B(C_6F_5)_3-Catalyzed Direct C3 Alkylation of Indoles and Oxindoles

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ABSTRACT: The direct C3 alkylation of indoles and oxindoles is a challenging transformation, and only a few direct methods exist. Utilizing the underexplored ability of triaryl boranes to mediate the heterolytic cleavage of α-nitrogen C–H bonds in amines, we have developed a catalytic approach for the direct C3 alkylation of a wide range of indoles and oxindoles using amine-based alkylating agents. We also employed this borane-catalyzed strategy in an alkylation-ring opening cascade.

KEYWORDS: catalysis, boranes, N-heterocycles, alkylation, indoles, oxindoles

Indoles and oxindoles are prevalent motifs in biologically active molecules.1 Classic indole syntheses involve ring construction.2 Another approach involves the functionalization of the readily accessible heterocycle core; yet, the direct and selective C3 alkylation of indoles and oxindoles is a surprisingly challenging transformation as the reaction with simple alkyl halides is often not synthetically useful.2,3 For example, with methyl iodide, 1,2-dimethylindole and 1-methylindole are unreactive,4 2-methylindole results in mixtures of N- and C-methylation,5 and oxindoles undergo dialkylation at C3.6 The installation of a methyl group is a worthwhile endeavor, considering the interest of medicinal chemists in the “magic methyl effect,”6 yet only a few methods exist for the direct C3 methylation of indoles and oxindoles (Scheme 1a). Direct C3 methylation is possible with CO_2/H_2 and a ruthenium catalyst.7 The catalytic use of B(C_6F_5)_3 in an asymmetric Mannich process.18 Wasa greatly advanced the strategy by reporting the catalytic use of B(C_6F_5)_3 in an asymmetric Mannich process.19 The iminium ions generated have also been used in electrocyclizations,20 and in the β-functionalization of amines.21,22 However, the use of this reactivity in catalytic C–C bond-forming reactions remains rare.23,24 Inspired by these reports and borrowing hydrogen alkylation reactions,25 we have applied this underutilized reactivity in challenging alkylation processes.

Here, we have developed a new strategy for the direct C3 methylation of indoles and oxindoles (Scheme 1c). The process utilizes a B(C_6F_5)_3-mediated α-N C(sp^3)–H bond cleavage events to activate readily available amine-based alkylation agents. Using this borane-catalyzed method, common undesired reactions, such as the N-methylation of
Scheme 1. B(C₆F₅)₃-Catalyzed α-N C(sp³)−H Bond Cleavage Used in the Methylation of Indoles and Oxindoles

a) Synthetic challenge: Direct C3 methylation of indoles and oxindoles

| Method of direct C3 methylation: | no direct method! |
|----------------------------------|-------------------|
| [Ru]cat.¹ | TM cat.² only |
| CH₂OH | (TM = P₂, ir, Co, Fe) |

Previously reported uses:
- Transfer hydrogenation/dehydrogenation
- Mannich type reactions
- Iminium electrolysis
- Enamine formation

b) B(C₆F₅)₃-mediated heterolytic C−H bond cleavage

c) B(C₆F₅)₃-catalyzed direct C3 alkylation of indoles and oxindoles (this work)

Beyond methylation: other alkylations including alkylation/ ring opening cascades

indoles, the formation of 3,3′-bisindolylmethanes, and the dialkylation of oxindoles, are not observed. In addition, the substrate scope is broad and encompasses 1-, 2-, and 1,2-substituted indoles, as well as other challenging alkylations, including a novel alkylation-rings opening cascade.

We began by investigating various aniline derivatives as methylating agents in the borane-catalyzed methylation of 1,2-dimethyl indole (1a) (Scheme 2). Generally, we discovered

Scheme 2. B(C₆F₅)₃-Catalyzed Methylation of Indole 1a with Various Alkylating Agents

Reactions were performed using 0.2 mmol of 1a. Yields were determined after 1H NMR spectrum analysis of the crude reaction mixture with an internal standard.

that a variety of aryl and diaryl amines were effective in methylating 1a using B(C₆F₅)₃ (10 mol %).²⁴ Electron-rich diaryl methyl amines, such as 4a and 6a, were determined to be optimal and allowed the formation of 2a in quantitative yields at ambient temperature.

We surveyed the scope of the B(C₆F₅)₃-catalyzed methylation of various 1,2-, 1-, and 2-substituted indoles and oxindoles and found that the reaction broadly tolerated a range of functional groups and substitution patterns (Scheme 3). Notably, the direct methylation of 1-methylindole (1f), which is a transformation that was previously absent from the literature,⁴ was successfully accomplished in high isolated yield (2f, 75%) using the B(C₆F₅)₃-catalyzed approach with methylating agent 6a.²⁵ 2-Substituted indoles (i.e., NH indoles, cf. 2l–2s) were efficiently methylated when 2,2,6,6-tetramethylpiperidine (TMP, 10 mol %) was used with alkylating agent 6a and B(C₆F₅)₃ (10 mol %).²⁶ Importantly, N-methylation was not observed with NH-bearing indoles. In contrast, N-alkylation, or mixtures of N- and C-alkylation, typically result when NH indoles are treated with methyl iodide under basic conditions.³ The successful reaction of 1-(cf. 2f–2k) and 2-substituted indoles (cf. 2l–2s) was surprising, given that B(C₆F₅)₃ has been reported to react readily with these classes of heterocycle to produce zwitterionic species.²⁷ 3,3′-Bisindolylmethanes, which are a common product formed in the reaction of formaldehyde or iminium electrophiles with indoles, were not observed.²⁸

Oxindoles (8a–8q) were successfully employed in the B(C₆F₅)₃-catalyzed methylation to give products 9a–9q. In this class of heterocycle, 1,2,2,6,6-pentamethylpiperidine (PMP, 13) was used as the alkylating agent and higher temperatures were required. Crucially, C3 dimethylation was not observed. Therefore, the borane-catalyzed process complements traditional alkylating agents: C3 dialkylation typically occurs when oxindoles are treated with methyl iodide under basic conditions.³

The methylation of 6-methylindole (cf. 2n) and unsubstituted oxindole (cf. 9n) occurred in low yield, presumably because of competitive coordination of N or O to the B(C₆F₅)₃ catalyst. Otherwise, across the different classes of substrates, the process tolerated a range of functional groups and substituents, such as OCH₃ (2d, 2f, 9i, 9k), F (2o, 9d), Cl (2d, 2p, 9e), Br (2q, 9f), CF₃ (9m), NO₂ (2e, 9j), CO₂Me (9c), and other carbonyl derivatives (9o, 9p), which contrasts the dogma sometimes associated with B(C₆F₅)₃-mediated processes.²⁹ We also performed the B(C₆F₅)₃-catalyzed methylation of 1,2-dimethylindole (1a) on a preparative scale, producing 1.3 g of 1,2,3-trimethylindole (2a) in 83% yield.³⁰

In addition, we briefly explored other challenging alkylation reactions using the B(C₆F₅)₃-catalyzed method and discovered that 1,2-dimethylindole (1a) was successfully ethylated (10a), decylated (11a) and benzylated (12a), at C3 using the ethyl- (6b), decyl- (6c), or benzyl- (4b) diaryl amines, respectively.³¹

The borane catalyst, B(C₆F₅)₃, is a commercially available white powder that forms a water adduct, H₂O·B(C₆F₅)₃, when exposed to moisture in air and is therefore routinely handled in an inert atmosphere.³² Inspired by related methods,³³ we developed a procedure where B(C₆F₅)₃ can be used as received from the supplier and weighed in air on the open bench, and the reaction performed using standard Schlenk line techniques (Scheme 4). Thus, H₂O·B(C₆F₅)₃ (10 mol %) was dissolved in the desired solvents (as received from the supplier) and treated with triethyl silane (20 mol %). The resultant solution contains active B(C₆F₅)₃ and O(SiEt₃)₂ that can be used directly in the alkylation of indoles and oxindoles to provide methylated indoles (2a, 2f, and 2l), benzylated indole (12a), and methylated oxindole (9a) in good yields. Therefore, this shows that access to specialized equipment (such as a dry glovebox), a separate purification of commercially available
B(C₆F₅)₃, and rigorously anhydrous solvent is not required in the B(C₆F₅)₃-catalyzed alkylation. Beyond methylation and alkylation, we also explored the B(C₆F₅)₃-catalyzed alkylation strategy in a novel alkylation-ring opening cascade process for the generation of functionalized indoles (Scheme 5). Product 15 contains a 4-(3-indolyl)butylamine motif that is found in several serotonergic/dopaminergic drug molecules, such as vilazodone, roxindole, siramesine, and carmoxirole. Upon reaction of N-aryl

**Scheme 3. Substrate Scope in the B(C₆F₅)₃-Catalyzed Alkylation of Indoles and Oxindoles**

| Reaction | Yield (%) | Condition |
|----------|-----------|-----------|
| 2a | 96%* | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2b | 98% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 2c | 75%* | B(C₆F₅)₃ (10 mol%), 13 (PMP, 2 equiv), 150 °C, P-xylene, 16 h. |
| 2d | 78% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2e | 82% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 2f | 78% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 8 h. |
| 2g | 73% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2h | 79% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 2i | 81% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2j | 75% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2k | 72% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |
| 2l | 65% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 25 °C, DCE, 16 h. |

**Scheme 4. Use of H₂O·B(C₆F₅)₃ in the Borane-Catalyzed Alkylation of Indoles and Oxindoles**

| Reaction | Yield (%) | Condition |
|----------|-----------|-----------|
| 9a | 72% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 9b | 65% | B(C₆F₅)₃ (20 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 10a | 71% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 11a | 81% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |
| 12a | 85% | B(C₆F₅)₃ (10 mol%), 6a (R = CH₃, 1.2 equiv), 95 °C, DCE, 16 h. |

**Scheme 5. B(C₆F₅)₃-Catalyzed Alkylation-Ring Opening Cascade**

B(C₆F₅)₃, and rigorously anhydrous solvent is not required in the B(C₆F₅)₃-catalyzed alkylation.

Beyond methylation and alkylation, we also explored the B(C₆F₅)₃-catalyzed alkylation strategy in a novel alkylation-ring opening cascade process for the generation of functionalized indoles 15 (Scheme 5). Product 15 contains a 4-(3-indolyl)butylamine motif that is found in several serotonergic/dopaminergic drug molecules, such as vilazodone, roxindole, siramesine, and carmoxirole. Upon reaction of N-aryl
pyrrolidines 14,17 indoles 1 and B(C₆F₅)₃ catalyst, a variety of 4-(3-indolyl)butylamines 15 were formed in good yields.38

In order to probe the mechanism and provide direct access to deuterated methyl groups at C₃ of indoles, we used deuterated methylation agent 6a-d₃ in the B(C₆F₅)₃-catalyzed methylation of indoles 1a and 11 under previously optimized conditions (Scheme 6a). Deuterated C₃ methyldines 2a-d₃ and 2l-d₃ were formed in high yield in both cases.39

**Scheme 6. Mechanistic Studies and Proposed Catalytic Cycle**

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1) N\(\text{CH}_3\) \(\text{B(C}_6\text{F}_5)_3\) (10 mol%) \(\text{D}_2\text{C} - \text{Na}_2\)
\(\text{D}_2\text{C} - \text{Na}_2\)
88% D
\(\text{2a-d}_3\) >99% D, 1.2 eq.
>95% D
\(\text{2a-d}_3\) 98% 4

b) 1) N\(\text{CH}_3\) \(\text{B(C}_6\text{F}_5)_3\) (10 mol%)
\(\text{H}_2\text{C} - \text{Na}_2\)
\(\text{H}_2\text{C} - \text{Na}_2\)

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Yields are isolated and %D incorporation was determined after \(^1\text{H}\) NMR spectrum analysis of the purified compounds. \(^1\text{H}\) DCE, 25 °C, 16 h, \(^1\text{H}\) TMP (10 mol %), toluene, 110 °C, 16 h.

**ASSOCIATED CONTENT**

Supporting Information
Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2020.0104936560 or from the lead authors upon request. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c01141.

Experimental procedures and spectroscopic data (PDF)

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**Notes**
The authors declare no competing financial interest.
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(24) See the Supporting Information for further details of optimization. Electron-rich diarylated amine are expected to be better hydride donors and, thus, undergo the B(C_{6}F_{5})_{3}-C−H cleavage more readily. (25) Amine 6a was found to be a more-general methylating agent versus 4a.

(26) The addition of TMP significantly improved the yield when NH indoles were used. See the Supporting Information.

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