Indole Functionalization

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Regio- and Stereoselective Allylation and Crotylation of Indoles at C2 Through the Use of Potassium Organotrifluoroborate Salts**

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Dedicated to Professor William B. Motherwell on the occasion of his 65th birthday

The site- and stereoselective functionalization of the indole ring system is an area of considerable recent interest, because of the importance of indoles as natural products, and as a result of their privileged status in biologically active targets and pharmaceuticals.[1] Approaches for selective C–C bond functionalization of indole rings include metal-catalyzed and organocatalyzed reactions,[2–5] which allow direct formation of both 3- and 2-substituted indoles or their indoline (2,3-dihydro-1*H*-indole) counterparts. Despite the obvious synthetic potential of the direct addition of organometallic nucleophiles to the C2 position of indoles, such strategies are only rarely encountered,[1] in large part because the indole ring itself is nucleophilic, and because the indole N–H bond is prone to deprotonation and consequent deactivation of the indole core for nucleophilic attack. In this context, the studies of Bubnov and co-workers on the addition of triallylborane and triprenylborane to indoles and other heterocycles are particularly noteworthy.[6,7] However, the low reactivity of the indole ring toward nucleophilic addition necessitates the use of the highly reactive triallylborane reagent at elevated temperatures, with addition occurring through reaction with the 3*H*-indole imine tautomer. The major disadvantages of this approach are the high reactivity of the borane reagents toward other functional groups, and the highly oxygen-sensitive and pyrophoric nature of these reagents, which necessitate specific handling techniques and preparation generally immediately prior to use. This requirement has limited the utility of this approach, and less-reactive nucleophiles, such as allylboronate esters, unfortunately do not undergo addition to indoles. The closely related reverse-prenylation protocol of Danishefsky and co-workers has utilized the more stable prenyl-9-BBN reagent.[8] However, this reagent must generally be used in excess to achieve acceptable yields in the addition reaction, and is inconvenient to prepare, as it requires sequential distillations for purification. Nevertheless, despite the problems associated with C2 allylation and prenylation methods, they have found utility in numerous complex natural product syntheses.[9] The development of more convenient protocols for the allylation and prenylation of the C2 position of indoles are therefore of considerable interest. We now report a general and selective C2 allylation of indoles using allylic trifluoroborate salts.

Over the last decade, several groups have reported the utility of organotrifluoroborate salts[10] as air- and moisture-stable reagents that act as synthetic equivalents to boronic acids.[11,12] While most reports of these salts have focused on their use for cross-coupling chemistry,[10] other synthetically useful applications have also emerged. For example, additions to electrophiles, including carbonyl groups and imines, under a variety of conditions, including the use of Lewis acid, phase transfer catalysis, montmorillonite K10 clay, indium and rhodium(I) catalysis, have been reported.[13] In each of these cases, the abstraction of fluoride ions presumably occurs to initially generate an allyldifluoroborane species, which can either react directly with the electrophile or be converted into another reactive allylation agent. We considered that the intermediacy of an in situ generated allyldifluoroborane species might similarly allow the addition to indoles via their 3*H*-indole tautomers. Initial reaction optimizations were carried out using potassium allyltrifluoroborate **1a** and indole **2a**. Activation by K10 led to only moderate yields of indoline **3a** because of competing side reactions of **2a**, while the use of an indium-based protocol, which had been successfully developed for additions to ketones,[13g] did not give the desired product **3a** (Table 1, entries 1 and 2). The use of a stoichiometric amount of $BF_3{\cdot}Et_2O$ afforded **3a** in good yield after 30 h (Table 1, entry 3). Use of a catalytic amount of $BF_3{\cdot}Et_2O$ (15 mol%) led to side reactions (indole dimerization[14]) at higher concentrations, while conversion was poor at lower concentrations. Catalytic $Yb(OTf)_3$ was also capable of promoting addition of **1a** to **2a** (Table 1, entry 4). Application of some of these conditions to reactions of indoles bearing substituents at the 2- and 3-positions and *E*- and *Z*-crotyltrifluoroborate salts **1b** and **1c** generally gave lower conversions with catalytic amounts of Lewis acids, while good conversions and yields were achieved using stoichiometric amounts of $BF_3{\cdot}Et_2O$ (Table 1, entries 5–15). Crotylations of **2a** occurred stereospecifically, giving **3b** and **3c** from reactions of **1b** and **1c**, respectively. The use of 2-methylindole required longer reaction times in order to achieve full conversion, while reactions of **1c** occurred more slowly than the corresponding reactions using **1a** or **1b**. *N*-Methylindole failed to give the desired product, even with a stoichiometric amount of $BF_3{\cdot}Et_2O$. Finally, reactions using the pinacol ester of allylboronic acid rather than **1a** gave poor results.

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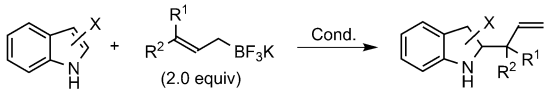
Table 1: Optimization of the reactions of indoles **2** with allyltrifluoroborate salt **1a** and crotyltrifluoroborate salts **1b** and **1c**.[a]



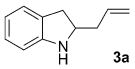
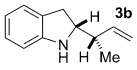
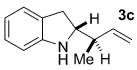
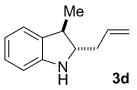
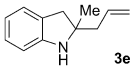
2

2a: X = H
2b: X = 3-Me
2c: X = 2-Me

1

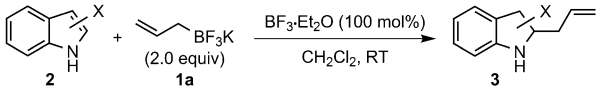
1a: R^1 = H, R^2 = H
1b: R^1 = H, R^2 = Me (*E*)
1c: R^1 = Me, R^2 = H (*Z*)

3

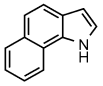
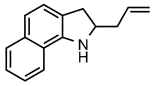
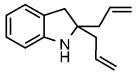
Entry	2	1	Cond.[a]		Product	Conv.[b] [%] (Yield)
1[c]	**2a**	**1a**	A	**3a**		50
2	**2a**	**1a**	B	**3a**		≤5
3	**2a**	**1a**	C	**3a**		100 (92)
4	**2a**	**1a**	D	**3a**		100 (79)
5	**2a**	**1b**	A	**3b**		100 (72)
6	**2a**	**1b**	C	**3b**		100 (88)
7	**2a**	**1c**	A	**3c**		<10
8	**2a**	**1c**	C	**3c**		100 (89)
9	**2a**	**1c**	D	**3c**		30
10	**2b**	**1a**	A	**3d**		≤5
11	**2b**	**1a**	C	**3d**		100 (83)[d]
12	**2b**	**1a**	D	**3d**		65[e]
13	**2c**	**1a**	A	**3e**		≤5
14	**2c**	**1a**	C	**3e**		91
15	**2c**	**1a**	D	**3e**		95

[a] Reactions were carried out for 30 h using substrates **1a** and **1b** and for 72 h using substrate **1c**. Conditions: A) montmorillonite K10 clay, CH_2Cl_2, H_2O; B) In (1.0 equiv), CH_2Cl_2, H_2O; C) $BF_3{\cdot}Et_2O$ (100 mol%), CH_2Cl_2; D) $Yb(OTf)_3$ (15 mol%), CH_2Cl_2. [b] Conversion was monitored by ^1H NMR analysis of the crude products. [c] The reaction was performed under an inert atmosphere for 48 h. [d] The d.r. was 2.1:1, based on ^1H NMR analysis of the crude product. [e] The d.r. was 1.7:1, based on ^1H NMR analysis of the crude product.

Table 2: Substrate scope for the allylation of indoles using potassium allyltrifluoroborate **1a**.[a]



2 **1a** **3**

Entry	X	2	3	Yield [%][b]
1	H	**2a**	**3a**	92
2	5-Br	**2d**	**3f**	90
3	5-Cl	**2e**	**3g**	92
4	5-F	**2f**	**3h**	79
5	5-OH	**2g**	**3i**	90
6	5-CO_2Me	**2h**	**3j**	86
7	7-Me	**2i**	**3k**	87[c]
8	3-Me	**2b**	**3d**	87[d]
9	2-Me	**2c**	**3e**	91
10	2-Ph	**2j**	**3l**	85[c]
11		**2k** 	**3m** 	38[e]
12		**2l** 	**3n** 	88[f]

[a] Reactions were carried out on a 0.50 mmol scale with respect to the indole substrates at a concentration of 0.125 M for 6-72 h. [b] Isolated yields. [c] 3.0 equiv of **1a** and $BF_3{\cdot}Et_2O$ were required over 62 h to achieve full conversion. [d] d.r. = 2.1:1, based on ^1H NMR analysis of the crude reaction mixture. [e] 52% conversion after 74 h. [f] 4.0 equiv of **1a** was used.

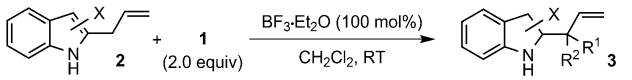
Reactions of **1a** with a variety of substituted indoles were surveyed under the optimized conditions with reaction times of 6–72 h (Table 2). Excellent yields were obtained using 5-substituted indoles, including those with electron-donating and electron-withdrawing substituents (Table 2, entries 2–6). Steric effects of substituents at the 2-, 3- and 7-positions of the indole ring were detrimental to the reaction progress, and longer reaction times were required to achieve full conversion. For example, full conversion was observed only after 72 h in reactions of the methyl-substituted indoles (Table 2, entries 7–9). Addition of **1a** to 3-methylindole gave **3d** in good yield, but with modest diastereoselectivity that favoured the *trans* product (Table 2, entry 8). Reactions of 2-substituted indoles required a longer reaction time and/or larger quantities of reagents to achieve full conversions (Table 2, entries 9 and 10). For example, 2-phenyl indole required 3.0 equivalents of **1a** and $BF_3{\cdot}Et_2O$ over 74 h to afford **3l** in 85% yield of isolated product. Allylation of the sterically demanding substrate **2k** was slow (Table 2, entry 11). Attempts to selectively monoallylate 3-chloroindole were unsuccessful, but the reaction using an excess of **1a** (4.0 equiv) led to the formation of α,α-diallylated indole **3n** as the sole product (Table 2, entry 12).

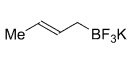
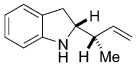
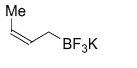
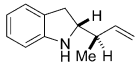
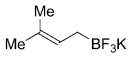
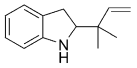
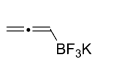
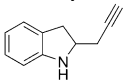
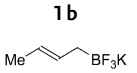
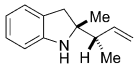
The scope of the procedure with other salts was also investigated (Table 3). Diastereospecific crotylation of indole occurred in good yields and diastereoselectivities using *E*- and *Z*-crotyltrifluoroborates (Table 3, entries 1–2). Reaction of the prenyltrifluoroborate salt **1d** also occurred in good yield to give the reverse-prenylated indoline **3o** (Table 3, entry 3). Reaction of the allenyltrifluoroborate salt **1e** under identical conditions led to propargylated indole **3p** as the sole product (Table 3, entry 4). This is the first example of a propargylation of indole using an allenylboron reagent. Finally, reaction of **2c** with **1b** also occurred to give **3q** with a good d.r.

The 2-substituted indoline products **3** are valuable synthetic intermediates.[1,3] A short metathesis-based synthetic route served to illustrate this, affording the diastereoisomeric dihydropyridoindolone products **5a** and **5b** in good yields from **3b** and **3c**, respectively (Scheme 1). The relative stereochemical assignment of **3b** and **3c** was also established, based upon the rigid cyclic structures of **5a** and **5b**, through a comparative analysis of ^3J and ^4J (^1H, ^1H) coupling constants and NOE correlations.[15]

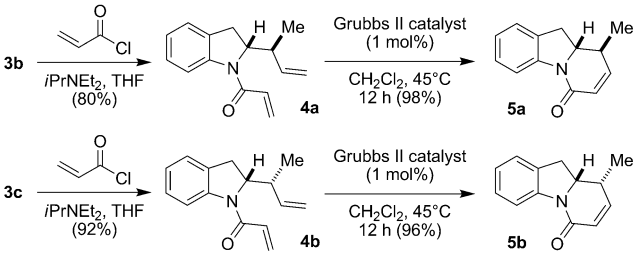
The observed results are consistent with additions of allylic boron difluoride intermediates to the *Z*-configured cyclic imine 3*H*-indole tautomers. Addition was not observed with *N*-methylindole, a substrate that cannot form the

Table 3: Substrate scope with respect to the allylating agent **2**.[a]



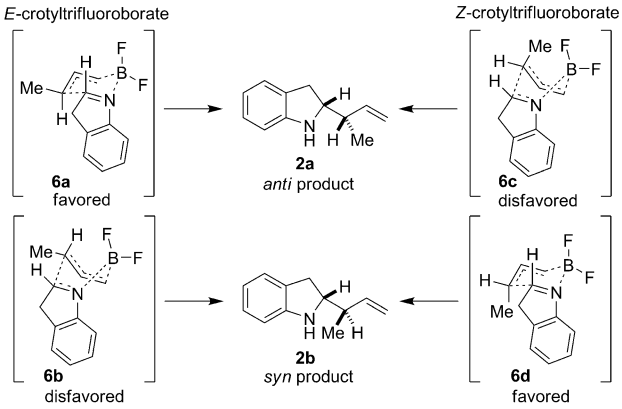
Entry	2	1	3	Yield [%][b] (d.r.)[c]
1	**2a**	**1b** 	**3b** 	95 (≥95:5)
2	**2a**	**1c** 	**3c** 	83[d] (≥95:5)
3	**2a**	**1d** 	**3o** 	89
4	**2a**	**1e** 	**3p** 	83
5	**2c**	**1b** 	**3q** 	91 (95:5)

[a] Reactions were carried out on a 0.50 mmol scale with respect to the indole substrates using the conditions shown in Table 2. [b] Yields of isolated products. [c] d.r. determined by ^{1}H NMR analysis of the crude products through comparison of resonances of the methyl groups with the most-upfield chemical shift. [d] Full conversion achieved using trifluoroborate salt **1c** (3.0 equiv) and BF_3·Et_2O (2.0 equiv) over 74 h.



Scheme 1. Synthesis of **5a** and **5b** from **3b** and **3c**, respectively.

requisite imine tautomer. The stereospecific crotylation of indole using the *E*- and *Z*-crotyltrifluoroborate salts to afford the *anti* and *syn* products **3b** and **3c**, respectively, is consistent with the addition occurring via a Zimmerman–Traxler-like transition state (Scheme 2). Thus, reactions via chair-like transition states **6a** and **6d** are favored over reactions via boat-like transition states **6b** and **6c** as a result of reduced *syn*-pentane-like interactions. The lower reactivity of the *Z*-crotyltrifluoroborate relative to its *E*-isomer can be attributed to greater destabilization based on the 1,3-diaxial-like steric interaction that occurs between the methyl group of the trifluoroborate and the indole ring in transition state **6d** relative to **6a**. The lower reactivity of C7-substituted indole derivatives can also be rationalized as a result of unfavourable steric interactions in the transition states.



Scheme 2. Plausible transition states for the crotylation of indole.

In summary, a general method for regio- and diastereoselective allyl-, crotyl-, allenyl-, and prenylation at the 2-position of unprotected indoles has been developed. The stability of the organotrifluoroborate salts that are used provides an operationally straightforward protocol for indoline synthesis, and avoids the use of sensitive triallylboron, prenyl-9-BBN, or related borane-based reagents. The synthetic significance of the reaction derives from the importance of indoles as synthetic targets, the ready availability of indole precursors, and the mild conditions employed. This study also illustrates the significant potential for identifying new reactivity profiles of organotrifluoroborate salts beyond their widespread application for cross-coupling chemistry. Further studies on the addition reactions of these salts to indoles, heterocycles, and other electrophiles will be reported in due course.

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Keywords: addition reactions · heterocycles · indoles · indolines · organotrifluoroborate

[1] For general reviews of indole chemistry, see: a) "Heterocyclic Scaffolds II: Reactions and Applications of Indoles": *Topics in Heterocyclic Chemistry*, *Vol. 26* (Ed.: G. W. Gribble), Springer, Berlin, **2010**; b) R. J. Sundberg, *Indoles*, Academic Press, London, **1996**; c) D. S. C. Black, R. J. Sundberg, G. W. Gribble in *Comprehensive Heterocyclic Chemistry II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, Oxford, **1996**, pp. 39–257; d) H. Döpp, D. Döpp, U. Langer, B. Gerding, *Houben-Weyl*, *Vol. E6b*, Thieme, Stuttgart, **1994**, pp. 546–1336.

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