$B(C_6F_5)_3$-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

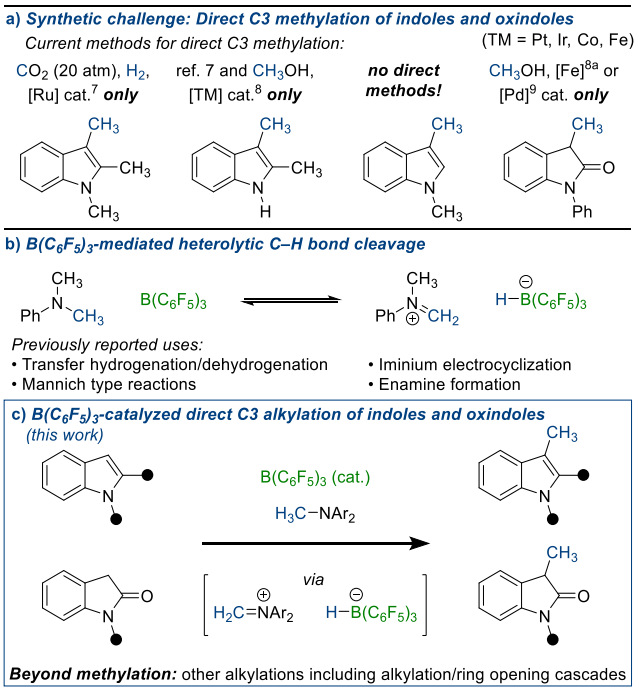
KEYWORDS: catalysis; boranes; N-heterocycles; alkylation; indoles; oxindoles.

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-dimethyl indole and 1-methyl indole are unreactive,[4] 2-methyl indole results in mixtures of *N*- and *C*-methylation,[5] and oxindoles undergo dialkylation at C3.[3] The installation of a methyl group is a worthwhile endeavor considering medicinal chemists interest 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 (e.g. for 1,2-dimethyl indole and 2-methyl indole),[7] and with borrowing hydrogen methods with methanol (e.g. for 2-methyl indole[8] and 1-phenyl oxindole).[8a,9] The direct methylation of 1-methyl indole is currently unknown.[4]

Owing to their intrinsic Lewis acidity, borane catalysts have found numerous applications in synthesis and are traditionally used to activate polarized bonds.[10] Triaryl boranes can also activate unpolarized bonds, such as H–H[11] and Si–H bonds.[12] In a similar vein, we considered if boranes could also be used to cleave heterolytically C(sp^3)–H bonds[13] and unveil new approaches to challenging transformations. Related to this, we were intrigued by a report by Santini that described the heterolytic cleavage of an α-nitrogen C(sp^3)–H bond during the stoichiometric reaction of dimethyl aniline and $B(C_6F_5)_3$ to form an iminium borohydride ion pair (Scheme 1b).[14] $B(C_6F_5)_3$-mediated α-N C(sp^3)–H bond cleavage[15] was unrecognized as a synthetic strategy for almost a decade until Stephan and coworkers reported its use in the transfer hydrogenation of imines.[16] Subsequently, Grimme and Paradies,[17a] Kanai,[17b] and Zhang[17c] disclosed methods for the dehydrogenation of *N*-heterocycles. A major breakthrough came when Erker reported the use of this unusual reactivity in C–C bond forming reactions where stoichiometric $B(C_6F_5)_3$ was used to generate iminium ions for Mannich type processes.[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.[19,20] Inspired by these reports and borrowing hydrogen alkylation reactions,[23] 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 event to activate readily available amine based alkylating agents. Using this borane-catalyzed method, common undesired reactions, such as *N*-methylation of indoles, formation of 3,3'-bisindolylmethanes, and 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-ring opening cascade.

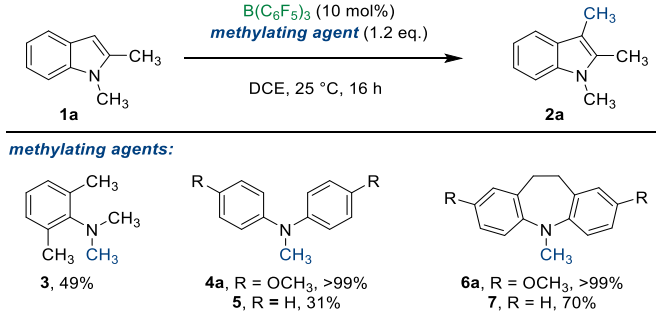
Scheme 1. $B(C_6F_5)_3$-catalyzed α-N C(sp^3)–H bond cleavage used in the methylation of indoles and oxindoles.



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

that a variety of aryl and diaryl amines were effective in methylating **1a** using $B(C_6F_5)_3$ (10 mol%).[24] Electron rich diaryl methyl amines, such as **4a** and **6a** were found to be optimal and allowed the formation of **2a** in quantitative yields at ambient temperature.

Scheme 2. $B(C_6F_5)_3$-catalyzed methylation of indole 1a with various alkylating agents.

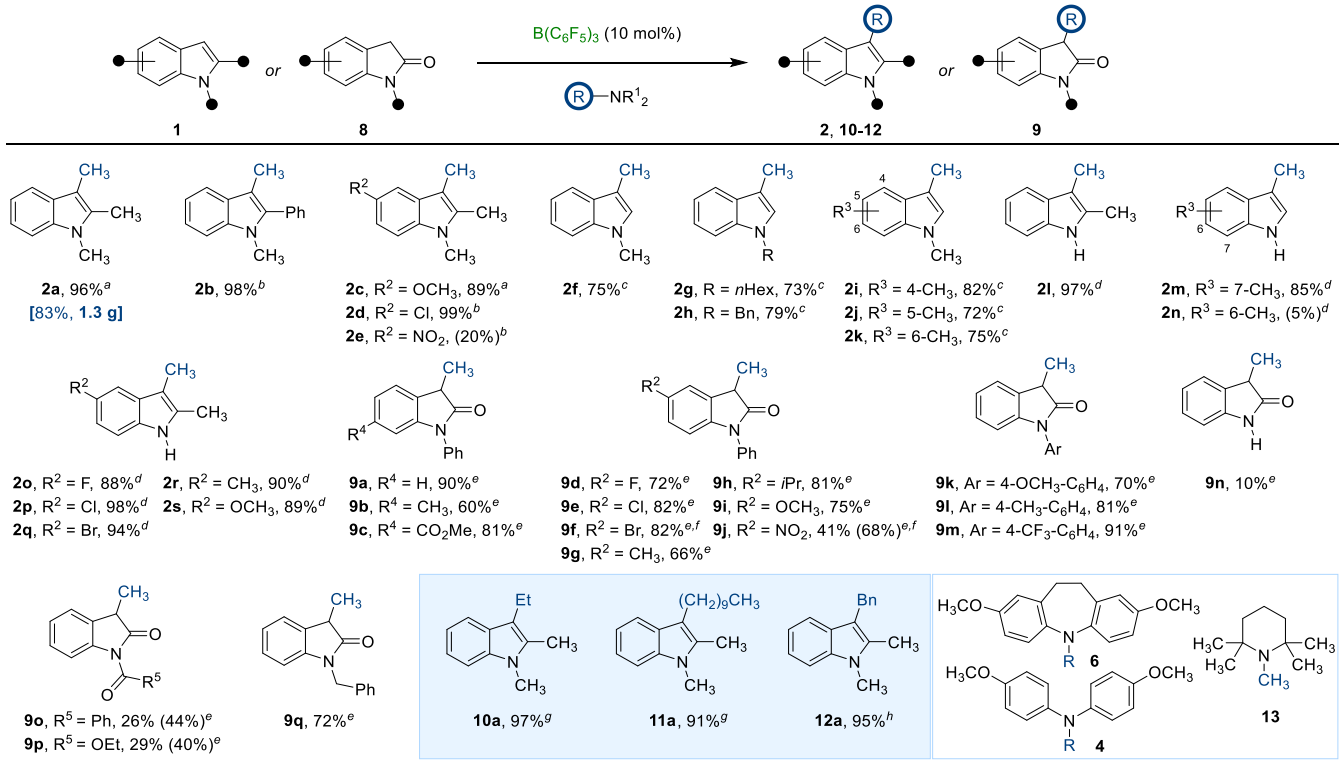


Reactions were performed using 0.2 mmol of **1a**. Yields were determined after ^{1}H NMR spectrum analysis of the crude reaction mixture with an internal standard.

We surveyed the scope of the $B(C_6F_5)_3$-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-methyl indole (**1f**), a transformation that was previously absent from the literature,[4] was successfully accomplished in high isolated yield (**2f**, 75%) using the $B(C_6F_5)_3$-catalyzed approach with methylating agent **6a**.[25] 2-Substituted indoles (i.e. NH indoles, *cf.* **2l–s**) were efficiently methylated when 2,2,6,6-tetramethylpiperidine (TMP, 10 mol%) was used with alkylating agent **6a** and $B(C_6F_5)_3$ (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.[5] The successful reaction of 1- (*cf.* **2f–k**) and 2-substituted indoles (*cf.* **2l–s**) was surprising given that $B(C_6F_5)_3$ has been reported to readily react with these classes of heterocycle to produce zwitterionic species.[27] 3,3'-Bisindolylmethanes, a common product formed in the reaction of formaldehyde or iminium electrophiles with indoles, were not observed.[28]

Oxindoles (**8a–q**) were successfully employed in the $B(C_6F_5)_3$-catalyzed methylation to give products **9a–q**. 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]

Scheme 3. Substrate scope in the $B(C_6F_5)_3$-catalyzed alkylation of indoles and oxindoles.



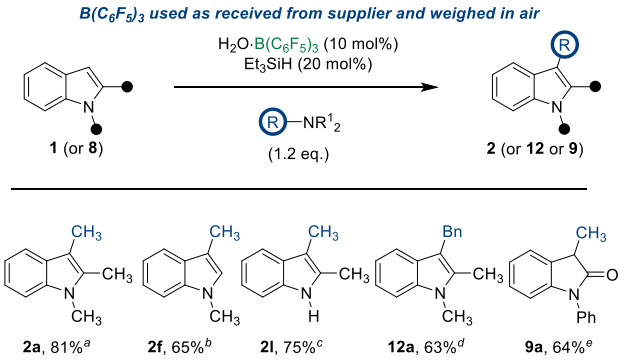
Reactions were performed using 0.5 mmol of **1** or **8**. Yields are isolated. Yields in parenthesis determined after ^{1}H NMR spectrum analysis of the crude reaction mixture with an internal standard. [a] $B(C_6F_5)$ (10 mol%), **6a** (R = CH_3, 1.2 eq.), 25 °C, DCE, 16 h. [b] $B(C_6F_5)_3$ (10 mol%), **6a** (R = CH_3, 1.2 eq.), 95 °C, DCE, 16 h. [c] $B(C_6F_5)_3$ (20 mol%), **6a** (R = CH_3, 1.2 eq.), 95 °C, DCE, 8 h. [d] $B(C_6F_5)_3$ (10 mol%), **6a** (R = CH_3, 1.2 eq.), TMP (10 mol%), 110 °C, toluene, 16 h. [e] $B(C_6F_5)_3$ (10 mol%), **13** (PMP, 2 eq.), 150 °C, xylenes, 16 h. [f] Combined yield of tautomers. [g] $B(C_6F_5)_3$ (10 mol%), **6b** (R = Et) or **6c** (R = $(CH_2)_9CH_3$) (1.2 eq.), 95 °C, DCE, 24 h. [h] $B(C_6F_5)_3$ (20 mol%), **4b** (R = Bn, 2 eq.), 150 °C, xylenes, 24 h.

The methylation of 6-methyl indole (*cf.* **2n**) and unsubstituted oxindole (*cf.* **9n**) occurred in low yield, presumably due to competitive coordination of N or O to the $B(C_6F_5)_3$ catalyst. Otherwise, across the different classes of substrates, the process tolerated a range of functional groups and substituents, such as OCH_3 (**2c**, **2s**, **9i**, **9k**), F (**2o**, **9d**), Cl (**2d**, **2p**, **9e**), Br (**2q**, **9f**), CF_3 (**9m**), NO_2 (**2e**, **9j**), CO_2Me (**9c**), and other carbonyl derivatives (**9o**, **9p**) which contrasts the dogma sometimes associated with $B(C_6F_5)_3$-mediated processes.[29] We also performed the $B(C_6F_5)_3$-catalyzed methylation of 1,2-dimethyl indole (**1a**) on a preparative scale, producing 1.3 g of 1,2,3-trimethyl indole (**2a**) in 83% yield.[30]

In addition, we briefly explored other challenging alkylation reactions using the $B(C_6F_5)_3$-catalyzed method and discovered that 1,2-dimethyl indole (**1a**) was successfully ethylated (**10a**), decylated (**11a**) and benzylated (**12a**), at C3 using the ethyl- (**6b**), decyl- (**6c**) or benzyl- (**4b**)[31] diaryl amines respectively.[32]

The borane-catalyst, $B(C_6F_5)_3$, is a commercially available white powder that forms a water adduct, $H_2O{\cdot}B(C_6F_5)_3$, when exposed to moisture in air and is therefore routinely handled in an inert atmosphere.[33] Inspired by related methods,[34] we developed a procedure where $B(C_6F_5)_3$ 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 $H_2O{\cdot}B(C_6F_5)_3$ (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 $B(C_6F_5)_3$ and $O(SiEt_3)_2$ 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**)[35] in good yields. Therefore, showing that access to specialized equipment (such as a dry glove box), a separate purification of commercially available $B(C_6F_5)_3$, and rigorously anhydrous solvent is not required in the $B(C_6F_5)_3$-catalyzed alkylation.

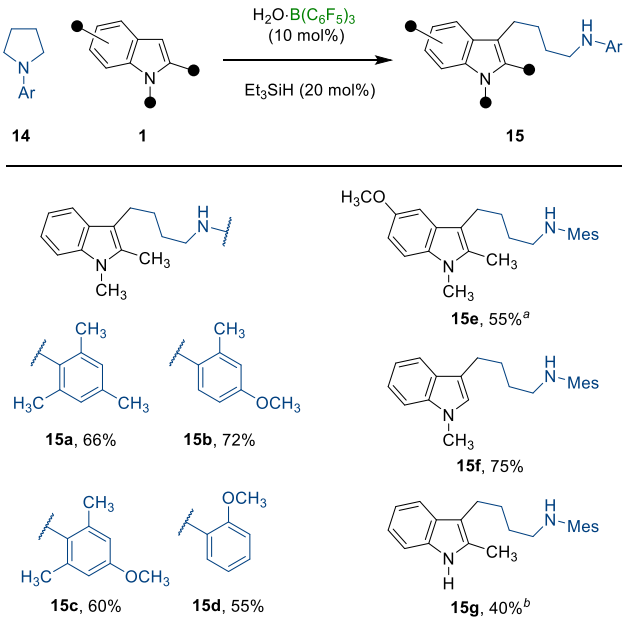
Scheme 4. The use of $H_2O{\cdot}B(C_6F_5)_3$ in the borane-catalyzed alkylation of indoles and oxindoles.



[a] **6a**, 25 °C, DCE, 16 h. [b] **6a**, $B(C_6F_5)_3$ (20 mol%), Et_3SiH (40 mol%), 95 °C, DCE, 8 h. [c] **6a**, TMP (10 mol%), 110 °C, toluene, 16 h. [d] **4b**, 150 °C, p-xylene, 24 h. [e] PMP (**13**) (2 eq.), 150 °C, p-xylene, 16 h.

Beyond methylation and alkylation we also explored the $B(C_6F_5)_3$-catalyzed alkylation strategy in a novel alkylation-ring opening cascade process for the generation of functionalized indoles **15** (Scheme 5). Products **15** contain a 4-(3-indolyl)butylamine motif that is found in several serotonergic/dopaminergic drug molecules, such as vilazodone, roxindole, siramesine, and carmoxirole.[36] Upon reaction of *N*-aryl pyrrolidines **14**,[37] indoles **1** and $B(C_6F_5)_3$ catalyst, a variety of 4-(3-indolyl)butylamines **15** were formed in good yields.[38]

Scheme 5. $B(C_6F_5)_3$-catalyzed alkylation-ring opening cascade.

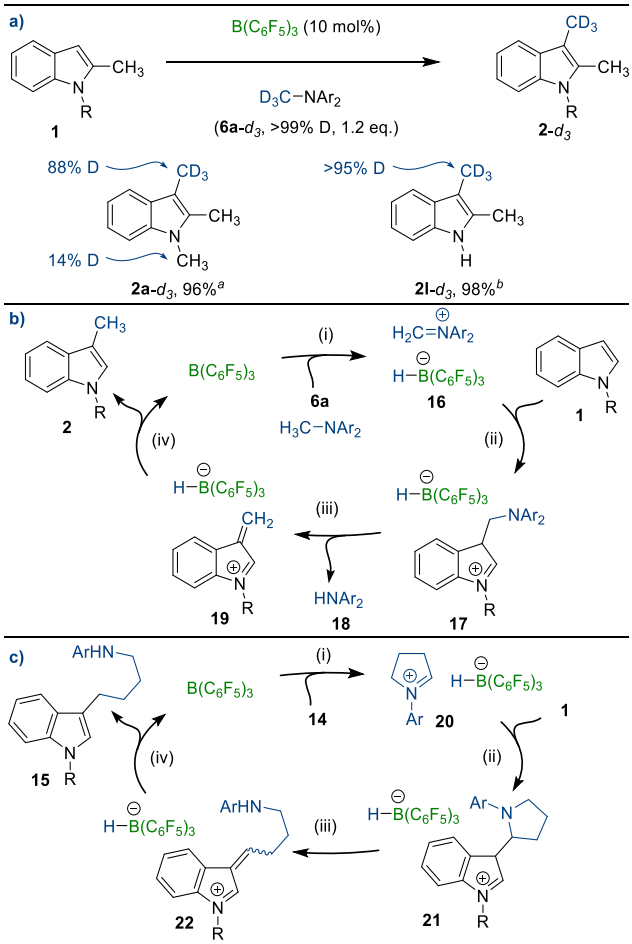


Standard conditions: $H_2O{\cdot}B(C_6F_5)_3$ (10 mol%), Et_3SiH (20 mol%), **14** (1 eq.), **1** (2.2 eq.), 1,2-$Cl_2C_6H_4$, 110 °C, 20–24 h. [a] DCE, 85 °C. [b] Toluene.

In order to probe the mechanism and provide direct access to deuterated methyl groups at C3 of indoles, we used deuterated methylating agent **6a**-*d3* in the $B(C_6F_5)_3$-catalyzed methylation of indoles **1a** and **1l** under previously optimized conditions (Scheme 6a). Deuterated C3 methyl indoles **2a**-*d3* and **2l**-*d3* were formed in high yield in both cases.[39]

Based on these results and literature precedent, we propose the following catalytic cycle for the $B(C_6F_5)_3$-catalyzed alkylation of indoles and oxindoles (Scheme 6b). The borane-catalyst mediates heterolytic cleavage, via hydride abstraction, of the α-N C(sp^3)–H bond in the amine based alkylating agents (**3**–**7**, **13**, **14**) forming iminium-borohydride ion pairs **16** (Scheme 6b, step i). Analogous ion pairs have been observed by Santini and coworkers using NMR spectroscopy (*cf.* Scheme 1A).[14] The electrophilic iminium **16** is trapped with an indole **1** (or oxindole **8**), forging a new C–C bond (step ii) in an analogous fashion to the Mannich reaction. Proton transfers enable the ion pair **17** to eliminate the amine **18** (which can be recovered from the reaction) via an $E1_{CB}$-type mechanism (step iii).[40] The α,β-unsaturated iminium-based ion pair **19** is reduced by the borohydride counterion, producing the alkylated indoles **2** (and oxindoles **9**) and regenerating the borane-catalyst (step iv). In the boron catalyzed alkylation/ring opening cascade process (*cf.* Scheme 5), the cyclic nature of the iminium **20** enables the amino fragment to be retained in products **15** after elimination (Scheme 6c).

Scheme 6. Mechanistic studies and proposed catalytic cycle.



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

In summary, we have developed a new approach to the direct C3 alkylation of indoles and oxindoles. Using a $B(C_6F_5)_3$-catalyst and amine derived alkylating agents, we exploit the underexplored ability of boranes to cleave heterolytically α-N C(sp^3)–H bonds in a catalytic C–C bond forming reaction. This method provides a metal-free and complementary approach to the few existing methods for the direct C3 alkylation of indoles. Unlike other procedures, this $B(C_6F_5)_3$-catalyzed methodology encompasses several classes of indole, including 1-, 2-, and 1,2-substituted indoles, and allows previously unreported direct methylations. The reaction displays broad scope and exceptional chemoselectivity, avoiding *N*-methylation and formation of 3,3'-bisindolylmethanes in indole substrates, and dialkylation in oxindoles. Other alkylations are also reported, including a novel alkylation-ring opening cascade process to generate privileged 4-(3-indolyl)butylamines from *N*-aryl pyrrolidines.

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ASSOCIATED CONTENT

Supporting Information.
Experimental procedures and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.
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/XXXX or from the lead authors upon request.

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(25) Amine **6a** was found to be a more general methylating agent versus **4a**.

(26) Addition of TMP significantly improved the yield when NH indoles were used. See supporting information.

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(28) For an example where 3,3'-bisindolylmethane products form, see: ref. 7.

(29) For an example of the impressive functional group compatibility of catalytic $B(C_6F_5)_3$ processes, see: Bender, T. A.; Payne, P. R.; Gagné, M. R. Late-Stage Chemoselective Functional-Group Manipulation of Bioactive Natural Products with Super-Electrophilic Silylium ions, *Nat. Chem*. **2018**, *10*, 85–90.

(30) The amine byproduct (*cf*. amine **18**, Scheme 6) was recovered in 98% yield.

(31) Benzylating agent **4b** was marginally better over the analogous alkylating agent based on amine **6**.

(32) Benzofurans, furans, benzothiophenes and thiophenes were unreactive, and pyrroles gave low yields. See supporting information for details.

(33) Schneider, A. F.; Chen, Y.; Brook, M. A. Trace Water Affects

Tris(pentafluorophenyl)borane-Catalytic Activity in the Piers–Rubinsztajn Reaction. *Dalton Trans*. **2019**, *48*, 13599–13606.

(34) For example, see: (a) Thomson, J. W.; Hatnean, J. A.; Hastie, J. J.; Pasternak, A.; Stephan, D. W.; Chase, P. A. Improving the Industrial Feasibility of Metal-Free Hydrogenation Catalysts Using Chemical Scavengers. *Org. Process Res. Dev*. **2013**, *17*, 1287–1292.

(35) In the case of oxindoles **9a**, yields were improved upon removal of the $O(SiEt_3)_2$ byproduct by simply applying vacuum. See Supporting Information.

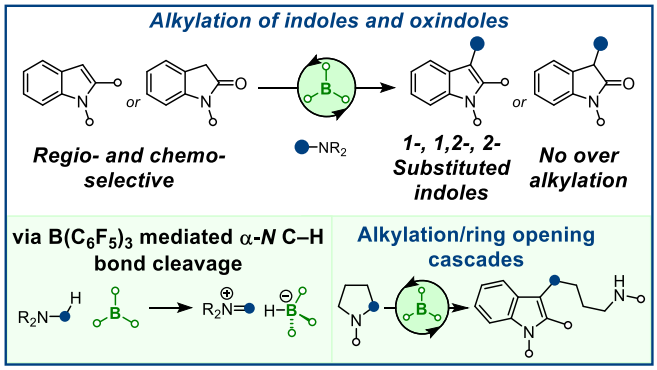
(36) (a) Schwartz, T. L.; Siddiqui, U. A.; Stahl, S. M. Vilazodone: A Brief Pharmacological and Clinical Review of the Novel Serotonin Partial Agonist and Reuptake Inhibitor. *Ther. Adv. Psychopharmacol.* **2011**, 81–87; (b) Gründer, G.; Wetzel, H.; Hammes, E.; Benkert, O. Roxindole, a Dopamine Autoreceptor Agonist, in the Treatment of Major Depression. *Psychopharmacology* **1993**, *111*, 123–126. (c) Sanchez, C.; Papp, M. The Selective Sigma2 Ligand Lu 28-179 has an Antidepressant-Like Profile in the Rat Chronic Mild Stress Model of Depression. *Behavioural Pharmacology* **2000**, *11*, 117–124; (d) Marchese, G.; Ruiu, S.; Casti, P.; Bartholini, F.; Saba, P.; Gessa, G. L.; Pani, L. Carmoxirole is Able to Reduce Amisulpride-Induced Hyperprolactinemia Without Affecting its Central Rffect. *Eur. J. Pharmacol*. **2002**, *447*, 109–114.

(37) Wasa has previously shown that *N*-aryl pyrrolidines undergo hydride abstraction, see ref. 19.

(38) Electron rich aromatic rings can be removed from nitrogen under oxidative conditions (*cf*. PMP protecting groups). For a relevant example, see ref. 19b.

(39) Partial deuterium incorporation at the *N*-CH_3 site of **2a**-*d3* may indicate that hydride abstraction may also occur at *N*-CH_3 or, that 1,5-prototropic shift in intermediate **19** (R = CH_3) occurs priors to hydride transfer (*cf*. Scheme 6b, step iv).

(40) Attempts to prevent the elimination and isolate the corresponding aminomethylation derivative of **17** were unsuccessful. For a related elimination-reduction sequence, see: Deb, M. L.; Baruah, P. K. Deamination of Indole Mannich Bases: An Efficient Route to 3-Benzyl/Alkylindoles via a Metal-Free Transfer Hydrogenation Under Microwave Irradiation. *Curr. Organocatalysis* **2016**, *3*, 84–89.


Alkylation of indoles and oxindoles
or
or
Regio- and chemo-selective
NR2
1-, 1,2-, 2-Substituted indoles
No over alkylation
via B(C6F5)3 mediated α-N C–H bond cleavage
Alkylation/ring opening cascades