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New Organolithium Addition Methodology to Diversely Functionalized Indoles

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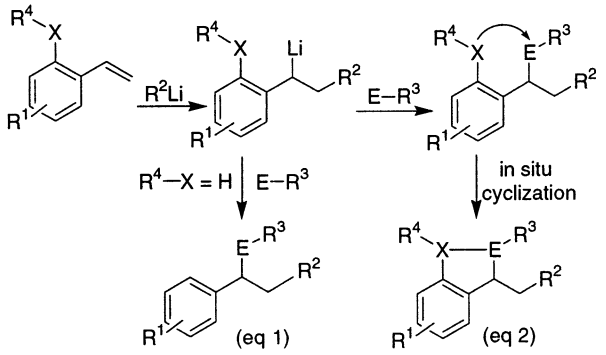
The key biochemical roles played by the indole ring in nature ensure that this modest heterocyclic system continues to attract intense scrutiny from medicinal and synthetic chemists. It is a common motif for drug targets, and as such the development of new diversity-tolerant routes to this privileged biological scaffold continues to be of significant benefit.[1] New multicomponent routes, which would facilitate the introduction of molecular diversity at all positions of the indole ring, would have applications for combinatorial library formation and natural product synthesis. Many recent advances in indole synthesis have focused on metal mediated procedures with copper, palladium, tin, titanium, and zirconium being the most prevalent.[2] Our novel approach is to exploit organolithium addition to functionalized styrenes with the C−C bond formation reaction as the key synthetic step. A significant benefit of this strategy is that it can provide a direct route for the introduction of further molecular diversity into the ring system. Other methods for indole synthesis utilizing organolithium reagents have been previously reported.[3]

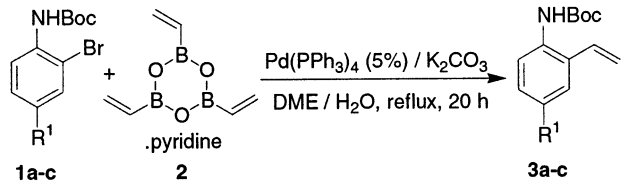
The anionic polymerization of styrenes using organolithiums is a well-established process, but recently it has been reported that polymerization can be avoided, thereby facilitating the development of its synthetic use. It was shown that addition of the organo group to the terminal carbon of styrene generated a new organolithium species which when trapped with electrophiles (E−R^3) provided a viable route to substituted aryl rings (eq 1).[4] This methodology exploits the window of opportunity for synthetic utility due to the difference in reactivity of the organolithium used for the addition and the resulting organolithium generated.



Our aim is to greatly expand the synthetic utility of this chemistry for the specific case of *ortho*-substituted styrenes. For these derivatives, it should be possible that upon generation of the lithiated intermediate via organolithium addition, and subsequent reaction with specific electrophiles, a cascade reaction process could be set up between the reacted electrophile (E−R^3) and *ortho*-substituent (X−R^4) components, facilitating an in situ ring-closing reaction to generate benzo-fused ring systems (eq 2). For this approach to be successful, it would require the correct combination of a reacting pair of *ortho*-substituent and electrophile. To test this concept, we chose Boc-protected *ortho*-amino substituted styrenes (X−R^4 = NHBoc) with dimethylformamide (DMF) or a substituted nitrile as the electrophile in an effort to make diversely functionalized indoles.

Generation of the required starting materials was achieved by employing a recently developed protocol for the synthesis of functionalized styrenes from aryl bromides **1** by Suzuki−Miyaura cross coupling with 2,4,6-trivinylcyclotriboroxane **2** (Scheme 1).[5] This method routinely provided the Boc-protected *ortho*-vinyl aniline derivatives **3** in high yields.

Scheme 1. Vinylation of Substituted *ortho*-(Bromo-aryl)-carbamic Acid *tert*-Butyl Esters **1**



1a-c **2** **3a-c**

3a R^1 = H (80%); **3b** R^1 = F (78%); **3c** R^1 = OCH$_3$ (85%)

The viability of the reaction sequence was tested using three *ortho N*-Boc vinyl anilines **3**, substituted with electron-donating or -withdrawing groups, and three alkyllithiums, *tert*-butyl, *sec*-butyl, and *n*-butyl, as a representative sample. The first electrophile investigated was DMF, which in the reaction sequence provides the C-2 carbon of the indole ring. The reaction of each combination of alkyllithium and **3** gave the desired *N*-Boc substituted indoles **4**, with isolated purified yields up to 84% (Table 1). We found that the addition reaction was most effective for *tert*-butyllithium at −78 °C, whereas for *n*-butyllithium it was advantageous to include TMEDA as an additive and raise the reaction temperature to −25 °C, as this achieved a more effective addition to the vinyl double bond.[6]

A proposed reaction sequence would be as follows: initial deprotonation of the carbamic ester NH of **3**, followed by addition of alkyllithium to the vinyl double bond providing the lithiated intermediate; subsequent addition of the electrophile DMF, which reacts with the anion generating an aldehyde precursor; and addition of aqueous acid facilitates ring closure by intramolecular attack of the carbamic ester nitrogen at the aldehyde to form a 2-hydroxy-indole **6**, which subsequently in situ dehydrates to the indole. If the acidification conditions are sufficiently mild, it is possible to isolate the substituted 2-hydroxy-2,3-dihydro-indole **6** as a mixture of isomers (Figure 1). Subsequent treatment with aqueous hydrochloric acid efficiently converts **6** into the corresponding indole **4**.

The deprotection of indoles **4** was readily accomplished by stirring at room temperature with 12 M HCl in ethyl acetate, generating **5** in excellent yields (Table 1). This deprotection method complements our indole synthesis as it allows either the protected

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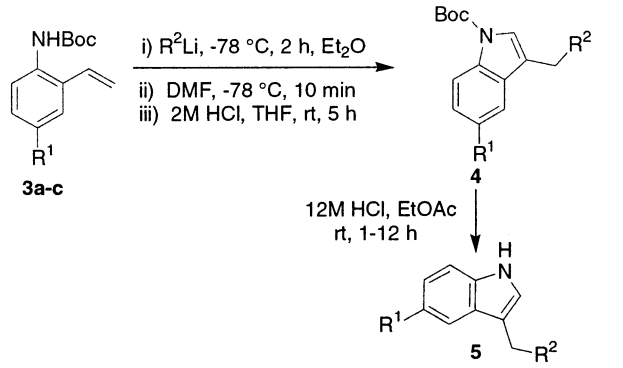
Table 1. Synthesis of 1,3,5- and 3,5-Substituted Indoles **4** and **5**



entry	**4/5**	R^1	R^2	**4** yield[a]	**5** yield[b]
1	**a**	H	*t*-Bu	75%	88%
2	**b**	H	*n*-Bu[c]	84%	97%
3	**c**	H	*s*-Bu	62%	83%
4	**d**	F	*t*-Bu	70%	87%
5	**e**	F	*n*-Bu[c]	71%	90%
6	**f**	F	*s*-Bu	43%	70%
7	**g**	OCH_3	*t*-Bu	77%	85%
8	**h**	OCH_3	*n*-Bu[c]	80%	65%

[a] Isolated purified yield. [b] Conversion of isolated **4** into **5**. [c] Reference 6.

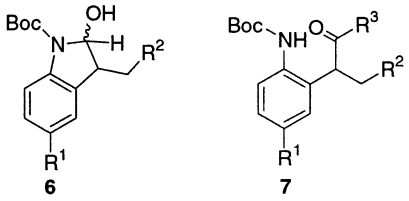
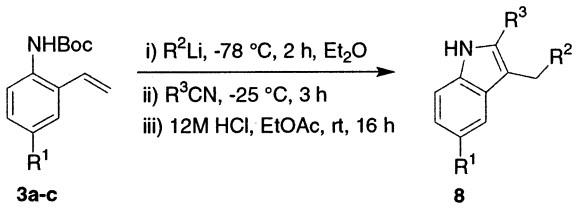


Figure 1. Proposed reaction intermediates.

or the deprotected indole to be isolated depending on the acidification conditions chosen.

The use of DMF as an electrophile precludes the direct introduction of a substituent at C-2 of the indole ring. The inclusion of functionality at this position can be achieved by a change in electrophile to a substituted nitrile. The addition of organolithium species to nitriles for heterocyclic synthesis is known.[7] Consequently, we repeated our organolithium addition methods but treated the lithiated intermediates with a range of substituted nitriles. The reaction of nitriles is slower than that with DMF, and an efficient reaction was achieved by stirring at −25 °C for 3 h. Subsequent treatment of the reaction mixture with 12 M HCl in ethyl acetate was successful for the direct generation of the *N*-unsubstituted 2,3,5-substituted indoles **8** in acceptable yields (Table 2). This reaction sequence was tolerant to the introduction of a range of C-2 substituents, including aryl (entries 1, 5, 7, 8), heteroaryl (entry 4), and sterically bulky alkyl groups (entries 2, 6) (Table 2). It was even successful when using 2,2-diethoxypropionitrile (entry 3) as an electrophile, which in addition to going through the complex reaction cascade sequence also underwent a further in situ deprotection of the acetal protecting group, thereby generating the 2-keto substituted indole **8c**. If the acidification conditions are sufficiently mild, reaction intermediates of type **7** (R^3 = nitrile substituent) are

Table 2. Synthesis of 2,3,5-Substituted Indoles **8**



entry	**8**	R^1	R^2	R^3	**8** yield[a]
1	**a**	H	*t*-Bu	Ph	65%
2	**b**	H	*t*-Bu	*t*-Bu	67%
3	**c**	H	*n*-Bu[b]	$COCH_3$	44%
4	**d**	H	*n*-Bu[b]		60%
5	**e**	F	*t*-Bu	Ph	40%
6	**f**	F	*n*-Bu[b]	*t*-Bu	54%
7	**g**	OCH_3	*t*-Bu	Ph	57%
8	**h**	OCH_3	*n*-Bu[b]	Ph	68%

[a] Isolated purified yield. [b] Reference 6.

observed, implying a reaction pathway similar to the DMF electrophile examples.

The combination of a vinylation procedure using boronic acid coupling chemistry with an organolithium addition-cyclization methodology gives a new entry into functionalized indole ring systems. The methodology is diversity tolerant, facilitating the introduction of aryl, hetero-aryl, alkyl, keto, halo, and ether substituents in varying positions around the indole scaffold. Utilization of this synthetic methodology for the generation of other heterocycles by modification of the reacting pair of the *ortho*-substituent and electrophile is currently underway.

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Supporting Information Available: Experimental procedures and compound characterization data for all indoles (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Gribble, G. W. *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Pergamon Press: New York, 1996; Vol. 2, pp 207−257.
(2) For reviews of different approaches, see: Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. Sundberg, R. J. *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Pergamon Press: New York, 1996; Vol. 2, pp 120−206.
(3) (a) For review, see: Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59. (b) Barluenga, J.; Sanz, R.; Granados, A.; Fananas, F. J. *J. Am. Chem. Soc.* **1998**, *120*, 4865. (c) Clark, R. D.; Muchowski, J. M.; Fisher, L. E.; Flippin, L. A.; Repke, D. B.; Souchet, M. *Synthesis* **1991**, 871. (d) Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767.
(4) (a) Wei, X.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 409. (b) Wei, X.; Johnson, P.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1109. (c) Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1996**, 187. (d) Seijas, J. A.; Pilar, M.; Tato, V.; Castedo, L.; Estevez, R. J.; Ruiz, M. *J. Org. Chem.* **1992**, *57*, 5283.
(5) Kerins, F.; O'Shea, D. F. *J. Org. Chem.* **2002**, *67*, 4968. The trivinylcyclotriboroxane, **2**, is available from Frontier Scientific.
(6) TMEDA was used as an additive. After addition of *n*-butyllithium at −78 °C, the temperature was raised to −25 °C for 2 h.
(7) Chen, J.; Song, Q.; Wang, C.; Xi, Z. *J. Am. Chem. Soc.* **2002**, *124*, 6238 and references therein.

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