles from *N*-aryl *β*-nitroenamines by a palladium-catalyzed intramolecular arene–alkene coupling reaction. This method utilizes catalytic amounts of relatively inexpensive Pd(PPh$_3$)$_4$. The enamines required for this transformation are readily available in one synthetic step from commercially available *o*-bromoanilines. This technology accesses indoles with functionalization at the 2-position, accommodating alkyl, aryl, or heterocyclic substituents. Substrate studies establish that the chemistry reported here affords good functional group tolerance and can also provide access to 3-carboalkoxy- and 3-cyanoindoles.

Acknowledgment. We thank the National Institutes of Health (GM089153 and DK072517) for generous financial support of this work. H.H.N. thanks Dr. John M. Knapp (UC Davis; Kurth Group) for helpful discussions. We also thank Ms. Kelli M. Farber (UC Davis; Kurth Group) for assistance in the collection of HRMS data.

Supporting Information Available. Full experimental details and characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS, and mp) of all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(18) A Hg(0) poisoning test was performed according to: Weddle, K. S.; Aiken, J. D.; Finke, R. G. *J. Am. Chem. Soc.* **1998**, *120*, 5653–66.

(19) Neumann, J. J.; Rakshit, S.; Dröge, T.; Würtz, S.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7298–303.

(20) (a) Peng, J.; Zhao, J.; Hu, Z.; Liang, D.; Huang, J.; Zhu, Q. *Org. Lett.* **2012**, *14*, 4966–9. (b) Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 5608–11. (c) Subba Reddy, B. V.; Begum, Z.; Jayasudhan Reddy, Y.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 3334–36.

(21) Kudo, M.; Perseghini, G.; Fu, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–84.

The authors declare no competing financial interest.