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"*Quick* and *Click*" Assembly of Functionalised Indole Rings *via* Metal-Promoted Cyclative Tandem Reactions

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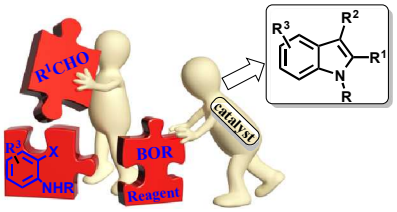
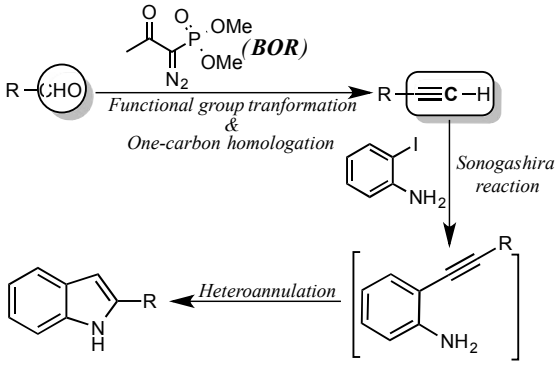


An efficient and convenient synthesis of a variety of decorated indoles using a three-component tandem metal-catalysed process is described. We propose here a new "synthetic kit" that allows for the "quick and click" assembly of indole rings using readily available, and inexpensive starting materials under environmentally friendly reaction conditions.

In recent years, many classic organic reactions have been revisited and redesigned with a modern twist in order to increase their efficiency and minimize their environmental impact.[1] The development of new reagents and/or catalysts has allowed for interesting improvements in the assembly of complex carbon frameworks that, in some ways, were unimaginable just a few decades ago using traditional organic techniques.[2] Although many of these processes have become highly efficient, the tedious and time-consuming problems associated with final purification are still difficult to address. These issues become increasingly complex in the diversity-oriented synthesis of a molecular target in which a multi-step approach is required to assemble different components and reagents. Moreover, each additional step involves a loss of material, which significantly reduces the final yields.

In this context, the domino (or cascade) reactions attempt to answer all these questions.[3] These domino reactions are not to be considered as being the sum of already known individual reactions; rather, they should be viewed as powerful tool to harmonise the best chemical processes in order to construct complex molecular scaffolds. In comparison to traditional single-step processes, the use of cascading reactions represents a true advantage from an atom-economy point of view, as these reactions drastically reduce the amount of waste that needs to be disposed. In a synthetic project, another feature that is too often neglected or is too weak is the access to a wide range of safe and affordable reagents, which should provide the highest degree of molecular diversity in the designed molecular target.

In light of these observations, we intend to develop a domino procedure for preparing a library of indoles that have elicited great interest from both the academic and industrial communities.[4] As part of our continued interest in the preparation of indole derivatives,[5] we intend to focus our attention on the Castro reaction,[6] which employs iodoanilines and alkyne derivatives as building blocks for preparing densely functionalized indole rings (Scheme 1).[7]

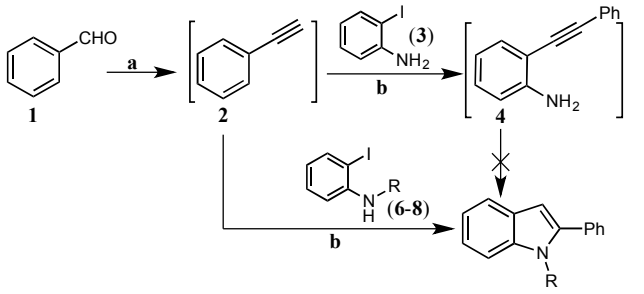


Scheme 1 Revised Castro indole synthesis via a cascade process. Bestmann-Ohira Reagent (BOR) = dimethyl-1-diazo-2-oxopropylphosphonate.

Unfortunately, the low commercial availability of alkynes and/or their high cost represent some of the main drawbacks of the Castro indole synthesis. Therefore, we plan to prepare a library of terminal alkynes starting from readily available reagents, such as aldehydes, and to subsequently use them without further purifications in the Sonogashira/Castro indole synthesis via a domino process (Scheme 1).[8]

The Bestmann-Ohira reaction,[9] a valuable modification of the Seyferth-Gilbert procedure,[10] allows to smoothly access to terminal alkynes directly from aldehydes or their synthetic surrogates at room temperature under very mild conditions, with a readily available and easy to handle reagent (BOR, dimethyl-1-diazo-2-oxopropylphosphonate).[11] In addition, the reaction conditions and by-products of this efficient one-carbon homologation of aldehydes into alkynes should not interfere with the subsequent chemical processes needed for the construction of an indole ring.

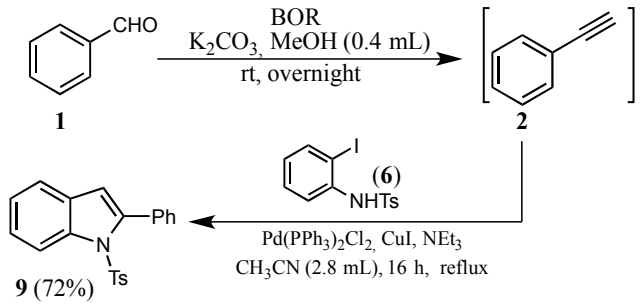
The alkynylation reaction was conveniently carried out in methanol by treating benzaldehyde **1** (0.5 mmol) with the Bestmann-Ohira reagent (0.6 mmol) in the presence of K_2CO_3 (1 mmol) overnight at rt. Moreover, 2-iodoaniline **3** (0.5 mmol), NEt_3 (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%) and CuI (5 mol%) were subsequently added to the crude reaction containing the in-situ generated phenylacetile **2**, and the resulting mixture was refluxed overnight. The desired indole **5** was recovered only in trace amounts, while the main reaction product was the 2-ethynylaniline **4** alongside the unreacted 2-iodoanilina **3**. We have also screened other metal catalytic systems with unfortunately no success results.



Scheme 2 Metal-catalysed domino indole synthesis from o-iodoaniline derivatives and benzaldehyde. Reagents and conditions: a) BOR, K_2CO_3, MeOH, rt, overnight. b) $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (5 mol%), NEt_3, reflux, overnight.

These preliminary results suggested that cyclization was the critical stage of the entire process and that it was necessary to match the reaction conditions used in the first step and the last step. We first tried to perform the indole synthesis by changing either K_2CO_3 or NEt_3, but also by using different bases; however, the final result did not improve. In addition, the use of other solvents, or a combination thereof, was examined, but they were found to be ineffective in promoting the cyclisation step. Only upon switching from 2-iodoaniline to the *N*-tosyl-2-iodoaniline **6** did the indole yield improve dramatically, up to 61% (Scheme 2, pathway 2).[12] The use of different *N*-protecting groups (Scheme 2, iodoanilines **7** and **8**) resulted in either low indole yields or recovered starting material yields (Scheme 2, products **10** and **11**).

Interestingly, when this one-pot three-steps construction of an indole ring was split into two different and consecutive reactions, we observed complete reagent conversion by using MeOH in the first step and acetonitrile in the remaining two steps. Therefore, we performed out a set of experiments designed to determine the best ratio between these two solvents in order to further improve the yield of the final indole. The best results were achieved by preparing the terminal alkynes from the corresponding aldehydes in the minimum volume of MeOH (0.4 mL) and by adding $Pd(PPh_3)_2Cl_2$ (3 mol%), and CuI (5 mol%) to this mixture, closely followed by a solution of *N*-tosyl-2-iodoaniline and NEt_3 in CH_3CN (2.8 mL).



Scheme 3 Optimisation of the reaction conditions.

While the conversion of aldehyde into alkynes took place smoothly at room temperature (overnight), the following Sonogashira coupling and metal-catalysed heteroannulation were best performed at reflux, for at least 16 hours, in order to ensure full conversion of the reagents. Under such optimised condition, benzaldehyde **1** and *N*-tosyl-2-iodoaniline **6** were uneventfully converted to the desired indole product **9** in a 72 % overall yield. A lower reaction temperature caused an appreciable reduction in the reaction rate and a significant decrease in the chemical yields. In the absence of either a Pd- or Cu-based catalyst, the reaction failed to provide the expected indole product.

With a clearer picture of the reaction parameters, we then tested the ratio of aldehyde/aniline with the aim of further improving the effectiveness of this reaction. Interestingly, a maximum indole yield of 84 % was obtained when the aldehyde proportion was switched from 1 to 1.5 equivalents.

The reaction time is a key parameter of the process as protected 2-ethynylaniline and indole **9** have a very close R_f and complete conversion of the alkyne intermediate **2** into the corresponding indole **9** is essential for a simplified work-up procedure.

It is interesting to note that the exposition of this one-pot/alkynylisation/coupling/cyclization process to microwave irradiation (MWI) allowed the reactions to be completed in less than 2 hours, in yields comparable to those that were thermally heated (Scheme 4).[13]

With these optimum conditions in hand, we have extended this synthetic protocol to other aldehyde derivatives in order to investigate the substrate scope of the reaction. The results are summarized in Scheme 4. Under standard conditions, the coupling reactions of **6** with various terminal alkynes, generated in-situ from both aromatic and aliphatic aldehydes, provided a diverse array of densely functionalised indoles in good to excellent yields (Scheme 4, products **9**-**35**).

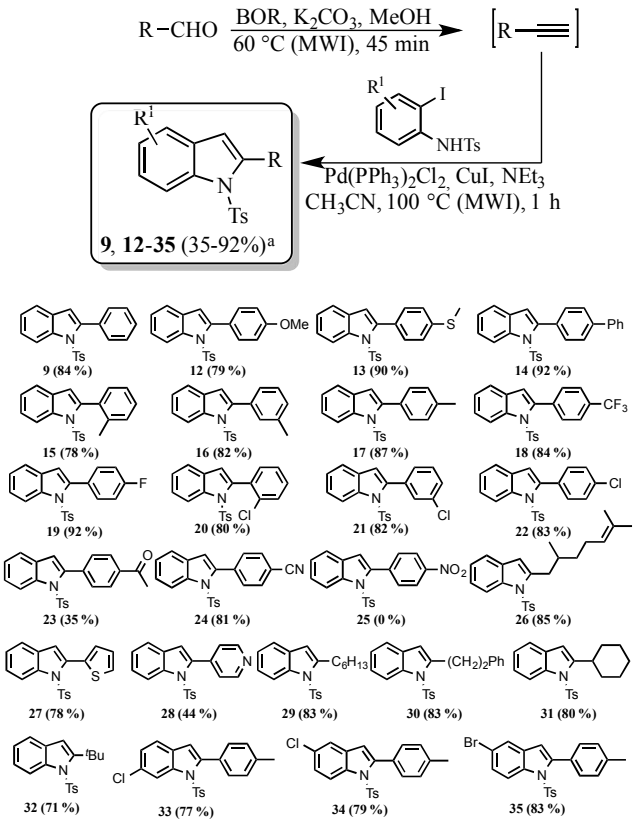
In general, the presence of electron-donating, and electron-withdrawing substituents on the aromatic aldehydes, with the exception of the carbonyl group (Scheme 4, product 23), did not significantly hamper the reaction, which proceeded smoothly leading to the expected products in good yields. Conversely, the reaction of a strongly electron-deficient aldehyde, such as 4-nitrobenzaldehyde with **6**, failed to give the corresponding product (Scheme 4, product **25**) despite increasing catalyst loading (up to 10 mol%) and/or prolonging the reaction time.

A wide range of other sensitive functionalities were tolerated, including fluoro- (Scheme 4, indole **19**), chloro- (Scheme 4, indoles **20**-**22**), carbonyl- (Scheme 4, indole **23**), cyano- (Scheme 4, indole **24**), olefin (Scheme 4, indole **26**), which are amenable to further manipulations.

Additionally, the procedure allowed for a quick and easy assembly of indole derivatives having heteroaryl residues such as the 2-thienyl, and 4-pyridyl rings (Scheme 4, products **27**–**28**).

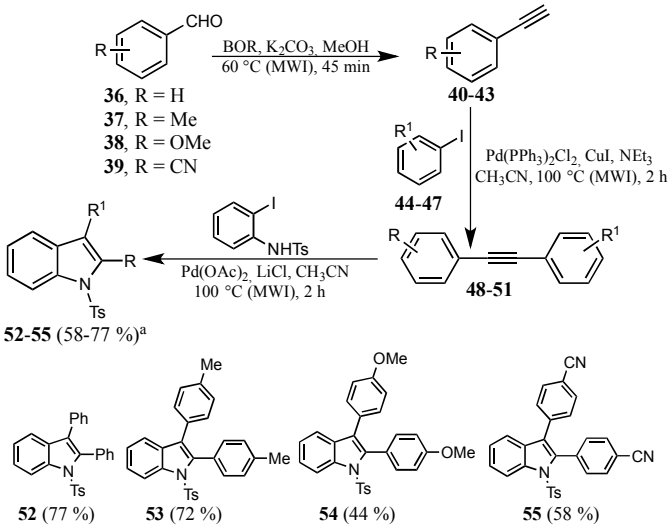
This methodology was not only restricted to aromatic aldehydes; good indole yields were also obtained for aliphatic enolisable linear aldehydes as well as for cyclic ones (Scheme 4, indoles **29**-**31**). These reaction conditions were also applicable to sterically hindered aldehydes such as pivalaldehyde, which led to indoles **32** in a 71 % isolated yield.

To broaden the substrate scope further, the reaction between 4-methylbenzaldehyde and a representative set of diversely substituted 2-iodoanilines was next successfully scrutinised and the results are compiled in Scheme 4 (indoles **33**-**35**). The successful preparation of 2-substituted indoles highlighted that the previous Sonogashira coupling step selectively occurred at the ortho-position, triggering the subsequent indole formation.



Scheme 4 Substrate scope of the domino metal-catalysed synthesis of indole derivatives. Reaction conditions were as follow: a) aldehyde (0.5 mmol), BOR (0.6 mmol), K_2CO_3 (1 mmol), MeOH (0.4 mL), 60 °C (MWI), 45 min. b) N-tosyl-2-iodoaniline derivative (0.33 mmol), NEt_3 (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (3 mol%), CuI (5 mol%), CH_3CN (2.8 mL) 100 °C for 1h. [a] Yield of isolated pure products.

The generality of this method was also demonstrated by applying the conditions optimised for 2-substituted indole substrates to a set of representative internal alkynes and the results are summarized in Scheme 5. Upon the completion of the reaction between aldehyde **36**-**39** and BOR, the resulting terminal alkynes **40**-**43** were then subjected to a cascade reaction, first with iodoarenes **44**-**47** in the presence of $Pd(PPh_3)_2Cl_2$ (3 mol%) and CuI (5 mol%) and then with *N*-tosyl-2-iodoaniline **6**, using $Pd(OAc)_2$ (5 mol%) and LiCl (0.33 mmol) as catalyst system. A careful study of the reaction parameters revealed that the presence of a source of chloride anions (either LiCl or *n*-Bu_4NCl) was beneficial to the reaction, as it maximised the indole yields.[4i] A variety of in-situ prepared internal alkynes **48**-**51** proved to be efficient partners for this domino process, thereby leading to the expected indoles **52**-**55** in various isolated yields (58−77%).



Scheme 5 Domino heteroannulation reaction with *in-situ* generated internal alkynes. [a] Yield of isolated pure products.

Conclusions

In summary, *N*-protected 2-iodoanilines were smoothly transformed into indoles by a sequential Castro reaction, employing aldehydes instead of the commonly used alkynes. Bestmann-Ohira reagent was fruitfully used to convert (*in-situ*) a variety of aldehydes into their corresponding homologated terminal alkynes. This tandem approach allows for the "quick and easy" assembly of an array of multi-substituted indole derivatives by taking advantage of the structural diversity of aldehydes. The entire process is promoted by a Pd- and Cu-based catalyst, is dramatically accelerated by microwave irradiation heating.

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† Electronic Supplementary Information (ESI) available: Experimental procedure, characterization data, copies of ^1H NMR, and ^{13}C NMR spectra. See DOI: 10.1039/c000000x/.

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