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# Pd$^{II}$-Catalyzed Di-*o*-olefination of Carbazoles Directed by the Protecting *N*-(2-Pyridyl)sulfonyl Group

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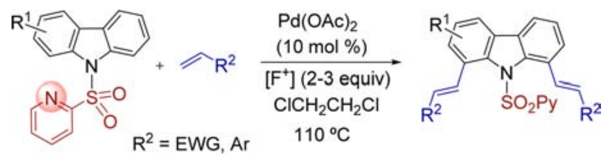
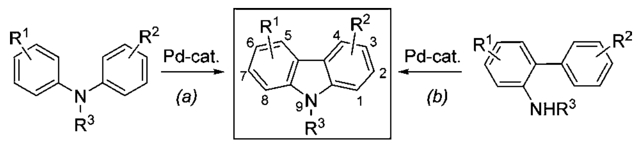
## ABSTRACT




**Despite the significance of carbazole in pharmacy and material science, examples of the direct C−H functionalization of this privileged unit are quite rare. The *N*-(2-pyridyl)sulfonyl group enables the Pd$^{II}$-catalyzed *ortho*-olefination of carbazoles and related systems, acting as both a directing and readily removable protecting group. This method features ample structural versatility, affording typically the double *ortho*-olefination products (at C1 and C8) in satisfactory yields and complete regiocontrol. The application of this procedure to related heterocyclic systems, such as indoline, is also described.**

The unique structural features and biological activities of carbazole derivatives, including anti-HIV, anticancer, and antibacterial activities, have led to a great impetus in the development of carbazole chemistry.[1] The properties imparted by this motif have also found applications in materials science as optoelectronic or luminescent materials.[2] The most versatile and practical methods for carbazole synthesis involve the metal-catalyzed cyclization of either diarylamine derivatives[3] (route *a*, Scheme 1) or 2-aminobiphenyl derivatives[4] (pathway *b*).

**Scheme 1.** General Catalytic Methods to Carbazole Derivatives




However, despite this significant progress, limitations still remain with regard to the type of substitution pattern that can be accessed. For instance, the synthesis of C1/C8-disubstituted carbazole derivatives[5] through these routes is problematic due to the steric congestion next to the reactive

(1) For the synthesis and biological activity of carbazoles: (a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193. (b) Roy, J.; Jana, A. K.; Mal, D. *Tetrahedron* **2012**, *68*, 6099.

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(3) For recent examples, see: (a) Liégault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (b) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4720. (c) Gensch, T.; Rönnefahrt, M.; Czerwonka, R.; Jäger, A.; Kataeva, O.; Bauer, I.; Knölker, H.-J. *Chem.—Eur. J.* **2012**, *18*, 770.

(4) For selected references, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (d) Youn, S. W.; Bihn, J. H.; Kim, B. S. *Org. Lett.* **2011**, *13*, 3738. For the synthesis of the carbazole nucleus from anilides and arenes by double C−H activation: (e) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115. For metal-free approach: (f) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. For both Cu-catalyzed and metal-free conditions: (g) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. See also: Lu, C.; Markina, N. A.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 11153.

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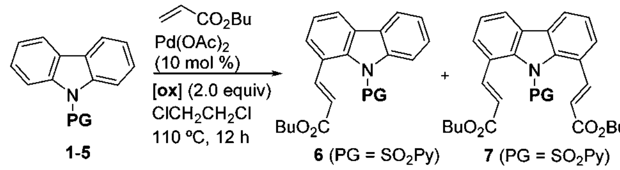
site, especially in route *a*. Because of the higher nucleophilic character of the C3 and C6 positions of the carbazole, the electrophilic substitution at the C3 and/or C6 positions constitutes an efficient alternative approach for the direct functionalization of the carbazole skeleton.[6] As a consequence of this electronic distribution, substitution at the less activated C1 and C8 of the carbazole typically requires prior protection of the 3,6-positions.[2a−c,5]

In stark contrast to the tremendous progress made with related nitrogen aromatic systems,[7] methods for the catalytic direct C−H functionalization of the carbazole core are quite rare, and only recently have the first successful examples appeared. Chu, Wu and co-workers disclosed the $Pd^{II}$-catalyzed direct *ortho*-arylation of carbazoles bearing a *N*-(pyridin-2-yl) directing group with potassium aryltrifluoroborates.[8] Patureau et al. have reported the direct dehydrogenative C1−N carbazolation of *NH*-carbazoles by the cooperative action of Ru and Cu catalysts.[9] Within this context, new methods for the regiocontrolled direct C−H functionalization, providing orthogonal selectivities to those currently available, as well as other types of functionalization, are of great interest in carbazole synthesis.

We have recently reported the $Pd^{II}$-catalyzed direct olefination of *N*-alkyl *N*-(2-pyridyl)sulfonyl anilines and arylalkylamines.[10] On the basis of the excellent structural flexibility displayed by this method, we hypothesized that it could be also extended to the C−H functionalization of carbazole derivatives. To our delight, this was indeed the case, and herein we disclose a reliable protocol for the $Pd^{II}$-catalyzed *ortho*-olefination of *N*-(2-pyridyl)sulfonyl carbazoles and structurally related heterocyclic systems. To the best of our knowledge, our work constitutes the first example of a Pd-catalyzed direct *ortho*-olefination of the carbazole nucleus.[11]

**Table 1.** Optimization of the *N*-Directing/Protecting Group




| entry | **PG** (substrate) | [**ox**] | conv (%)[a] | yield [**6**/**7**, (%)][b] |
|---|---|---|---|---|
| 1 | H (**1**) | [F+][c] | –[d] | – |
| 2 | Boc (**2**) | [F+][c] | –[d] | – |
| 3 | Ac (**3**) | [F+][c] | <5 | – |
| 4 | Ts (**4**) | [F+][c] | <5 | – |
| 5 | $-SO_2$(2-pyridyl) (**5**) | [F+][c] | 93 | 11/42 |
| 6 | $-SO_2$(2-pyridyl) (**5**) | [F+][c,e] | 70 | 20/22 |
| 7 | $-SO_2$(2-pyridyl) (**5**) | [F+][c,f] | 66 | 19/23 |
| **8** | **$-SO_2$(2-pyridyl) (5)** | **[F+][c,g]** | **100** | **–/64** |
| 9 | $-SO_2$(2-pyridyl) (**5**) | $PhI(OAc)_2$[g] | 95 | 16/58 |

[a] Based on starting material recovered after chromatographic purification. [b] Isolated yield after chromatography. [c] [F+] = *N*-fluoro-2,4,6-trimethylpyridinium triflate. [d] Complex reaction mixture. [e] 1.1 equiv of butyl acrylate was used. [f] 1.0 equiv of oxidant was used. [g] 4 equiv of butyl acrylate and 3.0 equiv of oxidant were used.

To evaluate the role of the protecting/directing group, a set of potentially coordinating protecting groups (**PG**) were examined in the reaction of carbazole derivatives **2**−**5** with butyl acrylate under the previously optimized conditions:[10] $Pd(OAc)_2$ (10 mol %), *N*-fluoro-2,4,6-trimethylpyridinium triflate ([F+], 2.0 equiv) as the oxidant[12] in $ClCH_2CH_2Cl$ at 110 °C (Table 1, entries 1−5). Both the unprotected *NH*-carbazole (**1**) and the *N*-Boc derivative **2** led to a complex mixture of products (entries 1 and 2), with the latter result suggesting that the Boc protecting group is too labile under the reaction conditions. Switching to an *N*-Ac group (substrate **3**) or an *N*-Ts group (**4**)[4d] resulted in the full recovery of the unreacted starting

(6) For instance, see: (a) Dierschke, F.; Grimsdale, A. C.; Müllen, K. *Synthesis* **2003**, 2470. (b) Maegawa, Y.; Goto, Y.; Inagaki, S.; Shimada, T. *Tetrahedron Lett.* **2006**, *47*, 6957. (c) Kumar, G. G. K. S. N.; Laali, K. K. *Tetrahedron Lett.* **2013**, *54*, 965.

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(8) Chu, J.-H.; Wu, C.-C.; Chang, D.-H.; Lee, Y.-M.; Wu, M.-J. *Organometallics* **2013**, *32*, 272.

(9) Louillat, M.-L.; Patureau, F. W. *Org. Lett.* **2013**, *15*, 164.

(10) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10927.

(11) For the *ortho*-directed lithiation/functionalization of carbazole: Katrizky, A. R.; Rewcastle, G. W.; Vazquez de Miguel, L. M. *J. Org. Chem.* **1988**, *53*, 794.

(12) Among other oxidants examined, $PhI(OAc)_2$ showed similar performance as [F+], whereas $Ce(SO_4)_2$ and $AgNO_3$ led to lower reactivity while still maintaining poor monoselectivity. Other oxidants such as $Cu(OAc)_2$, 1,4-benzoquinone, $Ag_2O$, $K_2S_2O_8$, oxone, or Tempo led to full recovery of the starting material. See Supporting Information for other oxidant screening results.

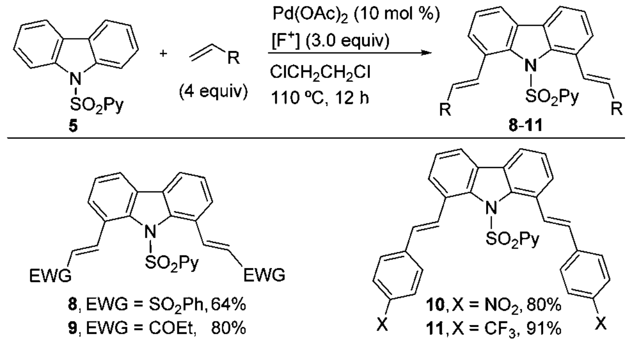
material, even after 24 h (entries 3 and 4). Pleasingly, carbazole **5** with an *N*-(2-pyridyl)sulfonyl group[10,13] provided a mixture of the mono- and diolefinated products **6** and **7**, respectively, in high conversion and complete *ortho* regiocontrol (entry 5).

Unfortunately, monoolefination selectivity could not be controlled by using reduced equivalents of either the acrylate or the oxidant (entries 6 and 7). The formation of significant amounts of the difunctionalized product **7** in both cases even at low conversions suggested a similar reactivity of both the starting substrate **5** and the monoolefination product **6**. However, high diolefination selectivity was achieved by simply adjusting the excess of alkene (4 equiv) and oxidant (3 equiv). The use of [$F^+$] resulted in a clean diolefination reaction, providing the C1/C8-disubstituted carbazole derivative **7** in 64% isolated yield[14] (entry 8), whereas $PhI(OAc)_2$ was found to be slightly less reactive (entry 9).

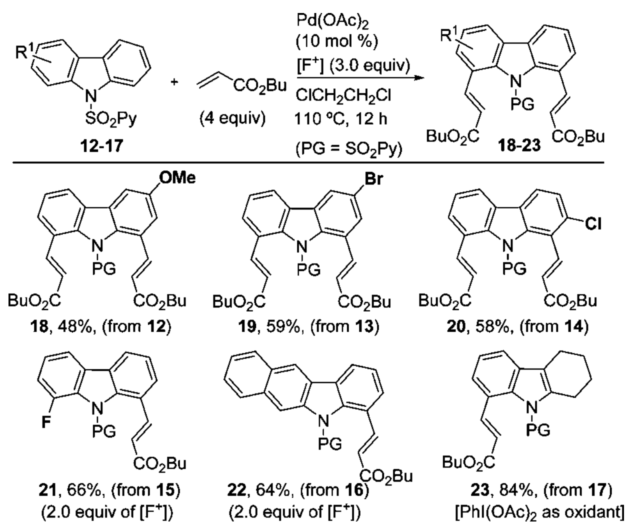
By using these optimized conditions, we next explored the alkene scope of the reaction. The results are summarized in Scheme 2. Other monosubstituted electrophilic alkenes, such as phenyl vinyl sulfone or ethyl vinyl ketone, were also capable reactants in the model diolefination reaction with carbazole **5**, leading to the corresponding dialkenylated products **8** and **9** in good isolated yields (64% and 80%). Interestingly, styrene derivatives bearing electron-withdrawing substituents ($NO_2$ or $CF_3$) at the *para*-position of the phenyl ring were found to be excellent coupling partners (products **10** and **11**, 80% and 91% yield). Unfortunately, styrene itself provided poor reactivity (mixtures of mono- and diolefinated products in 60% conversion).

A series of variously substituted carbazole derivatives were then subjected to olefination with butyl acrylate (Scheme 3). In general, both electron-rich and -deficient substrates performed well in this reaction, thereby enabling the construction of polysubstituted carbazoles in acceptable yields (**18**–**22**, 48–66% yield). Of special importance, carbazoles containing halogen atoms, including chlorine and bromine, are also compatible with this catalytic system (**19** and **20**). This observed orthogonal reactivity relative to the $Pd^0$-catalyzed cross-coupling chemistry is useful for subsequent product derivatization. As expected, a blocking fluorine substituent at C1 in substrate **15** caused exclusive monoolefination at C8 (product **21**, 66% yield).

**Scheme 2.** Olefin Scope for $Pd^{II}$-Catalyzed Diolefination




**Scheme 3.** Substrate Scope for $Pd^{II}$-Catalyzed Olefination



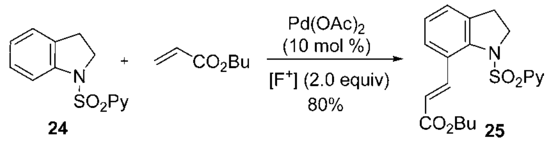

Regarding the alkenylation of related heterocyclic systems, the more sterically congested *N*-(2-pyridyl)sulfonyl benzo[*b*]carbazole reacted at the less hindered *ortho* site with complete regiocontrol to give the monoolefinated derivative **22** (64% yield). Likewise, the successful use of the partially saturated hexahydrocarbazole derivative turned out to be viable, producing exclusive *ortho*-monoolefination at the aromatic ring in high yield (product **23**, 84%). This result drew our attention to indoline derivatives because this motif is also prevalent in many natural products and pharmaceutical targets[15] and because the direct catalytic C7–H olefination of the indoline skeleton has been only scarcely documented.[16] Pleasingly, the reaction of the *N*-(2-pyridyl)sulfonyl indoline (**24**) with butyl acrylate (2.0 equiv) under the standard reaction conditions produced the alkenylated product at C7 **25** in isolated 80% yield (Scheme 4).

(13) For use of the *N*-(2-pyridyl)sulfonyl directing group in C–H functionalization reactions, see: (a) García-Rubia, A.; Gómez Arrayás, R.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (b) García-Rubia, A.; Urones, B.; Gómez Arrayás, R.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676. (c) Rodríguez, N.; Romero-Revilla, J. A.; Fernández-Ibáñez, M. A.; Carretero, J. C. *Chem. Sci.* **2013**, *4*, 175. For use of the related (2-pyridyl)sulfinyl group: (c) García-Rubia, A.; Fernández-Ibáñez, M. A.; Gómez Arrayás, R.; Carretero, J. C. *Chem.—Eur. J.* **2011**, *17*, 3567. (d) Romero-Revilla, J. A.; García -Rubia, A.; Gómez Arrayás, R.; Fernández-Ibáñez, M. A.; Carretero, J. C. *J. Org. Chem.* **2011**, *76*, 9525. (e) Richter, H.; Beckendorf, S.; García Mancheño, O. *Adv. Synth. Catal.* **2011**, *353*, 295. (f) Yu, M.; Liang, Z.; Wang, Y.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 4987.

(14) Although the $^1$H NMR of the crude reaction mixture was rather clean, showing mainly the diolefinated product, the difficulty in its complete chromatographic separation from the trace amount of unidentified byproducts resulted in a moderate 64% yield.

(15) For recent examples of indoline synthesis: He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944 and references cited therein.

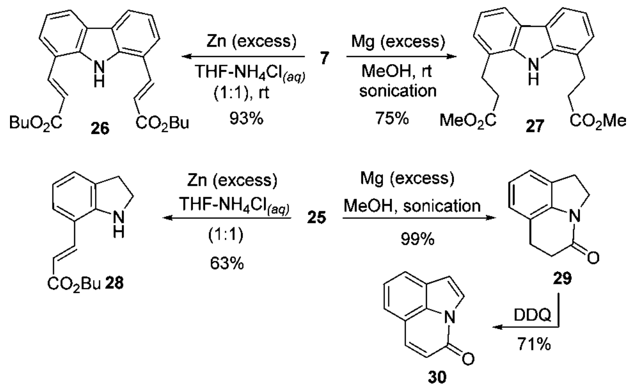
**Scheme 4.** C−H Olefination of Indoline **24**



The easy reductive removal of the 2-pyridylsulfonyl group under mild conditions to generate the free *NH*-carbazoles led us to realize the full synthetic utility of this method. Interestingly, the sulfonyl cleavage could be directed to the selective formation of either alkenyl- or alkyl-substituted free carbazoles, depending on the reducing agent used (Scheme 5). Simple treatment of derivative **7** with an excess of Zn powder in a 1:1 mixture of THF and saturated aq $NH_4Cl$ at rt led to the corresponding free carbazole **26** in 93% yield without affecting the sensitive acrylate moiety. Instead, treatment of **7** with magnesium turnings (MeOH, rt, sonication) afforded the dialkylated free carbazole **27** (75% yield). These complementary deprotection protocols can also be applied with comparable efficiency to the indoline derivative **25**, as exemplified in its transformation into the desulfonylated products **28** and **29**. In the latter case, the deprotection simultaneously triggers the cyclization of the free *NH*-indoline under the reaction conditions to give the tricyclic compound **29**.[17] The easy aromatization of this product with DDQ furnishes the pyrroloquinolinone framework of **30**, which is found in some biologically relevant indole based alkaloids,[16b,18] and whose derivatives are known to show unusual photosensitizing properties.[19]

In summary, we have demonstrated the ability of the *N*-(2-pyridyl)sulfonyl group to serve as a directing and readily removable protecting group in the $Pd^{II}$-catalyzed regiocontrolled C1/C8 diolefination of carbazoles, as well as the *ortho*-olefination of some structurally related nitrogen heterocyclic systems such as indolines. Because of the good structural versatility in both alkene and heteroarene coupling components, this protocol enables rapid access to functionally dense motifs found in relevant heterocyclic systems.

**Scheme 5.** Deprotection of Olefinated *N*-(2-Pyridyl)sulfonyl Carbazoles and Indolines



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

The authors declare no competing financial interest.

(16) (a) Yi, C. S.; Yun, S. Y. *J. Am. Chem. Soc.* **2005**, *127*, 17000. For the intramolecular C7−H arylation of indolines via a metal-free, single-electron transfer mechanism, see: (b) De, S.; Ghosh, S.; Bhunia, S.; Sheikh, J. A.; Bisai, A. *Org. Lett.* **2012**, *14*, 4466. For the observation of 2,7-disubstitution in the Pd-catalyzed C−H olefination of indoles: (c) Fanton, G.; Coles, N. M.; Cowley, A. R.; Flemming, J. P.; Brown, J. M. *Heterocycles* **2010**, *80*, 895. For a directed *ortho*-lithiation approach to C-7-substituted indoles: (d) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899.

(17) For the synthesis of **29** and its use as an intermediate in the synthesis of a potent and selective CYP11B1 inhibitor for the treatment of Cushing's syndrome, see: Yin, L.; Lucas, S.; Maurer, F.; Kazmaier, U.; Hu, Q.; Hartmann, R. W. *J. Med. Chem.* **2012**, *55*, 6629.

(18) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068.

(19) Pyrrolo[3,2,1-*ij*]quinolin-4-one (**30**) has been previously prepared using a ketene cyclization under flash vacuum pyrolysis conditions (at 950 °C): McNab, H.; Nelson, D. J.; Rozgowska, E. J. *Synthesis* **2009**, 2171. See references cited therein for photophysical properties of this type of system.