Functionalization of 2-Bromo-*N*-Benzyl Indole via Lithium-Bromide Exchange

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ABSTRACT

The carbofunctionalization of 2-bromo-*N*-benzyl indole via lithium-bromide exchange is presented. The reaction scope is demonstrated by providing a variety of substrate examples that deliver carbofunctionalized products in good-to-excellent yields. The competition between nucleophilic addition and proton transfer is discussed.

Keywords:

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C-2 substituted indoles are a common structural motif among natural products, many of which display intriguing biological activities.¹ The introduction of a carbon substituent at the indolic 2-position is clearly essential to the synthesis of such targets and this bond formation has been achieved by a variety of different approaches. For example, Heck,^{2a} Sonogashira,^{2b} Stille,^{2c} and Suzuki^{2d} cross-coupling reactions using the corresponding 2-halogenated indoles have been used successfully to install a carbon substituent at the 2-position. Direct C-H lithiation of the 2-position is an attractive alternative that has been achieved using *N*-methyl indoles as well as a variety of other nitrogen protecting groups.³ However, this process is problematic for *N*-benzyl indoles due to competing benzylic deprotonation.^{3b,4} For example, we have observed that at low temperatures, metalation of *N*-benzyl indole (**1**) using *n*-BuLi occurs at the benzylic position to afford alkylated product **3a** following addition of acetophenone. C-2 metalation has been observed at higher temperatures, but the overall yield is poor (**1** → **3b**),⁵ and uncharacterized debenzylated products also are formed⁶ (Scheme 1). Therefore, the use of direct metalation is not the most suitable route to access 2-lithio-*N*-benzyl indoles.

Scheme 1. Regiospecific alkylations of *N*-benzyl indole (**1**) at the C-2 and benzylic positions as a function of temperature.

The utilization of 2-halogenated *N*-benzyl indoles in lithium-halogen exchange reactions for the carbofunctionalization of the 2-position presents another alternative. Earlier work by Merlic et al. on the synthesis of indole 2-boronic esters hinted that this transformation was possible using *n*-BuLi in THF.^{5a} Recently, we reported a lithium-bromide exchange reaction of 2-bromo-*N*-benzyl indole (**4**)⁷ using *n*-BuLi, and the subsequent addition of the derived 2-lithioindole **2b** to carbonyl compound **5** furnished alcohol **6** in good yield (Scheme 2).⁸ This obvious but previously unexplored method is therefore a better alternative to direct C-2 metalation for the carbofunctionalization of the indolic 2-position.

Scheme 2. Previous work on the C-2 carbofunctionalization of 2-bromo-*N*-benzyl indole (**4**) via lithium-bromide exchange.

Since 2-lithio-*N*-benzyl indole (**2b**) was scarcely available by direct metalation, the scope of its addition reactions with aldehyde and ketone electrophiles has not been explored. In this report, we document the scope of this reaction by providing several carbonyl substrate examples (Table). *n*-BuLi proved effective at metalation and the use of the more dangerous *s*- or *t*-BuLi was not necessary to achieve this transformation. The lithium-bromide exchange reaction was first attempted using 2 equivalents of *n*-BuLi in order to facilitate HBr elimination from the presumed intermediate *n*-BuBr. Unfortunately, this procedure

was complicated by a competition between the 2-lithioindole and unreacted *n*-BuLi for the carbonyl electrophile. Therefore, use of 1 equivalent of *n*-BuLi relative to the brominated indole was critical for the success of this reaction.

We began the screening process by using acetophenone (**7**) as the electrophile, which resulted in a good yield of the tertiary alcohol product **15** (Table, entry 1). Incorporating electron donating or withdrawing groups on the aryl ring of acetophenone (**7**) afforded the alcohol products in similar yields as in the electronically unperturbed case (Table, entries 2-3). Installing vicinal quaternary centers using this chemistry proved to be challenging, as addition of the 2-lithioindole intermediate to the hindered pinacolone (**10**) only gave traces of the alcohol product **18**, even after prolonged reaction time at room temperature or at reflux (Table, entry 4). However, the less hindered methyl isopropyl ketone (**11**) did participate in the reaction and delivered a good yield of the addition product **19** (Table, entry 5). An α,β -unsaturated ketone **12** also participated in the reaction, although reduced yields were observed due to the formation of unidentified by-products (Table, entry 6).

Table. Lithium-bromide exchange and addition of the derived lithiate to ketones and aldehydes.^a

Entry	Substrate	Time (hr)	Product	Yield (%) ^b
1		2		73
2		3		75
3		3		78
4		24		trace ^c
5		3		67
6		3		53
7		3		84
8		3		70
9		3		76

^aReaction conditions: 1.2 eq. of indole **4**, 1.2 eq. of *n*-BuLi, and 1.0 eq. ketone/aldehyde in THF. ^bAll reported % yield values reflect isolated, pure product. ^cThe reaction solution was stirred for 24 hours at room temperature

and then it was brought to reflux. Only trace amounts of the product were seen by ¹H NMR spectroscopy.

Aldehydes were suitable electrophiles in the addition reaction as well. For example, cyclohexane carboxaldehyde (**13**) (Table, entry 7) and dihydrocinnaldehyde (**14**) (Table, entry 8) afforded their respective alcohol products in very good yields. Gratifyingly, nucleophilic addition to hindered pivaldehyde (**15**) also afforded the desired product **23** in very good yield after only 3 hours of stirring (Table, entry 9), which clearly demonstrates that sterics are not an insurmountable impediment for aldehyde addition to the lithiate derived from **4**.

In all of the presented entries, alkylation at the benzylic position was not observed; it has been documented that lithium-halogen exchange can sometimes exceed the rate of proton transfer.⁹ However, a potential problem in the reaction of the basic 2-lithiated *N*-benzyl indole (**2b**) with ketones and aldehydes possessing α -protons is α -deprotonation of the carbonyl compound to afford 2-*H*-*N*-benzyl indole. Since this issue might contribute to limiting the yield of product formation, we decided to probe this mechanistic option. Deuterated acetophenone (**24**) was submitted to the same reaction conditions as in the Table, entry 1 (Scheme 3). The resultant alcohol product **25** was fully deuterated at the methyl group and no 2-deuterated *N*-benzylindole (**26**) was observed. This experiment confirms that the rate of addition of the lithiated indole **2b** to the carbonyl of the added electrophile is faster than the proton transfer pathway.

Scheme 3. Deuterium studies in the reaction of lithiated *N*-benzyl indole (**2b**) with deuterated acetophenone (**26**).

In conclusion, we have developed a reaction for the carbonyl functionalization of the 2-position of *N*-benzyl indoles. 2-Bromo-*N*-benzyl indole (**4**) can undergo lithium-bromide exchange and subsequent nucleophilic addition to aldehydes and ketones. The reaction was shown to have a wide carbonyl substrate scope, with some steric limitations, and delivered good-to-excellent yields of the secondary and tertiary alcohol products. This transformation presents a better alternative to the direct lithiation/alkylation at the indolic 2-position of *N*-benzyl indoles, which has been shown to be a very low-yielding reaction.

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Supplementary Material

Spectral characterization data for the new alcohol products in entries 1-9 can be found in the supplemental material.

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Graphical Abstract

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