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A Novel Approach to 3-Methylindoles by a Heck/Cyclization/Isomerization Process

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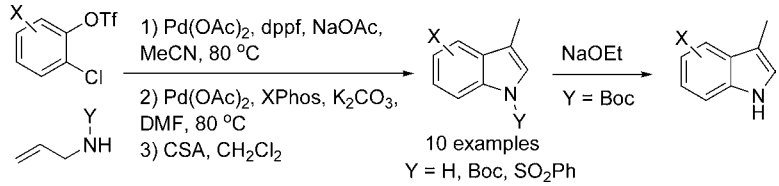
ABSTRACT

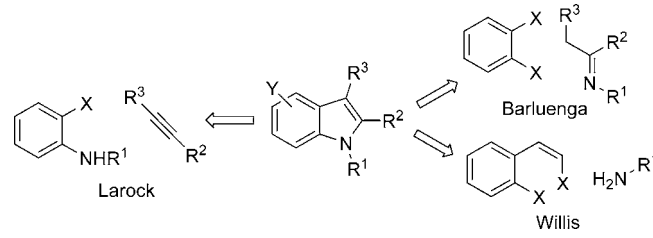


A novel synthesis of 3-methylindoles from chlorotriflates through a Heck reaction, carbamate/aryl chloride coupling, and isomerization sequence is presented. The three-step sequence is highly efficient and general, enabling the regiocontrolled synthesis of substituted indoles in short order.

Functionalized indoles are prevalent structural motifs that are found in many natural products and drug molecules, and as such there has been a considerable synthetic effort directed toward their synthesis. These endeavors have provided the synthetic community with a variety of methods for the synthesis of variously substituted indoles with the subject extensively covered in a number of review articles.[1]

Despite the existence of many classical routes to indoles, most of these have been superseded by transition metal-catalyzed methods, which afford the indole in a more selective fashion, while tolerating a wide variety of functional groups. Extensive work has demonstrated the efficiency of the palladium-catalyzed synthesis of indoles.[1d] Most of these reported methods for the preparation of indoles have concentrated on building the five-membered ring of the indole onto a suitably substituted benzene ring; usually the indole nitrogen is present as an aniline and the heterocycle is then formed via carbon−carbon (C−C) bond construction.[1b] Alternatively, C−C bond formation may be followed by cyclization onto a suitably positioned aniline as exemplified in the Larock[2] indole synthesis as well as the cyclization of 2-alkynylaniline derivatives (Scheme 1).[3] Even though this chemistry is widely applicable, some highly substituted halo-anilines are not easily accessible, and the alkyne partner can be expensive. A less developed strategy toward indoles, involving C−C bond formation prior to cyclization in a carbon−nitrogen (C−N) bond forming process onto an aryl halide, has been the focus of recently published work. The Barluenga group demonstrated the synthesis of indoles through

Scheme 1. Larock, Barluenga, and Willis Approaches to Indoles



(1) (a) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875–2911. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (c) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874–5883. (d) Li, J. J.; Gribble, G. W., Eds. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, UK, 2000.

(2) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652–7662.

(3) (a) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31–32. (b) Kakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845–1847.

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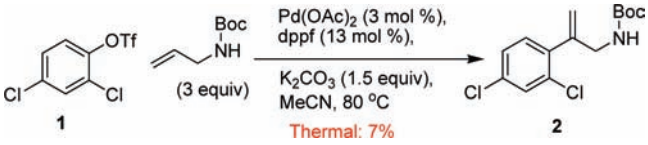
a sequence of C-arylation and intramolecular N-arylation when dihalobenzene derivatives were reacted with anions derived from imines.[4a] While this provided a new approach to 2,3-substituted indoles, dihalobenzene precursors are not readily available, and the imine precursors also required preparation. During the course of our studies the Barluenga group extended this work to *o*-chlorosulfonates; however, the efficiency of the indole formation was highly dependent on the aryl substitution pattern, and chlorononaflates were in some cases required to obtain good yields.[4b] Another example of indole formation by amination of a suitably functionalized benzene ring has been disclosed by Willis et al. This group employed a palladium-catalyzed double amination of bis-activated styrene with primary amines to generate the corresponding sterically demanding N-substituted indoles.[5] Again, while this approach provided a new entry into indole systems the more elaborate styrenyl precursors can be challenging to prepare.[6]

During a recent program we were challenged to develop a reliable synthesis of a highly substituted 3-methylindole fragment. The substitution pattern of the indole fragment often dictates which particular indole synthesis will be suitable, with starting material availability and functional group tolerance being two major considerations. Most currently available indole syntheses showed limitations, such as poor selectivity or the requirement of lengthy syntheses of suitably functionalized aryl precursors when applied to our target. This led us to initiate a fundamentally new strategy for the synthesis of our desired indole.

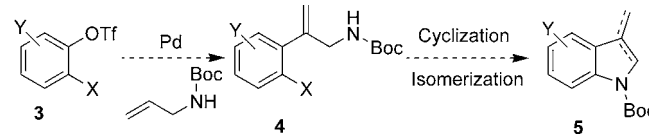
During an exhaustive examination of the current literature, we were drawn to the work of Hallberg, who has demonstrated a regioselective Heck reaction between aryl triflates such as **1** and *N*-Boc allylamine to give the corresponding 2-aryl-substituted allylcarbamate **2** (Scheme 2).[7] Overall the method lacked generality, while the yield for the *o*-chloro example we required was poor under thermal conditions; the reaction required microwave irradiation to obtain a 63% yield, and these conditions are difficult to achieve on scale.

Scheme 2. Regioselective Heck Reaction, Hallberg et al.



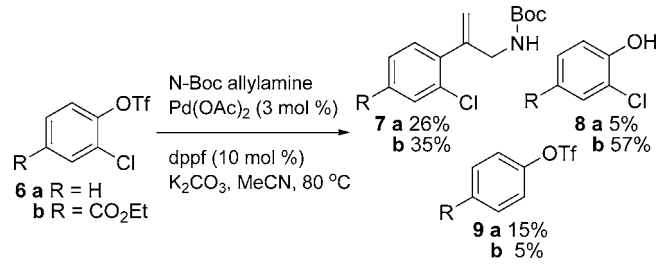
We reasoned that if the Heck reaction could be improved and conditions for the cyclization of this carbamate onto the *o*-aryl chloride could be identified, then the indole could be constructed in short order from commercially available building blocks. Hence, a Heck reaction between **3** and *N*-Boc allylamine would give **4** (Scheme 3). Cyclization (Cu or Pd mediated using the *o*-halide) would then give **5**; it was unknown whether the double bond would isomerize during the cyclization or remain *exo* and require a separate isomerization. Jørgensen has shown that 2-iodobromobenzenes react with allylamine in a palladium-catalyzed aryl amination−Heck cyclization cascade to give indoles directly, with amination occurring prior to the Heck cyclization.[8] However, most dihalogenated reagents are not commercially available and would require multistep sequences for their production, dictating that this method would not lead to a general process for indole construction.

Scheme 3. Proposed Indole Synthesis



Cognizant that both the accessibility of the reagents and the simplicity of the indole synthesis contribute to the overall effectiveness of the transformation, our investigations began by studying chlorotriflates **6** (prepared in one step from the corresponding commercially available 2-chlorophenols).[9] The chlorotriflate was chosen as chlorophenols are widely available from commercial sources.[10] Subjecting both **6a** and **6b** to the Heck reaction conditions developed by Hallberg, we found that considerable amounts of phenol **8** or des-chloro **9** were generated, especially with **6b** (Scheme 4). As well as the problematic hydrolysis, poor conversions of **6a** (46%) were observed. While this reaction provided the key carbamates **7a** and **7b** for cyclization studies, to support our novel indole preparation, the Heck reaction required optimization.

Scheme 4. Heck Reaction on Chlorotriflate **6**



It was believed that the choice of base could be critical in minimizing the formation of the phenol and hence provide a more efficient Heck reaction. A screen of inorganic and organic bases in the Heck reaction with aryl triflate **6b** was performed.[11] From this screen NaOAc was identified as a more efficient base for the transformation, giving 87% conversion, with 79% **7b** and 8% des-Cl **9b**. The amount of *N*-Boc allylamine was also reduced from 3 equiv to 1.2 equiv, further improving the original Hallberg work.

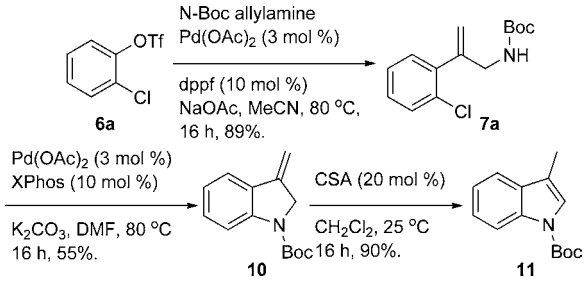
(4) (a) Barluenga, J.; Jiménez-Aquino, A.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 1529–1532. (b) Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031–4041.

(5) (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 403–406. (b) Fletcher, A. J.; Bax, M. N.; Willis, M. C. *Chem. Commun.* **2007**, 4764–4766. (c) Hodgkinson, R. C.; Schulz, J.; Willis, M. C. *Org. Biomol. Chem.* **2009**, *7*, 432–434.

(6) Tadd, A. C.; Matsuno, A.; Fielding, M. R.; Willis, M. C. *Org. Lett.* **2009**, *11*, 583–586.

These new conditions were employed with chlorotriflate **6a**, giving **7a** in 89% yield after chromatography (Scheme 5). Our attention next turned to the novel cyclization of **7a** to **10** (methylene-substituted indoline assumed). Various Pd/ligand and Cu/ligand catalysis systems were screened for the cyclization **7a**−**10**, and our first hit was discovered when we attempted the C−N bond-forming reaction in DMF.[12] This formed the indoline **10** in 21 LCAP (liquid chromatography area percent).

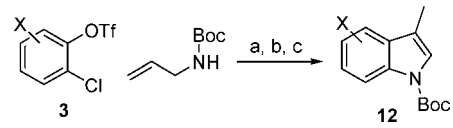
Scheme 5. Demonstration of the Indole Synthesis

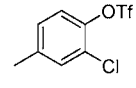
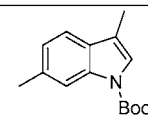
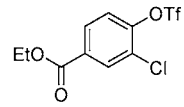
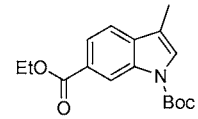
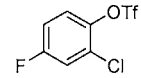
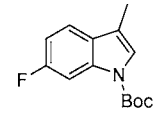
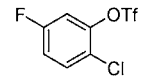
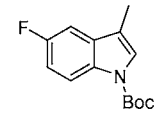
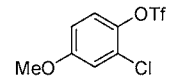
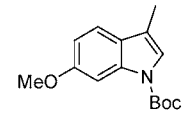
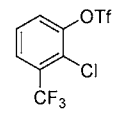
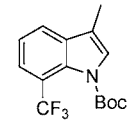
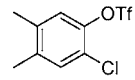
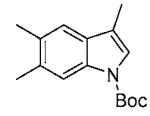
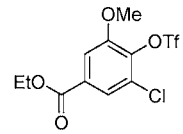
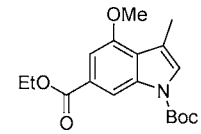


Optimizing this further we found XPhos was the preferred ligand for the cyclization of **7a** to **10**, with K_2CO_3 in DMF at 80 °C.[13] These conditions for the cyclization gave **7a**−**10** in 55% isolated yield after chromatography. The *exo*-orientation of the double bond in **10** was proven by ^{1}H NMR analysis, and the double bond was isomerized efficiently with camphorsulfonic acid (CSA)[14] to give the Boc-protected 3-methylindole **11**. This result successfully demonstrated our original hypothesis drawn up in Scheme 3. As each reaction was sufficiently clean the route shown in Scheme 5 could be streamlined; hence at the end of the Heck reaction a solvent switch to DMF was performed, followed by addition of the cyclization catalyst, ligand, and base. At the end of the cyclization reaction the methylene-substituted indoline could be isomerized by treating with CSA, which gave the Boc-indole **11**.[15] This three-step sequence avoided unnecessary operations and gave **11** in 60% yield, which corresponds to yields of >84% per step.

We next showed the generality of this process toward the synthesis of Boc-protected 3-methylindoles (Table 1). A variety of substitution on the chlorotriflate was tolerated including electron-withdrawing groups (entries 2 and 8), an electron-donating group (entry 5), as well as methyl and fluoro substitution (entries 1, 3, 4, and 7). This method is noteworthy in the generality to prepare 4-, 5-, 6-, and 7-substituted indoles with high efficiency and in short order from commercially available chlorophenols. Additionally, more highly substituted chlorotriflates were also used (entries 7 and 8), further showing the scope of this chemistry to prepare functionalized Boc-protected 3-methylindoles. The three-step sequence to substituted indoles gave yields ranging from 54% to 80%, which corresponds to a yield of 81% to 92% over each step in the sequence. All the examples in Table 1 have been demonstrated on between 1 and 120 g of starting chlorotriflate, showing that this chemistry is reliable and scalable. What is also striking is the efficiency of the Heck reaction, which can now be utilized as a general method to prepare a range of 2-aryl-substituted allylcarbamates. Additionally, the intermediate methylene-substituted indolines are also useful structures in their own right.

Table 1. The Preparation of Various 3-Methylindoles



entry	chloro triflate (**3**)	indole (**12**)	yield (%)[b]
1			71
2			77
3			67
4			65
5[c]			65
6			54
7			67
8[c]			80

a Reagents and conditions: (i) *N*-Boc allylamine (1.2 equiv), $Pd(OAc)_2$ (3 mol %), dppf (10 mol %), NaOAc (1.2 equiv), MeCN, 80 °C, 15−24 h. (ii) $Pd(OAc)_2$ (3 mol %), XPhos (10 mol %), K_2CO_3 (1.5 equiv), DMF, 80 °C, 15−18 h. (iii) CSA (20 mol %), CH_2Cl_2, 25 °C, 48 h. [b] Isolated yield after column chromatography of the indole product. [c] K_2CO_3 (1.5 equiv) was used as the base in the Heck reaction.

(7) (a) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544–549. (b) For a discussion of mechanism and regioselectivity in the Heck reaction, see: Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.

(8) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem., Int. Ed. Engl.* **2008**, *47*, 888–890.

(9) See the Supporting Information for the synthesis of the chlorotriflates from the corresponding chlorophenols.

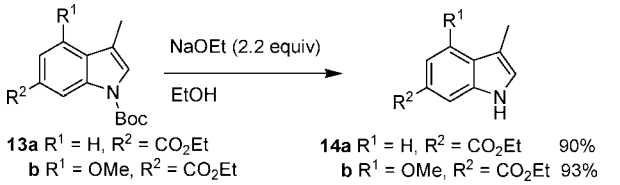
(10) *o*-Bromo triflates were found to not be as efficient in the Heck reaction.

(11) For the full table from the base screen, please see the Supporting Information.

Current syntheses to these intermediates involve numerous steps, which are often nonselective and require functionalized aryl precursors.[16] The outlined method for their preparation significantly simplifies the synthesis of these compounds.

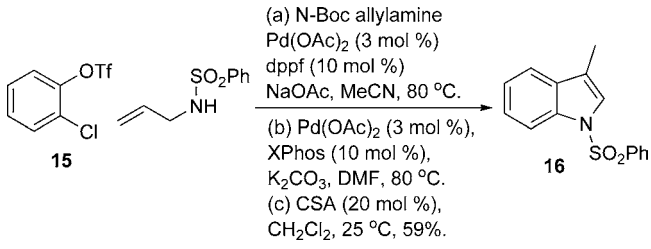
The Boc-indoles could be deprotected in a straightforward manner by treatment with NaOEt in EtOH[17] to provide the free indoles for further elaboration at the N-1 position, Scheme 6.

Scheme 6. Removal of the Boc Group To Give Free Indoles



Benzenesulfonyl allylamine was also found to be a viable allyl source in this reaction, generating the corresponding *N*-sulfonate indole with the same efficiency as the Boc allylamine through the three steps, further demonstrating the utility of this indole synthesis, Scheme 7. This is of particular interest as *N*-sulfonyl indoles are often used in active drug molecules.[18]

Scheme 7. Use of Benzenesulfonyl Allylamine



In summary, we have demonstrated a novel and scalable synthesis of 3-methylindoles from chlorotriflates through a Heck reaction, amide/aryl chloride coupling, and isomerization sequence. The 2-chlorophenols are commercially available, and the three-step sequence to substituted indoles is highly efficient, enabling the regiocontrolled synthesis of substituted indoles in short order. Additionally, the Heck reaction of aryl triflates with protected allylamines has been optimized and is now efficient for the preparation of synthetically useful 2-aryl-*N*-Boc allylamines. The utilization of these 3-methyl indoles as well as chemistry using the methylene-substituted indoline intermediates is the focus of further investigations and will be reported in due course.

Acknowledgment. We wish to thank Simon Hamilton and David Murray (Analytical Research MSD, Hoddesdon) for mass spec analysis.

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

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(12) CuI (10 mol %) with L-proline (20 mol %) also gave a small amount of the desired methylene-substituted indoline (11%). Attempts to optimize this proved fruitless with messy reaction profiles, forming multiple products.

(13) Investigations into a single catalyst system for the Heck reaction and cyclization have so far proved elusive.

(14) Tietze, L. F.; Buhr, W. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1366–1368.

(15) While it was possible to directly charge CSA at the end of the cyclization reaction, the process benefitted from a quick aqueous workup prior to addition of CSA.

(16) (a) Lin, H.; Kazmaier, U. *Eur. J. Org. Chem.* **2009**, 1221–1227. (b) Ma, J.; Yin, W.; Zhou, H.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2009**, *74*, 264–273. (c) Tercel, M.; Denny, W. A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 509–519. (d) Tidwell, J. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11797–11810. (e) Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941–1942. (f) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796–4807.

(17) Qiu, X.-L.; Zhu, J.; Wu, G.; Lee, W.-H.; Chamberlain, A. R. *J. Org. Chem.* **2009**, *74*, 2018–2027.

(18) Tsai, Y.; Dukat, M.; Slassi, A.; MacLean, N.; Demchyshyn, L.; Savage, J. E.; Roth, B. L.; Hufesein, S.; Lee, M.; Glennon, R. A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2295–2299.