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Mechanistic Studies into Amine-Mediated Electrophilic Arene Borylation and Its Application in MIDA Boronate Synthesis

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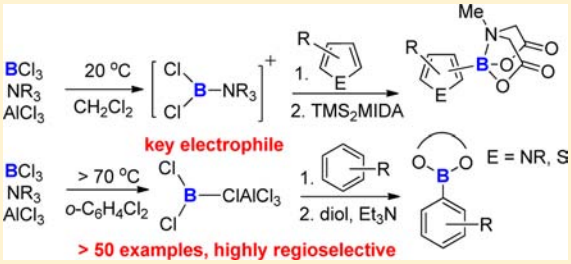
Supporting Information

ABSTRACT: Direct electrophilic borylation using Y_2BCl (Y_2 = Cl_2 or *o*-catecholato) with equimolar $AlCl_3$ and a tertiary amine has been applied to a wide range of arenes and heteroarenes. *In situ* functionalization of the $ArBCl_2$ products is possible with TMS_2MIDA, to afford bench-stable and easily isolable MIDA-boronates in moderate to good yields. According to a combined experimental and computational study, the borylation of activated arenes at 20 °C proceeds through an S_EAr mechanism with borenium cations, $[Y_2B(amine)]^+$, the key electrophiles. For catecholato-borocations, two amine dependent reaction pathways were identified: (i) With $[CatB(NEt_3)]^+$, an additional base is necessary to accomplish rapid borylation by deprotonation of the borylated arenium cation (σ complex), which otherwise would rather decompose to the starting materials than liberate the free amine to effect deprotonation. Apart from amines, the additional base may also be the arene itself when it is sufficiently basic (e.g., *N*-Me-indole). (ii) When the amine component of the borocation is less nucleophilic (e.g., 2,6-lutidine), no additional base is required due to more facile amine dissociation from the boron center in the borylated arenium cation intermediate. Borenium cations do not borylate poorly activated arenes (e.g., toluene) even at high temperatures; instead, the key electrophile in this case involves the product from interaction of $AlCl_3$ with Y_2BCl. When an extremely bulky amine is used, borylation again does not proceed via a borenium cation; instead, a number of mechanisms are feasible including via a boron electrophile generated by coordination of $AlCl_3$ to Y_2BCl, or by initial (heteroarene)$AlCl_3$ adduct formation followed by deprotonation and transmetalation.



INTRODUCTION

Aryl and heteroaryl boronates ($ArB(OR)_2$) are ubiquitous synthetic building blocks. This is due to their versatility (especially in Suzuki-Miyaura cross-coupling), low toxicity, and enhanced stability relative to hard organometallic carbon nucleophiles.[1,2] Numerous effective routes to aryl boronates exist; however, these generally require aryl halide or pseudohalide intermediates.[2,3] Direct borylation, the conversion of Aryl-H to Aryl-$B(OR)_2$, represents a more efficient approach, and considerable progress has been made in this area using iridium catalysts.[4−8] The amine-mediated intermolecular boron analogue of Friedel−Crafts chemistry represents a new approach for the direct borylation of arenes and heteroarenes.[9−11] The excellent regioselectivity observed in electrophilic borylation is controlled by arene electronic effects in synergy with steric effects and thus is complementary to directed lithiation (*ortho*-directed or C−H acidity controlled)[12−14] and iridium catalysis (sterically controlled).[4−8] Electrophilic borylation, particularly with BCl_3-derived electrophiles, is already established as a useful addition to the synthetic toolbox for $ArB(OR)_2$ production. However, questions concerning substrate scope, the reaction limitations, and the exact mechanistic sequence leading to formation of $ArB(OR)_2$ still remain to be addressed.

Recent developments in amine-mediated electrophilic borylation are built upon the pioneering work of Lappert and Muetterties. They reported the borylation of alkyl-arenes using highly electrophilic mixtures of BCl_3 and $AlCl_3$ with activated Al to sequester the protic byproduct.[15−18] The mechanism and the active electrophile were not identified in these systems. Muetterties proposed that explicit solvation was important, implicating $[Cl_2B(solvent)][AlCl_4]$ (solvent = arene),[16] whereas Olah favored a $Cl_2B(\mu\text{-}Cl)AlCl_3$ electrophile.[19] Irrespectively, the aggressive conditions used in these reports limited applications due to incompatibility with many functional groups and heteroarenes.[16,20−22] A key advantage of amine-mediated electrophilic borylation is that a strong boron Lewis acid releases a Brønsted base during the borylation process. This Brønsted base ultimately captures the proton from electrophilic aromatic substitution (S_EAr), thus preventing protodeboronation.[13,23] In preliminary communications, we demonstrated that

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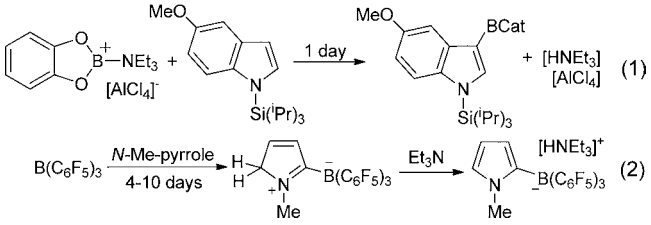
amine-mediated electrophilic borylation produced high yields of $ArB(OR)_2$ even for an acid-sensitive heteroarene containing a methoxy group (eq 1).[9]



Overall, electrophilic borylation represents the heterolytic cleavage of an arene C−H bond by a boron Lewis acid and an amine base. This is reminiscent of the activation of alkynes by frustrated Lewis pairs (FLPs)[24] and the stepwise reaction of *N*-Me-pyrrole with $B(C_6F_5)_3/NEt_3$. The latter reaction proceeds via a zwitterionic borylated arenium cation which is deprotonated by subsequent addition of Et_3N to generate the heteroarylborate (eq 2).[25,26] A related mechanism is feasible for intermolecular electrophilic borylation, but to date, the key electrophiles are not definitively known. Three- or four-coordinate (at boron) transition states and C−H insertion or S_EAr mechanisms are feasible, with both mechanisms finding precedence in intramolecular electrophilic borylation.[27−29]

Identification of the active electrophile in direct borylation is complicated by multiple equilibria (Figure 1). $[Y_2B(amine)][AlCl_4]$ (Y_2 = Cl_2 or *o*-catecholato) undergoes reversible halide transfer from aluminum to boron resulting in the concomitant presence of Lewis acidic "$AlCl_3$" species and $Y_2B(amine)Cl$.[30] The latter can react further, reversibly forming free amine and Y_2BCl. A range of electrophilic species can therefore be present in solution, each one potentially viable for the borylation of arenes (Figure 2, type I to V). Importantly, the key electrophile is not limited to boron. Borylation may proceed by initial interaction of "$AlCl_3$" with an activated arene.[31,32] Subsequent deprotonation to $[ArylAlCl_3]^-$ and transmetalation with Y_2BCl would then yield $ArBY_2$ (Figure 2, bottom).

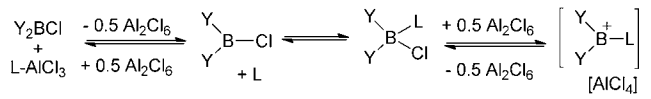


Figure 1. Key equilibria present in formation of $[Y_2BL][AlCl_4]$.

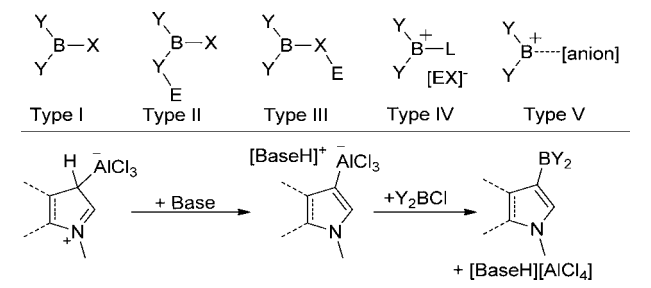


Figure 2. Top: possible boron electrophiles for direct borylation, X = Cl, Br, or H; E = Lewis acid; [anion] = weakly coordinating anion; L = neutral ligand. Bottom: transmetalation mechanism.

Herein is presented an extensive substrate exploration for amine-mediated electrophilic borylation. This is coupled with the development of a simple route to install *N*-methyliminodiacetic acid (MIDA) as a boron protecting group post borylation. The factors controlling isomerization and deboronation have also been elucidated, enabling the production of a single regioisomer in most cases. Combined experimental and computational studies indicate that a range of borylation pathways are feasible depending on conditions and reagents. The most viable borylation method (from cost and scope perspectives), using Y_2BCl, $AlCl_3$, and an inexpensive amine at 20 °C, proceeds by S_EAr with a borenium cation (a three-coordinate boron cation)[33,34] as the key electrophile. However, for less activated arenes (e.g., toluene) amine-mediated borylation requires temperatures >70 °C and borenium cations are not the active electrophile.

RESULTS AND DISCUSSION

B-halo-1,3,2-benzodioxaborole (CatBX) is insufficiently electrophilic for the borylation of even strongly activated arenes (e.g., indoles). While BCl_3 and *N*-Me-indole slowly produced a mixture of borylated and protonated indole (4 days, Figure 3),

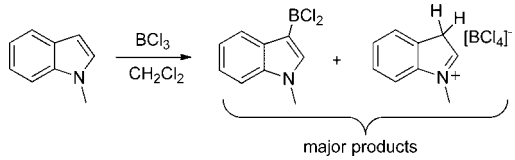


Figure 3. Reaction of *N*-Me-indole with BCl_3.

BCl_3 does not borylate 2-Me-thiophene (with or without a base). Enhancement of electrophilicity at boron relative to Y_2BCl is therefore essential. This can be achieved by forming either a borenium cation (type IV) or a neutral electrophile (type II/III, Figure 2), with each a feasible strong boron electrophile.[29,34,35]

Substrate Scope. Borenium cations, or electrophiles derived from them, are more reactive than the Y_2BCl precursors enabling the borylation of a wide range of activated arenes. $BCl_3/AlCl_3$/amine derived electrophiles are more reactive than catechol analogues, e.g., $[CatB(NEt_3)][AlCl_4]$, **1**$[AlCl_4]$ (or the electrophile derived from it). **1**$[AlCl_4]$ borylates only the most highly activated arenes such as indoles, pyrroles, anilines, and azulene (Table 1). Borylation with **1**$[AlCl_4]$ proceeds in high yield and with excellent regioselectivity from electronic control (azulene is borylated exclusively at C1, entry 13; iridium catalysis produces both the C1 and C2 isomers).[36] Borylation using $BCl_3/AlCl_3$/amine derived electrophiles not only has a wider arene scope than with $[\mathbf{1}]^+$, but produces $ArylBCl_2$, a more versatile intermediate than ArylBCat (produced using $[\mathbf{1}]^+$). MIDA protected boronate esters are readily synthesized *in situ* from $ArylBCl_2$ post borylation. Optimum conditions for MIDA esterification of $ArylBCl_2$ use the bis-trimethylsilyl ester of MIDA (TMS_2MIDA). While it is necessary to use ≥2 equiv of pinacol and Et_3N in the esterification to ArylBPin (due to a competitive reaction with $[AlCl_4]^-$ producing $[Et_3NH]_2[\{(PinH)AlCl_2\}_2Cl_2]$),[37] only 1 equiv of TMS_2MIDA is required. This new route to aryl MIDA-boronates does not require the synthesis and isolation of heteroaryl boronic acid intermediates. This is particularly important for heterocycles, as heterocyclic boronic acids are often sensitive to protodeboronation. Furthermore, our combined electrophilic borylation/MIDA protection protocol for heteroarenes proceeds at temperatures ≥0 °C and <30 °C. This is in contrast to current methods which require cryogenics for boronic acid synthesis

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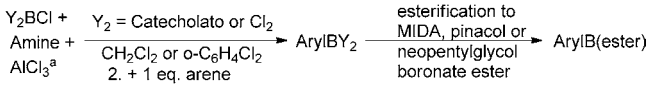
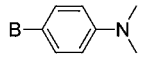
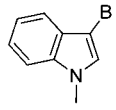
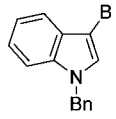
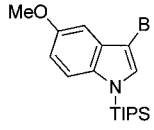
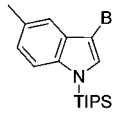
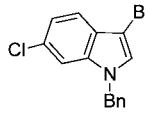
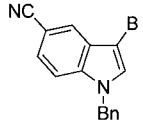
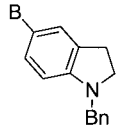
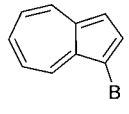
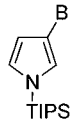
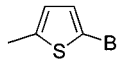
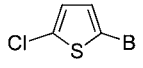
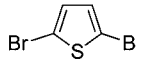
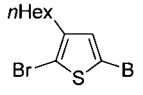
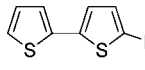
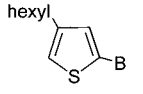
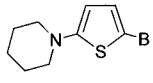
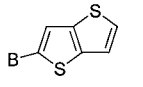
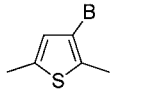
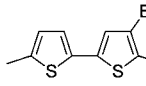
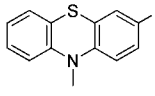
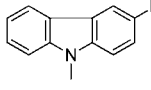
Table 1. Substrate Scope for Electrophilic Arene Borylation



Entry	Product	Ester[b]	Y / amine	Time[c] / Temp[d] (h, °C)[c]	Yield (%)[e]
1		Pin	Cat/Et_3N	1 / 20	85
2		Pin	Cat/Et_3N	4 / 20	93
3		Pin	Cl/2,6-lut	14 / 20	83
4		MIDA	Cl/2,6-lut	14 / 20	64
5		MIDA	Cl/2,6-lut	14 /20	67
6		Pin	Cat/Et_3N	30 / 20	88
7		Pin	Cl/Me_2NTol	3 / 20	77
8		Pin	Cat/Et_3N	24 / 20	86
9		Pin	Cat/Et_3N	18 / 20	67
10		-	Cat/Me_2NTol	1 /20	>95[f]
11		MIDA	Cl/2,6-lut	24 / 20	47
12		Pin	Cat/Et_3N	1 / 20	96
13		Pin	Cat/Et_3N	2 / 20	79
14		Pin	Cat/Et_3N	72 / 20	89
15		Pin	Cat/Me_2NTol	1 / 20	95
16		-	Cat/PCy_3	15 / 20	>95[f]
17		MIDA	Cl/2,6-lut	14 / 20	53
18		MIDA	Cl/Me_2NPh	6 / 20	48
19		MIDA	Cl/Me_2NTol	3 / 20	85
20		MIDA	Cl/Me_2NPh	1 / 20	76
21		Neop	Cl/Me_2NTol	3 /20	84
22		MIDA	Cl/Me_2NPh	48/ 20	66
23		MIDA	Cl/Me_2NPh	48/20	68
24		MIDA	Cl/Me_2NPh	24 / 20	36
25		-	Cat/Me_2NTol	3 / 20	>95[f]
26		Pin	Cl/2,6-lut	18/20	86
27		MIDA	Cl/Me_2NPh	1 / 20	71
28		MIDA	Cl/Me_2NTol	7 / 20	68[g]
29		Pin	Cat/Et_3N	1 / 20	62
30		Pin	Cl/Me_2NTol	1 / 20	81
31		Pin	Cl/2,6-lut	18/20	0
32		MIDA	Cl/Me_2NPh	1 / 20	68
33		MIDA	Cl/Me_2NPh	1 /20	39
34		MIDA	Cl/Me_2NPh	14 /20	39
35		Pin	Cl/Me_2NTol	14/20	76
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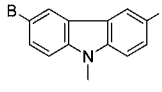
37		Pin	Cl/Me_2NTol	16/20	49

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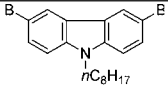
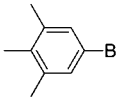
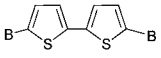
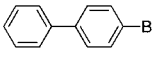
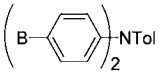
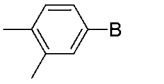
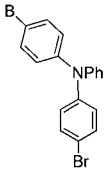
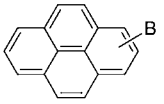
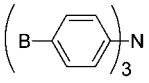
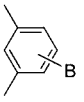
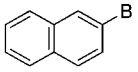
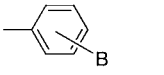
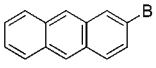
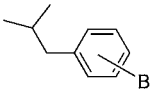
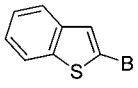
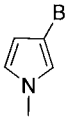
Table 1. continued

Entry	Product	Ester[b]	Y / amine	Time[c] / Temp[d] (h, °C)	Yield (%)[e]	Entry	Product	Ester[b]	Y / amine	Time[c] / Temp[d] (h, °C)	Yield (%)[e]
38		MIDA	Cl/Me$_2$NPh	16/20	49	48		Pin	Cl/Me$_2$NTol	24/120	67
								MIDA	Cl/Me$_2$NTol	24/120	49
39		Pin	Cl/Me$_2$NTol	24/20	83	49		Pin	Cl/Me$_2$NTol	36/120	54
								MIDA	Cl/Me$_2$NTol	28/120	54
40		Pin	Cl/Me$_2$NTol	18/20	81	50		Pin	Cl/Me$_2$NTol	36/120	67
41		Pin	Cl/Me$_2$NTol	24/20	86	51		Pin	Cl/Me$_2$NTol	48/80	52[h]
						52		Pin	Cl/Me$_2$NTol	75/120	55[i]
						53		MIDA	Cl/Me$_2$NPh	288/20	13[j]
42		Pin	Cl/Me$_2$NTol	22/120	74	54		Pin	Cl/Me$_2$NTol	64/120	55[k]
43		Pin	Cl/Me$_2$NTol	24/80	68	55		-	Cl/Me$_2$NTol	4/110	58[l]
44		MIDA	Cl/Me$_2$NTol	24/120	51	56		-	Cl/Me$_2$NTol	21/110	75[m]
						57		-	Cl/Me$_2$NTol	16 /20	13[n]
45		Pin	Cl/Me$_2$NTol	14/120	50	58		-	Cl/Me$_2$NTol	18/150	85[o]
46		MIDA	Cl/Me$_2$NTol	24/120	50	59		Pin	Cl/Me$_2$NTol	90/150	63[p]
47		Pin	Cl/Me$_2$NPh	40/80	52	60		MIDA	Cl/Me$_2$NTol	3/20	62
		MIDA	Cl/Me$_2$NPh	24/100	55	61		Pin	Cl/Me$_2$NTol	3/20	75

[a,b]For exact borylation and workup procedures, see Supporting Information. [c]Time before esterification. [d]Reactions at 20 °C were performed in CH_2Cl_2; those at elevated temperatures in o-$C_6H_4Cl_2$. [e]Isolated yields unless otherwise stated. [f]In situ yields by ^{1}H NMR spectroscopy. [g]Isolated as a 93:7 mix of the 2,4:2,3-regioisomers. [h,i]C1:C2 ratios are 1.5:1 and 1:1, respectively. [j]Only the C2 isomer observed. [k]2:1 mixture of the 2,4:3,5 borylated isomers. [l−n]All in situ yields by ^{1}H NMR spectroscopy, *p*:*m* ratios are 5.1:1, 5.4:1, 2.1:1, respectively. [o]In situ yield by ^{1}H NMR spectroscopy, *p*:*m* ratio 5.2:1. [p]Prior to esterification, *p*:*m* ratio = 4.0:1; after esterification and isolation, *p*:*m* ratio = 4.2:1.

and temperatures >110 °C for efficient MIDA installation.[23,38,39] Thus, this new approach to MIDA boronates has advantages over established routes to these increasingly popular cross coupling precursors.

Borylation scope with $Y_2BCl/AlCl_3$/amine derived electrophiles was found to be highly dependent on the basicity of the amine. The greatest arene substrate scope is observed when using $Me_2NPh \approx Me_2NTol$ > 2,6-lutidine > Et_3N. It is noteworthy that no borylation of 3-X-*N*,*N*-dimethylaniline (X = H, Br, or Cl) was observed when these anilines were combined with $BCl_3/AlCl_3$ at 20 °C. In contrast, mixtures of CatBCl, 3-X-*N*,*N*-dimethylaniline, and $AlCl_3$ rapidly produced [4-(CatB)-3-X-$C_6H_3(NMe_2H)$][$AlCl_4$] at 20 °C (Figure 5).[37] The disparity is attributed to different equilibrium positions (Figure 1) which with $CatBCl/AlCl_3$ allow free (thus not deactivated by Lewis acid coordination) 3-X-*N*,*N*-dimethylaniline and the active boron electrophile to be present concomitantly. At temperatures ≥70 °C, borylation of 3-X-*N*,*N*-dimethylaniline is observed with $BCl_3/AlCl_3$ indicating free aniline is present at raised temperatures. As weakly activated arene substrates required high temperatures (≥70 °C) for borylation, the widest arene scope is achieved using BCl_3, Me_2NTol, and $AlCl_3$.

Figure 4. Electrophilic borylation with protection steps.

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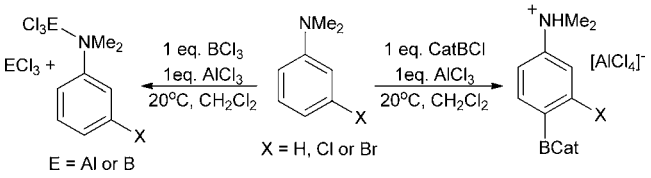
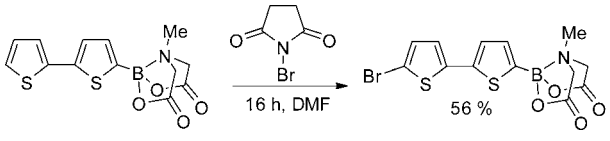


Figure 5. Reactivity of BCl_3 and CatBCl electrophiles with $AlCl_3$ and 3-X-*N*,*N*-dimethylaniline (X = H, Cl, or Br).

Heteroarene borylation using BCl_3, amine, and $AlCl_3$ proceeds in moderate to high yield to provide the regioisomers expected from S_EAr.[40] For *N*-R-indoles (R = Me, Benzyl, TIPS), borylation occurs only at C3 (entries 3−5, 7, and 11) complementary to iridium catalyzed[8] and deprotonation approaches (both C2 selective).[13] For thiophenes, borylation occurs exclusively at the α position (entries 18−31). Post borylation MIDA and pinacol installation is facile for both thiophenes and indoles. Pinacol can be replaced in the esterification step with the less expensive diol neopentylglycol (neop, entry 21), with no loss in isolated yield. The good regioselectivity afforded by synergic steric and electronic control is demonstrated by 3-hexyl-thiophene undergoing borylation predominantly at C5 (entry 28 ca. 93% by ^{1}H NMR spectroscopy with 7% the C2 borylated product,). When both thiophene α positions are substituted, borylation proceeds at the β position (entries 32−33). Thiophenes and indoles containing electron withdrawing and donating groups, e.g., alkyl, halide, dialkylamino, methoxy, and cyano, are all amenable to electrophilic borylation. The compatibility of the latter two functional groups to a strong boron Lewis acid is notable. This is presumably due to a more rapid reaction of the boron Lewis acid at the nucleophilic C3 position of indole. Indeed, attempts to borylate the less activated arene anisole (Mayr nucleophilicity of 1.18)[41] led instead to ether cleavage. NO_2, CF_3, and C═O containing groups were also not compatible with electrophilic borylation, presumably due to the high fluoro- and oxophilicity of the strong B/Al-based electrophiles present.

While borylation of 1,2-disubstituted arenes under iridium catalysis produces regioisomers,[8] the sensitivity to electronic effects ensures excellent regioselectivity in electrophilic borylation. *N*-Methyl-phenothiazine and *N*-alkyl-carbazole both produce a single regioisomer, with borylation always proceeding *para* to NR_2 (entries 34−36). Electrophilic di- (entries 37−39) and triborylation (entry 42) of di- and tri-arylamines is also facile. The additional borylations proceed despite the installation of the mesomerically deactivating -BY_2 group (electronically comparable to cyano).[42] Protection of boron is limited to pinacol in the absence of long alkyl chain substituents as the di-MIDA functionalized aryl boronates are extremely poorly soluble. Direct, regioselective diborylation and the monoborylation of halo-arenes (entries 22−24 and 41) is of particular importance as it represents a simple one-step route to polymerization precursors used in organic-electronics. Bifunctional heteroarenes can also be accessed through subsequent bromination of (thienyl)B(MIDA) with NBS (e.g., eq 3). The



(3)

sequential electrophilic borylation/MIDA protection/bromination process is amenable to larger-scale synthesis. When applied to 3-hexyl thiophene on a 25 mmol scale, this affords 6.6 g of the bifunctional heteroarene in an overall 69% yield.

At raised temperatures, less activated arenes can also be monoborylated using stoichiometric BCl_3, Me_2NTol, and $AlCl_3$ provided that the arene is more nucleophilic than benzene. The borylation of benzene itself was extremely slow even at 130 °C, establishing a lower nucleophilicity limit below which borylation does not proceed. This is exemplified by the complete absence of borylation of *o*-dichlorobenzene even after 7 days at 130 °C. A range of weakly activated arenes undergo electrophilic borylation with the sterically least hindered isomer generally the only product observed (entries 43−50). For example, naphthalene and anthracene (entries 43−46) are monoborylated, with boron exclusively at the C2 position in the products despite C1 and C9, respectively, being the kinetically preferred sites.[43] Diborylation is not observed due to the reduction in the nucleophilicity of these weakly activated arenes post installation of -BCl_2.[41] The selective monoborylation of these polyaromatic hydrocarbons (PAHs) is in contrast to other direct borylation routes which provide a mixture of mono- and bis-borylated products.[44,45] Benzothiophene also afforded the thermodynamic borylated product exclusively (entry 47) with no C3 regioisomer observed (C2 and C3 have similar reactivity in S_EAr, but C2 is the thermodynamic product).[46,47] In contrast, pyrene was borylated (entries 51−53) to give a mixture of C1 and C2 regioisomers at 80 and 120 °C. *Meta*-xylene (entry 54) and toluene (entry 55−57) also reacted to give mixtures of kinetic and thermodynamic regioisomers (boron at C4 and C5 for *m*-xylene and C3 and C4 for toluene). The relative regioisomer ratios did not change significantly during borylation (relative ratio range of 5.3:1 to 6:1 *para* to *meta* for toluene during borylation at 110 °C over 7 days).

Factors Controlling Isomerization during Borylation. The regioisomer ratios of borylated products formed using the $BCl_3/AlCl_3$/aluminum system were previously studied and found to be complicated by the formation of the Brønsted superacid, HCl-$AlCl_3$.[16,17] This superacid induced extensive intramolecular isomerization and intermolecular *trans*-alkylation (e.g., borylated toluene and mesitylenes produced during xylene borylation).[48] In contrast, amine mediated electrophilic borylation occurs with no *trans* alkylation (by NMR and GC-MS) and relatively less positional isomerization (for toluene and *m*-xylene). This suggested more effective sequestering of the Brønsted acid byproduct, preventing HCl-$AlCl_3$ induced *trans*-alkylation. Isobutyl benzene is a useful probe for superacids, as in the presence of HCl-$AlCl_3$, it undergoes rapid isomerization to *sec*-butyl benzene.[49] Borylation of isobutyl benzene with $BCl_3/Me_2NTol/AlCl_3$ produced only *meta* and *para* regioisomers of borylated isobutyl benzene with no *sec*-butyl products observed (entries 58−59, by NMR spectroscopy and GC-MS). The absence of any isobutyl to *sec*-butyl isomerization during borylation precludes formation of HCl-$AlCl_3$. It is also consistent with a mechanism where the amine is deprotonating the borylated arenium intermediate. Deboronation of (C_6alkyl$_x$H$_{5-x}$)BCl_2 is known to only occur with HCl-$AlCl_3$.[17] Therefore, the regioisomer ratios in amine mediated electrophilic borylation of alkyl arenes/PAHs are controlled by the rate of intramolecular migration relative to the rate of deprotonation of the borylated arenium complex (Figure 6). The regioisomer ratio was strongly temperature

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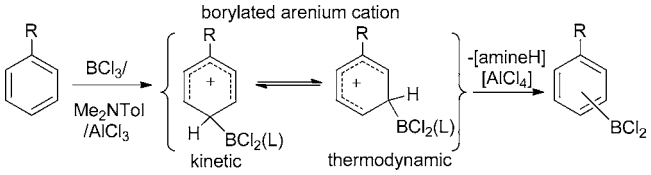


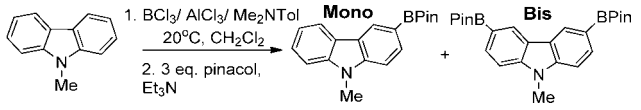
Figure 6. Isomerization during electrophilic arene borylation (L = amine or $AlCl_4$ or nothing).

dependent. At 20 °C, the borylation of pyrene and toluene with $BCl_3/AlCl_3/Me_2NTol$ was significantly slower but produced considerably more of the thermodynamic borylated products (C2- and *meta*, respectively, entries 51−53, 55−57).[50] Therefore, at lower temperatures the deprotonation of the σ complex is slower relative to intramolecular migration enabling a greater degree of positional isomerization. This effect will be exacerbated by the extremely low concentration of free amine at 20 °C (as indicated by the absence of borylation of Me_2NPh by $BCl_3/AlCl_3$ with effectively all amine coordinated to Lewis acids at 20 °C).

In contrast to PAHs and alkyl-arenes, where isomerization to the thermodynamic favored arenium cation occurs at 20 °C, the borylation of *N*-Me-pyrrole at 20 °C using equimolar $BCl_3/Me_2NTol/AlCl_3$ was highly selective for the kinetic C3 position (ca. 95% by in situ ^{1}H NMR spectroscopy). The isolation of the C3 borylated regioisomer in good yield (entries 60 and 61) is a unique example of pyrrole C3 selective direct borylation that does not require deactivation of C2 by a bulky protecting group at nitrogen.[51] While S_EAr of *N*-Me-pyrrole generally gives products from C2 functionalization, the C3 position is the kinetically favored site with hard electrophiles.[52] When isomerization is occurring rapidly in the pyrrolenium cation the thermodynamic C2 product dominates. When there is no isomerization and the electrophile is "hard", as in the silylation of *N*-Me-pyrrole with $TMSOTf/NEt_3$, the C3 product dominates (≥90%). The C2 isomer is only present as a minor product (≤10%) from direct silylation at C2.[52] With 3-(BCl_2)-*N*-Me-pyrrole the observed major product, the electrophile derived from BCl_3/Me_2NTol and $AlCl_3$ also reacts at C3 and does not undergo intramolecular isomerization. The disparity to the extensive isomerization observed with alkylarene borylation at 20 °C we attribute to more rapid deprotonation of the borylated arenium complex of *N*-Me-pyrrole. Rapid deprotonation may be facilitated by another equivalent of *N*-Me-pyrrole acting as the Brønsted base. In contrast, toluene is an extremely poor base and deprotonation of the borylated toluenium cation will require free Me_2NTol, which at 20 °C is present at extremely low concentration.

During a number of borylations, the product distribution (mono vs bis borylation, relative regioisomer ratios) was found to be sensitive to reagent stoichiometry. During the attempted monoborylation of *N*-Me-carbazole when even a slight excess of $AlCl_3$ was used the 3,6-diborylated carbazole was observed as a minor product (Table 2), which increased over time concomitantly with *N*-Me-carbazole. This indicated that the initial monoborylated product was undergoing deboronation. Accurate stoichiometric control is challenging to realize with commercial BCl_3 solutions due to variations in molarity. Exact stoichiometric control can be achieved by preforming (amine)-BCl_3, which precipitates analytically pure on addition of 1 equivalent of amine to a heptane solution of BCl_3. An alternative to preforming (amine)BCl_3 is using a slight excess

Table 2. Stoichiometry Dependent Product Distribution



entry	BCl_3 (equiv)	$AlCl_3$ (equiv)	base (equiv)	time (h)	mono[a] (%)	bis[a] (%)
1	1	1.1	1.05	1	60	11
2	1	1.1	1.3	14	76	<1

[a]Isolated yields post chromatography.

of amine. For example, the selective monoborylation of *N*-Me-carbazole proceeds with either exact equimolar stoichiometry or an excess of amine (Table 2, entry 2).

N-Me-pyrrole was chosen to investigate the factors affecting regioisomer distribution. Borylation with **1**[$AlCl_4$] produced mixtures of C2/C3 monoborylation and the 2,4-diborylated product in ratios that were sensitive to the stoichiometry of $CatBCl:AlCl_3:NEt_3$. The addition of 1.3 equiv of $AlCl_3$ and 1 equiv of 2,6-di-*tert*-butylpyridine (termed dTBP and used to sequester adventitious "H^+") to a mixture of 2- and 3-catecholboryl-*N*-methylpyrrole, **2** and **3**, respectively (ratio 76:24) did not change the relative ratio of **2**:**3**. However, slow formation of 2,4-diborylated *N*-Me-pyrrole, **4**, was observed. The formation of **4** during deboronation proceeds as the combination of $CatBCl/AlCl_3$/dTBP is itself a highly effective borylating agent (discussed in more detail in a later section) able to borylate **2** (or **3**). In contrast, in the absence of dTBP the addition of $AlCl_3$ (0.1 equiv) to the mixture of **2** and **3** (ratio 76:24) resulted in rapid isomerization with **3** dominating after 1 h. For borylated five-membered heterocycles, protodeboronation occurs with the C2 isomer in preference to the C3 regiosiomer.[53,54] Compound **2** is thus more susceptible to protodeboronation than **3**, consistent with the relative increase in **3** over time. This indicates that a strong Brønsted acid (at adventitious levels from partially hydrolyzed $AlCl_3$) can induce C2 to C3 isomerization. Therefore, with the more nucleophilic heteroarenes there are two separate deboronation processes: (i) Brønsted acid catalyzed (via an arenium cation intermediate, Figure 7 left); (ii) Lewis acid initiated deboronation (Figure 7, right). The latter does not occur with $(C_6alkyl_xH_{5-x})BCl_2$ where deboronation only occurs with $HCl-AlCl_3$.[48]

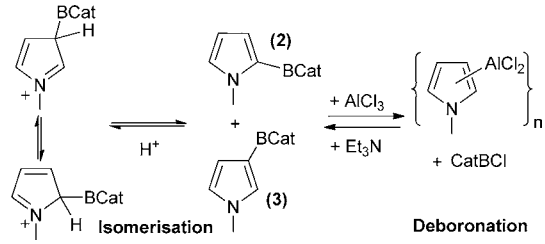


Figure 7. Deboronation/isomerization of *N*-Me-(CatB)-pyrrole.

Further evidence for deboronation of heteroaryl boronate esters by $AlCl_3$ came from the addition of $AlCl_3$ to pure **3**. This led to the rapid (<10 min) formation of CatBCl as the only boron containing product along with a broad ^{27}Al NMR resonance at 103 ppm, attributed to oligomers of $\{(heteroaryl)-AlCl_2\}_n$ (Figure 7, right).[55] Interestingly, addition of Et_3N to this mixture led to the regeneration of **3** with $Et_3N-AlCl_3$ produced as the major byproduct. Presumably, coordination of

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Et_3N to Al in $\{(heteroaryl)AlCl_2\}_n$ generates a better aluminum leaving group post halide transfer from CatBCl to Al. Importantly, there was no formation of **2** during this process precluding interconversion of **2** and **3** mediated by $AlCl_3$. Deboronation was also observed on addition of $AlCl_3$ to 3-(CatB)-*N*-Me-indole producing CatBCl and a broad ^{27}Al resonance at 104 ppm. No intermediates were observed during this rapid deboronation with $AlCl_3$. Deboronation of 3-(CatB)-*N*-Me-indole was slower with $GaCl_3$. The ^1H NMR spectrum showing that all the proton resonances of 3-catecholboryl-*N*-methylindole were shifted downfield. The indole C2 proton, in particular, was shifted downfield by 0.94 ppm, consistent with the coordination of $GaCl_3$ to C3 of 3-catecholboryl-*N*-methylindole.

While direct borylation is highly effective for the generation of $ArB(OR)_2$, are borenium cations the active electrophile and what is the exact mechanistic sequence? There is evidence that is consistent with $[Y_2B(amine)]^+$ cations being active electrophiles. For example, the arene substrate scope is dependent on amine nucleophilicity (e.g., entries 30−31) which could be attributed to different borenium cation electrophilicities. However, the equilibria present using $[AlCl_4]^-$ allow more than one electrophile/mechanism to be feasible. Furthermore, it is noteworthy that after heating equimolar $BCl_3/AlCl_3/Me_2NTol$ in o-$C_6H_4Cl_2$ to 100 °C for 10 min (common borylation conditions) the ^{11}B NMR spectrum showed no borenium cation. The only boron containing products were BCl_3 and $(amine)BCl_3$. To reduce mechanistic complexity, the anion was changed from $[AlCl_4]^-$ to more robust weakly coordinating anions to preclude halide transfer equilibria. Electrophiles derived from Lewis acid coordination to Y_2BX (types II and III in Figure 2) and a transmetalation mechanism involving initial "$AlCl_3$" attack on an arene are thus excluded. Catechol borenium cations partnered with weakly coordinating anions were predominantly used in this section due to their reduced sensitivity relative to dichloro analogues. $[Cl_2B(amine)]^+$ partnered with weakly coordinating anions are accessible but only *in situ*. These salts proved extremely challenging to isolate in analytically pure form due to their extreme electro- and oxophilicity.

Using Robust Weakly Coordinating Anions. CatB(Me_2NPh)(OTf), **5**, was readily synthesized from TMSOTf and equimolar CatBCl/Me_2NPh. A four-coordinate neutral formulation was indicated by the ^{11}B NMR chemical shift of 9.7 ppm (in CD_2Cl_2) and further confirmed by X-ray diffraction studies (Figure 8, left). Compound **5** has structural metrics comparable to CatBCl(NEt_3).[56] The short B−OTf bond length (1.481(10) Å) is only marginally longer than the catechol B−O distances consistent with a strong B−OTf interaction. **5** was stable at 20 °C with no Me_2NPh borylation observed with or without addition of excess Me_2NPh (in CH_2Cl_2 or C_6D_6). The absence of Me_2NPh borylation with **5** is in contrast to the reactivity of CatBCl/$AlCl_3$/Me_2NPh which undergoes rapid borylation at 25 °C. The absence of borylation suggests no dissociation of amine or triflate from **5** at 20 °C. This is also consistent with the lack of reaction between **5** and Et_3N at 20 °C. Borylation of Me_2NPh was observed on heating **5** to 90 °C in the presence of excess Me_2NPh, indicating that an electrophilic three-coordinate boron species is accessible at raised temperature. However, with the observed strong coordination of triflate to boron this does not discriminate between $[CatB(Me_2NPh)]^+$ or CatB(OTf) being the active borylating agent. A related neutral electrophile, 9-BBNNTf$_2$, does borylate activated arenes in the presence of a non-coordinating amine to scavenge the protic byproduct.[11]

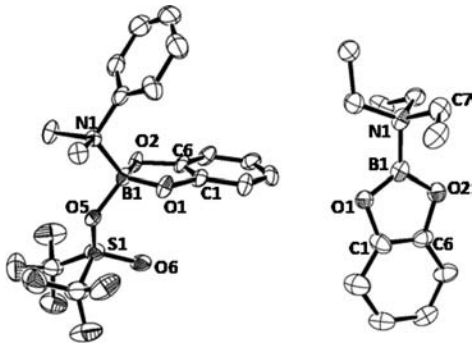

Figure 8. ORTEP representations of left, **5**, and right, the cationic portion of **1**[**CbBr$_6$**]. Hydrogens are omitted for clarity and thermal ellipsoids are at 50% probability. Selected bond lengths (Å) and angles (°) for **5**: B1−O5 = 1.481(10), B1−N1 = 1.618(9), B1−O1 = 1.428(9), B1−O2 = 1.435(9), O1−B1−O2 = 108.4(6). For **1**[**CbBr$_6$**]: B1−N1 = 1.515(16), B1−O1 = 1.339 (15) B1−O2 = 1.377(15), O1−B1−O2 = 113.9(3).

The synthesis of borenium cations using the more weakly coordinating anions [*closo*-1-H-$CB_{11}H_5Br_6$]$^-$ and [B(3,5-$C_6H_3Cl_2)_4$]$^-$ (termed $CbBr_6$ and BAr_{Cl}, respectively) was facile. Combination of Ag[$CbBr_6$][57] and CatBCl(Et_3N) formed **1**[**CbBr$_6$**]. **1**[**CbBr$_6$**] displayed an ^{11}B NMR resonance (in CD_2Cl_2) for the cation comparable to **1**[**AlCl$_4$**]. The formulation as **1**[**CbBr$_6$**] was structurally confirmed (Figure 8, right) with the angles at B1 summing to 360° and the shortest (Cat)B···Br contact being >5 Å. $[BAr_{Cl}]^-$ congeners were accessed by stoichiometric combination of CatBCl, Na[BAr_{Cl}],[58] and amine. **1**[**CbBr$_6$**] and **1**[**BAr$_{Cl}$**] cannot form type II or III electrophiles (Figure 2), while anion coordination (type V) is highly unlikely in the presence of superior nucleophiles (such as amines) due to the extremely weakly coordinating nature of these anions.[59] Borenium systems containing either anions react analogously in borylations supporting their robust and weakly coordinating nature.

The addition of 1 equivalent of Me_2NPh, or *N*-Me-indole, to **1**[**CbBr$_6$**] led to complete arene borylation in 2 and 5 h, respectively (in CD_2Cl_2), closely comparable to the reactivity of **1**[**AlCl$_4$**]. The borenium cation $[\mathbf{1}]^+$ is therefore an active borylating species, as no other electrophiles can be feasibly formed from **1**[**CbBr$_6$**]. It is noteworthy that no additional base was required for the borylation of Me_2NPh and *N*-Me-indole with recrystallized (thus strictly stoichiometric) **1**[**CbBr$_6$**]. This indicates that either these arenes act as Brønsted bases (Figure 9, left pathway) or that Et_3N is released sufficiently early in the borylation process to act as the base in a concerted or stepwise process (Figure 9 center and right pathways). The involvement of the anion in the deprotonation step is precluded as the anion is an extremely weak base (H[$CbBr_6$] is a Brønsted superacid able to protonate benzene).[60] Precedence for *N*-Me-indole acting as a base during borylation was previously observed in the reaction of BCl_3 with *N*-Me-indole (Figure 3). As the product CatB(heteroaryl) does not bind Et_3N to any significant extent (by ^{11}B NMR spectroscopy), Et_3N will rapidly dissociate from arylBCat(amine). The released Et_3N will then rapidly deprotonate $[H(heteroarene)]^+$; thus, all mechanisms in Figure 9 are consistent with $[Et_3NH]^+$ being the only protonated species observed during borylation with **1**[**CbBr$_6$**].

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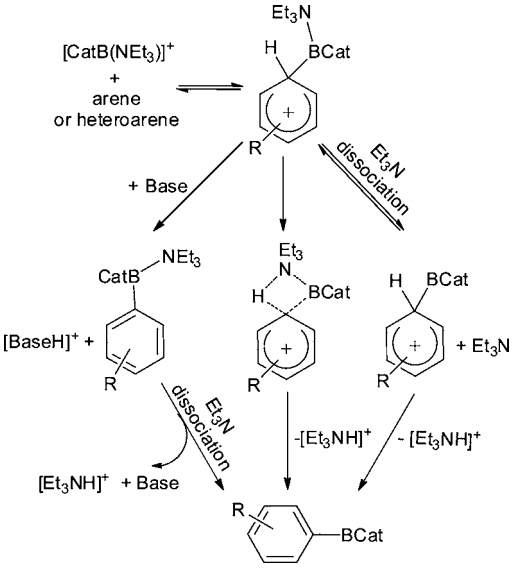

Figure 9. Borylation pathways using $\mathbf{1}[\mathbf{CbBr_6}]$ or $\mathbf{1}[\mathbf{BAr_{Cl}}]$ (base = an activated arene, e.g., Me_2NPh or *N*-Me-indole).

Surprisingly, $\mathbf{1}[\mathbf{CbBr_6}]$ (or $\mathbf{1}[\mathbf{BAr_{Cl}}]$) borylated *N*-TIPS-pyrrole only extremely slowly (<5% in 72 h by NMR spectroscopy). In contrast, the complete borylation of *N*-TIPS-pyrrole with $\mathbf{1}[\mathbf{AlCl_4}]$ took place in 72 h. The anion dependency must be an effect of the halide transfer equilibria (Figure 1) present when using $\mathbf{1}[\mathbf{AlCl_4}]$. Presumably, the equilibria result in another compound vital for borylation being present in solution at a low (unobservable by NMR spectroscopy) concentration. We surmised that this was either (i) free Et_3N to deprotonate the borylated arenium cation or (ii) another more reactive electrophile (e.g., of type II or III). To probe the effect of a free Lewis base on borylation, dTBP (dTBP = 2,6-di-*tert*-butyl-pyridine) and PPh_3 were added to $[\mathbf{1}]^+$ partnered with $[CbBr_6]$ or $[BAr_{Cl}]$. In all cases, there is no Lewis adduct formation; thus, these combinations represent borocation frustrated Lewis pairs (FLPs).[24] The FLP $\mathbf{1}$-$[\mathbf{CbBr_6}]$/dTBP did not accelerate the borylation of *N*-TIPS-pyrrole with minimal borylation observed (<5%, 24 h, Figure 10). In contrast, the FLP $\mathbf{1}[\mathbf{BAr_{Cl}}]/PPh_3$ resulted in the complete borylation of *N*-TIPS-pyrrole in <1 h. The presence of a free Brønsted base that has sufficient basicity and is below a certain steric threshold is therefore essential for the borylation of *N*-TIPS-pyrrole using $[\mathbf{1}]^+$. As Et_3N is a stronger base than PPh_3 and has a similar steric profile (cone angles 150° and

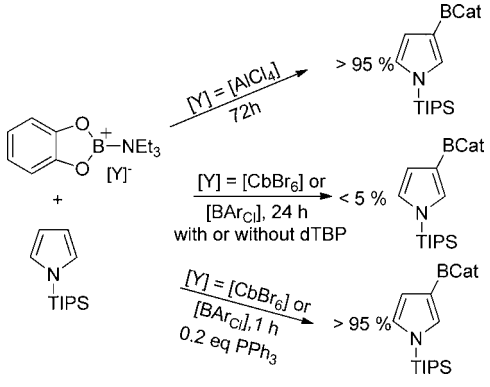

Figure 10. Borylation of *N*-TIPS pyrrole with $[\mathbf{1}]^+$ cations.

145°, respectively),[61] it precludes deprotonation proceeding by dissociation of Et_3N from the arenium cation and deprotonation via a concerted intramolecular proton transfer to Et_3N. Consequentially, *N*-Me-indole must be acting as the Brønsted base during borylation of *N*-Me-indole with $[\mathbf{1}][\mathbf{CbBr_6}]$. It is presumably the combination of significantly greater sterics and the lower basicity of *N*-TIPS-pyrrole relative to *N*-Me-indole[62] that prevents *N*-TIPS-pyrrole acting as a Brønsted base during borylation. The successful, though slow, borylation of *N*-TIPS-pyrrole with $\mathbf{1}[\mathbf{AlCl_4}]$ is therefore attributed to a low concentration of free Et_3N generated by the various equilibria.

When borenium cations are partnered with $[AlCl_4]^-$ FLP formation is often precluded by competitive halide transfer. Thus, addition of Me_2NTol to $\mathbf{1}[\mathbf{AlCl_4}]$ rapidly formed $CatBCl(Me_2NTol)$ and Et_3N-$AlCl_3$.[30] Pleasingly, the combination of PPh_3 and $\mathbf{1}[\mathbf{AlCl_4}]$ leads to a stable FLP. The lack of halide transfer is attributed to the lower nucleophilicity of PPh_3 (relative to Me_2NTol) toward aluminum.[63] The use of the FLP $\mathbf{1}[\mathbf{AlCl_4}]/PPh_3$ in borylation reactions that previously took days with just $\mathbf{1}[\mathbf{AlCl_4}]$ reduced reaction times to <1 h for complete borylation. Furthermore, the use of the FLP $\mathbf{1}[\mathbf{AlCl_4}]/PPh_3$ prevented decomposition of highly Lewis acid sensitive heteroarenes enabling the regioselective C5 borylation of 2-methylfuran and 2-methoxyfuran (Figure 11). Furans are not amenable to borylation using only the borenium cation $[\mathbf{1}]^+$ due to competitive heteroarene decomposition reactions.

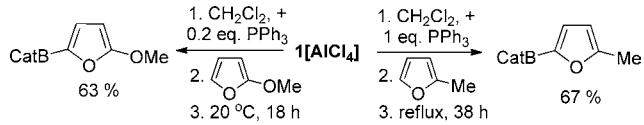

Figure 11. Borylation of 2-R-furan with $\mathbf{1}[\mathbf{AlCl_4}]/PPh_3$.

The primary product, if an S_EAr mechanism commencing from a borenium cation is operating, is a borylated arenium cation. Unfortunately, no intermediates were observed during the borylation of a wide range of arenes and heteroarenes with $[\mathbf{1}]^+$. Arenium cations are, however, observable on addition of the more electrophilic cations $[Cl_2B(amine)][AlCl_4]$ (amine = Et_3N or Me_2NTol) to *N*-TIPS-pyrrole at 20 °C. The borylated arenium cations, **6(amine)** (Figure 12 center), have ^{11}B NMR

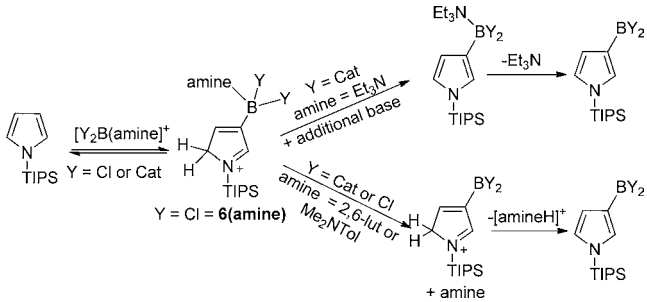

Figure 12. Reactivity of *N*-TIPS pyrrole toward $[Y_2B(amine)]^+$.

resonances (δ_B 6.1 and 6.6 ppm) indicative of a four-coordinate boron center and comparable to $(\eta^1\text{-}C_5Me_5)BCl_2(NMe_3)$ (δ_B 5.1 ppm).[64] In contrast, with $[Cl_2B(2,6\text{-lutidine})]^+$ the expected intermediate **6(2,6-lut)** is not observable; instead, *N*-TIPS-pyrrole is extremely rapidly borylated to $ArylBCl_2$ (complete in <30 min with $[AlCl_4]^-$ or $[BAr_{Cl}]^-$ anions). Presumably, the combination of the lower nucleophilicity (relative to Et_3N) and

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greater steric bulk of lutidine (relative to Me_2NTol) favors faster dissociation of 2,6-lut from the four-coordinate boron center in **6(2,6-lut)**. This generates an equivalent of Brønsted base enabling subsequent rapid deprotonation. The rapid (<1 h) borylation of *N*-TIPS-pyrrole by $[CatB(Me_2NTol)][BAr_{Cl}]$ also indicates that dissociation of amines from borylated arenium cations can be facile with catechol-based borenium cations provided the amine is more weakly nucleophilic than Et_3N. There are thus two distinct deprotonation mechanisms (Figure 12): (i) when amine dissociation from the borylated arenium cation is extremely slow (e.g., with $[\mathbf{1}]^+$), deprotonation requires an additional base and occurs at a 4 coordinate, at boron, intermediate; (ii) with less nucleophilic amines, dissociation from the borylated arenium cation is faster, presumably forming a three coordinate (at boron) cationic intermediate, and an equivalent of free base for deprotonation. Although a concerted deprotonation mechanism cannot be excluded in the second case. This mechanistic divergence can be utilized to selectively produce the kinetic or thermodynamic borylated isomer. Equimolar $BCl_3/AlCl_3/Me_2NTol$ predominantly borylates *N*-Me-pyrrole to provide the kinetic C3 borylated product (in a 5:95 C2:C3 regioisomer ratio) due to rapid deprotonation of the arenium cation intermediate. In contrast, the borylation of *N*-Me-pyrrole using $\mathbf{1}[\mathbf{AlCl_4}]$ produces the thermodynamic C2 borylated regioisomer as the major product (4:1 C2:C3) at reaction times <1 h or in the presence of a proton sponge.[37]

The use of $[CbBr_6]^-$ and $[BAr_{Cl}]^-$ has demonstrated definitively that borenium cations are active borylating electrophiles. However, attempts to borylate toluene with $[(Me_2NTol)BCl_2][CbBr_6]$ (formed by hydride abstraction from $(Me_2NTol)BHCl_2$ with $Ph_3C[CbBr_6]$[65]) in o-$C_6H_4Cl_2$ failed, with no borylation observed at 110 °C without (after 3 days) or with (after 24 h) the hindered base 2,4,6-tri^{t}Bu-pyridine (tTBP). Therefore, another, non-borenium cation, borylating electrophile must be present in Y_2BCl/amine/$AlCl_3$ systems at the raised temperatures used to borylate toluene and other weakly activated arenes. To prevent the formation of a borenium cation, the combination of an extremely bulky amine with Y_2BCl and $AlCl_3$ was investigated.

Borylation without Borenium Cations. The 2,6 and 2,4,6-*tert*-butyl-substituted pyridines (dTBP and tTBP, respectively) were selected as suitable "noncoordinating" bulky bases. Equimolar $BCl_3/AlCl_3$/tTBP gave no evidence for borenium cation formation (by NMR spectroscopy). However, this mixture did react rapidly with 2-Me-thiophene, with complete borylation within 10 min (20 °C in CH_2Cl_2). In contrast, $BCl_3/AlCl_3$/tTBP did not borylate toluene at ambient temperatures (<5% in 6 h by ^{11}B NMR spectroscopy). This is in contrast to the rapid (1 h) borylation of toluene reported with $BCl_3/AlCl_3$/activated aluminum (at 35 °C).[15−17] At raised temperatures, $BCl_3/AlCl_3$/tTBP does borylate toluene (at 110 °C > 95% conversion by ^{11}B NMR spectroscopy after 21 h). Successful borylation indicates that a more reactive electrophile is present relative to the borenium cation $[Cl_2B(Me_2NTol)][CbBr_6]$. It is also noteworthy that using $BCl_3/AlCl_3$/tTBP *para*-borylated toluene was the predominant product (ca. only 7% of *meta* isomer is observed, compared to 5:1 *para*:*meta* ratio with $BCl_3/AlCl_3/Me_2NTol$). This is remarkable selectivity for the Friedel−Crafts functionalization of toluene, and is superior when compared to direct borylation under iridium catalysis (*para*:*meta* borylation 31:69 ratio).[66] The borylation of pyrene proceeded analogously with significantly more of the kinetic 1-borylated isomer formed using tTBP as base compared to borylation with Me_2NTol (both at 120 °C for 75 h; Figure 13).

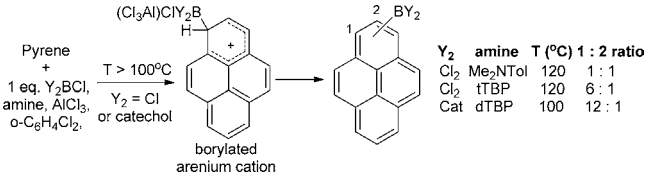

Figure 13. Borylation using equimolar Y_2BCl, $AlCl_3$, and TBP.

The increase in formation of the kinetic regioisomer is consistent with a rapid deprotonation of the borylated arenium cation intermediate by tTBP minimizing intramolecular migration. Equimolar CatBCl/$AlCl_3$/dTBP also generated an effective borylation agent which was more reactive than $[\mathbf{1}]^+$. For example, CatBCl/$AlCl_3$/dTBP rapidly diborylated *N*-Me-carbazole, whereas $\mathbf{1}[\mathbf{AlCl_4}]$ does not borylate this substrate. Importantly, CatBCl/$AlCl_3$/dTBP does not borylate toluene (24 h, 110 °C). This confirms that CatBCl is not disproportionating to produce BCl_3, which does borylate toluene with TBP and $AlCl_3$. The more activated arenes, pyrene and fluorene, are borylated at 100 °C with CatBCl/$AlCl_3$/dTBP. Formation of the thermodynamic product is also minimized using hindered TBP bases with CatBCl (Figure 13).

The hindered TBP pyridines will be more weakly bound to the Lewis acids (compared to Me_2NTol) due to steric destabilization. This enables a higher concentration of free base to be present and consequentially a more rapid deprotonation step. Weak coordination of TBP to BCl_3 is indicated by the ^{11}B NMR spectrum of equimolar Cl_3B/dTBP (δ ^{11}B 44.9 ppm at 20 °C, CD_2Cl_2) revealing only a small upfield shift. On addition of $AlCl_3$, this forms BCl_3 (δ ^{11}B 46.0 ppm) and dTBP-$AlCl_3$ (δ ^{27}Al broad at 103.5 ppm). In contrast, coordinating amines (Me_2NTol) form stronger adducts with ECl_3 (e.g., equimolar BCl_3 and Me_2NTol has an ^{11}B NMR resonance at 10.4 ppm). Thus, there will be an extremely low amount of free Me_2NTol present in solution, resulting in slower deprotonation and more isomerization.

With no boron electrophile other than BCl_3 (or CatBCl) observed by NMR spectroscopy during borylation with Y_2BCl/TBP/$AlCl_3$, a number of mechanisms are feasible. These include (i) borylation via a type II or III electrophile (Figure 14 top) or (ii) an organometallic transmetalation route (Figure 14 bottom). The inability of $BCl_3/AlCl_3$/tTBP to borylate toluene to any significant degree at 20 °C is in contrast to Muetterties system, precluding formation of $BCl_2(\mu\text{-}Cl)AlCl_3$ (or $[(areneH)BCl_2][AlCl_4]$) at this temperature. The borylation of toluene with $BCl_3/AlCl_3$/TBP does occur at raised temperatures (≥70 °C) suggesting that under more energetic conditions a type II or III electrophile (or $[(areneH)BCl_2][AlCl_4]$) is accessible. With $BCl_3/AlCl_3$/TBP, the active electrophile in the borylation of less activated arenes is presumably identical to that operating in the original report by Muetterties. The presence of the TBP amine prevents heteroarene decomposition and *trans*-alkylation (intermolecular Brønsted superacid induced alkyl scrambling) due to more effective proton trapping.

With more nucleophilic arenes (e.g., indoles/thiophenes), borylation is extremely rapid at 20 °C; thus, a transmetalation mechanism is also feasible. While neutral AlX_3 Lewis acids interact weakly with benzene,[67,68] the greater nucleophilicity of

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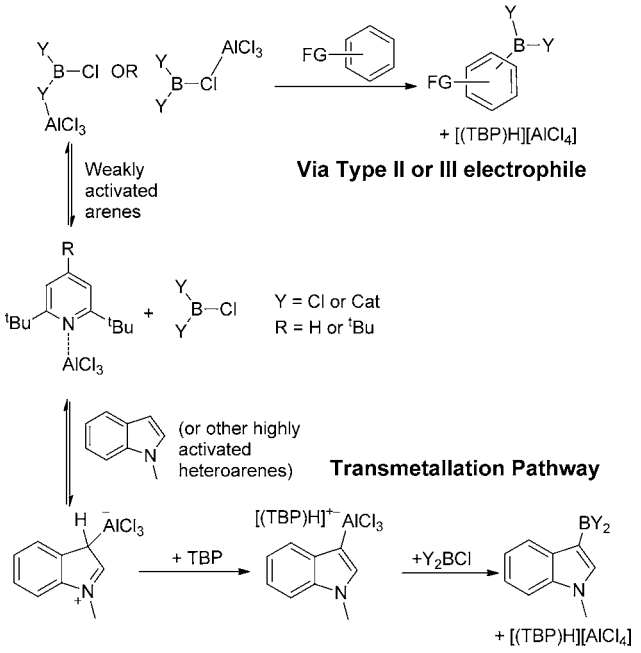

Figure 14. Proposed non-borenium borylation pathways.

activated heteroarenes will result in a stronger interaction with $AlCl_3$ to form zwitterionic arenium-ECl_3 species (Figure 14 bottom left). Deprotonation by TBP to form $[(\text{heteroaryl})\text{-}AlCl_3]^-$ (a carbanion equivalent) and transmetalation with Y_2BCl would then afford $ArylBY_2$. To probe this mechanism, *N*-Me-Indole was added to equimolar CatBH/$AlCl_3$ mixtures at 20 °C in o-$C_6H_4Cl_2$. As expected, *N*-Me-indole has a greater nucleophilicity toward $AlCl_3$ relative to CatBX species, with a new ^{27}Al NMR resonance centered at 110 ppm observed consistent with {*N*-Me-indole)·$AlCl_3$. Confirmation of this product as {N-Me-indole)·$AlCl_3$, **9**, was provided by single crystal X-ray diffraction analysis (Figure 15). The gallium analogue, {*N*-Me-indole)·$GaCl_3$, **10**, was also structurally characterized. The structural metrics for **9** and **10** are similar, including shortened N1−C2 bonds and elongated C2−C3 bonds relative to free *N*-Me-indole. The E-C3 distances are

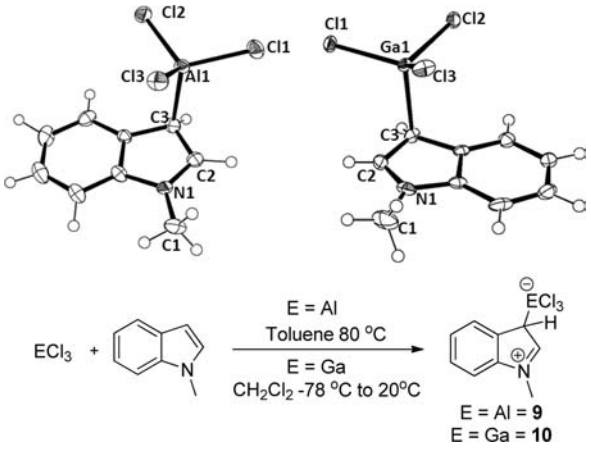

Figure 15. Schematic and ORTEP representations of **9** and **10** with thermal ellipsoids at 50% probability. Selected bond lengths (Å) for **9**: N1−C1 = 1.448(11), N1−C2 = 1.332(10), C2−C3 = 1.404(12), C3−Al1 = 2.083(8). For **10**: N1−C1 = 1.463(4), N1−C2 = 1.322(4), C2−C3 = 1.421(5), C3−Ga1 = 2.105(5).

short (Al1−C3 = 2.083(8) and Ga1−C3 = 2.105(3) Å) consistent with a strong interaction and are considerably shorter than (toluene)$Al(C_6F_5)_3$ (Al−C = 2.366(2) Å).[69] This emphasizes the effect of high arene nucleophilicity on increasing adduct strength. The E-C distances in **9** and **10**, in fact, more closely approach that of $[ArylECl_3]^-$ species (e.g., Ga−C = 1.944(8)Å in $([(Et_2O)Li][Cl_3Ga(C_6H_2{}^iPr_3)])_2$).[70]

Compounds **9** and **10** represent a step on the proposed transmetalation pathway, with coordination of ECl_3 lowering the pK_a of *N*-Me-indole. However, attempts to deprotonate **9** and **10** with dTBP predominantly formed insoluble and intractable material (in CH_2Cl_2 and in o-$C_6H_4Cl_2$). $[HdTBP]^+$ was observed in these reactions suggesting that deprotonation of **9** and **10** is taking place. In contrast, the addition of the slightly less bulky base, PCy_3, did not deprotonate **9** and **10**; instead, this produced $Cl_3E\text{-}PCy_3$ and *N*-Me-indole. Furthermore, a combination of *N*-Me-indole and $Me_2NTol\text{-}AlCl_3$ (a significant $AlCl_3$ containing species present from combining $Y_2BCl/Me_2NTol/AlCl_3$) in o-$C_6H_4Cl_2$ resulted in no reaction.

Combined, the studies with weakly coordinating anions and TBP bases indicate the following: (i) a transmetalation mechanism is not possible when the base is less bulky than TBP; (ii) in borylation reactions using coordinating amines, more activated arenes are borylated at 20 °C by borenium cations; (iii) less activated arenes (e.g., pyrene, toluene) are only borylated by Type II/III electrophiles; (iv) when the amine is Me_2NTol or TBP, less activated arenes only undergo significant borylation at high temperatures precluding formation and borylation by Olah's proposed $Cl_2B(\mu\text{-}Cl)AlCl_3$ electrophile at 20 °C. Thus, at ambient temperatures with coordinating amines the borenium cation, $[Y_2B(\text{amine})]^+$, is the most important borylating electrophile. To seek further support for these conclusions and elucidate borylation mechanistic details, each of the key proposed mechanisms were probed computationally for the CatBCl system.

Computational Studies. The theoretical study of the borylation reaction was carried out at the M06−2X/6-311+G(2d,2p)//M06−2X/6-31G(d,p) level using a computational model composed of CatBCl, $AlCl_3$, trimethylamine, and *N*-Me-indole. In the following discussion, all energies are relative to the four reactants at infinite distance and have been corrected to account for solvation effects.

Figure 16 summarizes the three products possible from a combination of CatBCl, $AlCl_3$, and trimethylamine. The

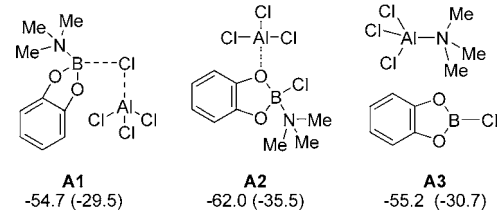

Figure 16. Relative $E(G_{298})$ in CH_2Cl_2 (kcal/mol) for different species prior to addition of *N*-Me-indole.

borenium cation optimizes as $CatBNMe_3(\mu\text{-}Cl)(AlCl_3)$ (**A1**) in contrast to the experimentally synthesized $[CatB(NEt_3)][AlCl_4]$. $CatBNMe_3(\mu\text{-}Cl)(AlCl_3)$ has a significantly longer bridging Al−Cl bond (2.33 Å compared to 2.11 Å for the remaining three Al−Cl distances) and a short B−Cl contact (2.06 Å). This is consistent with the facile chloride transfer

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observed with [CatB(amine)][$AlCl_4$], which presumably proceeds by attack of an external base on CatB(amine)(μ-Cl)($AlCl_3$).[30] The lowest energy structure using this computational model was found to involve oxygen coordination to $AlCl_3$ (**A2**).[71] Coordination of the amine to the aluminum center (**A3**) with no interaction between the boron atom and the Lewis base is predicted to have similar stability to the borenium cation.

The sequence of elementary steps for borylation of *N*-methyl-indole starting from the borenium cation is depicted in Figure 17. Addition of *N*-Me-indole to the borenium cation

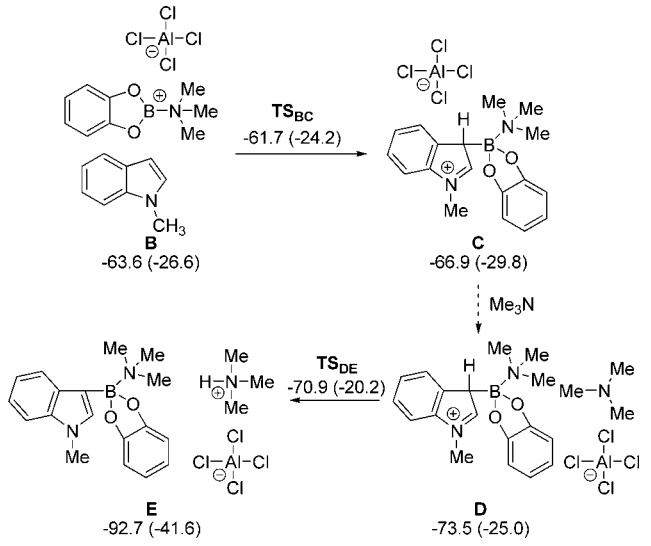

Figure 17. Relative *E* (G_{298}) in CH_2Cl_2 (kcal/mol) for the borenium pathway including a second molecule of Me_3N as Brønsted base.

[CatB(NMe_3)][$AlCl_4$] is calculated to be weakly exothermic with a very low barrier to formation of the σ complex between the boron electrophile and *N*-Me-indole (**TS$_{BC}$**). The σ complex, **C**, is the key intermediate en route to the aryl boronate ester. Borylation is calculated to proceed by an S_EAr mechanism, in line with the experimentally observed borylated arenium cations. There was no evidence for a competing C−H insertion mechanism as found during intramolecular borylation with electrophilic borocations containing a B−H moiety.[27] Likewise, intramolecular proton transfer from the C3−H to NMe_3 through a four-membered transition state was not found computationally.[28] The [$AlCl_4$]$^-$ anion was also found to be insufficiently basic to deprotonate the arenium cation. This is consistent with the superacid HCl−$AlCl_3$ being orders of magnitude more acidic than protonated *N*-Me-indole. No transition state could be optimized for the dissociation of NMe_3 from the σ complex **C**. The barrier for B−N bond breaking was thus estimated as roughly 25 kcal/mol by gradually stepping the B−N distance and applying a solvation correction to the electronic energy of each point.[37] A 25 kcal/mol barrier is consistent with borylation with **1**[**CbBr$_6$**] requiring a second equivalent of base due to slow B-NEt_3 cleavage in the σ complex at 298 K.

The only deprotonation process with a sufficiently low barrier to be consistent with the observed reactivity at 20 °C involved the addition of a further equivalent of base to the σ-complex. When the base is a second equivalent of Me_3N (**TS$_{DE}$**) or an equivalent of PPh_3, the calculated Gibbs energy barriers of the deprotonation step are low, 9.6 and 16.5 kcal mol^{-1}, respectively.[37] The energetically favored formation of the aryl boronate ester should therefore be rapid with both PPh_3 and Et_3N. Experimentally, the borylation of highly activated arenes with the [**1**]$^+$/PPh_3 FLP is indeed fast (<10 min). However, borylation with **1**[**AlCl$_4$**] and no additional base, where the base is presumably Et_3N generated through equilibrium processes, is slower. The slower borylation with **1**[**AlCl$_4$**] is attributed to the equilibrium positions effectively suppressing the amount of free Et_3N present in solution. In the borylation of *N*-Me-indole with **1**[**CbBr$_6$**], the presence of free Et_3N is precluded; thus, *N*-Me-indole was proposed to be the base. The borylation of *N*-Me-Indole with **1**[**CbBr$_6$**] proceeded to >95% within 5 h, in contrast with <10 min using the FLP [**1**][**AlCl$_4$**]/PPh_3. This disparity suggests a considerably higher barrier to deprotonation when *N*-Me-indole is the Brønsted base. Computationally, $\Delta G^{\ddagger}$ for deprotonation using another molecule of N-Me-indole (instead of Me_3N or PPh_3) was 23 kcal/mol above the σ complex, consistent with the observed rate of reaction. The deprotonation is actually endothermic when *N*-Me-indole is the base, but subsequent rapid amine dissociation from neutral 3-(CatB(NMe_3))-*N*-Me-indole will result in deprotonation of the protonated indole and formation of [Me_3NH][$AlCl_4$] generating an overall exothermic reaction. Thus, the computational results support a S_EAr mechanism with the borenium cation [**1**]$^+$ viable as the active electrophile, provided a secondary base is present to deprotonate the σ complex.

We also considered the direct borylation of *N*-Me-indole using CatBCl($AlCl_3$) as the electrophile, with NMe_3 only acting as a Brønsted base abstracting the proton on the C3 position to liberate the product. Due to the high nucleophilicity of *N*-Me-indole, geometry optimization of the complex between nucleophile and electrophile spontaneously converges to a σ-complex, **F**. Despite repeated attempts, no transition state for B−C formation could be found. Proton abstraction (**TS$_{FG}$**) was extremely facile (Figure 18), as testified by the negative barrier

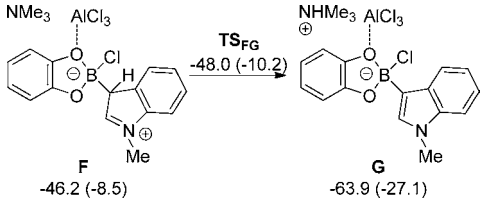

Figure 18. Relative *E* (G_{298}) in CH_2Cl_2 (kcal/mol).

obtained after adding vibrational corrections to the calculated energies. However, the ease of the process does not render this pathway favored with respect to the borenium mechanism, as all the stationary points lie significantly higher in energy than those depicted in Figure 17.

An alternative pathway involving transmetalation is depicted in Figure 19. Optimization of *N*-Me-indole and $AlCl_3$ resulted in a barrierless formation of a σ-complex, **H**. This can be easily deprotonated by Me_3N (**TS$_{HI}$**) to form adduct **I**. Upon addition of one molecule of CatBCl, the resulting adduct undergoes a stepwise transmetalation, beginning with the attack of the boron electrophile on C3 (**TS$_{JK}$**). The final step of the pathway involves a concerted 1,3-halide shift/Al−C bond breaking (**TS$_{KL}$**), liberating the borylation product. While the reaction barriers in this pathway are also very low, the optimized stationary points again lie significantly higher in

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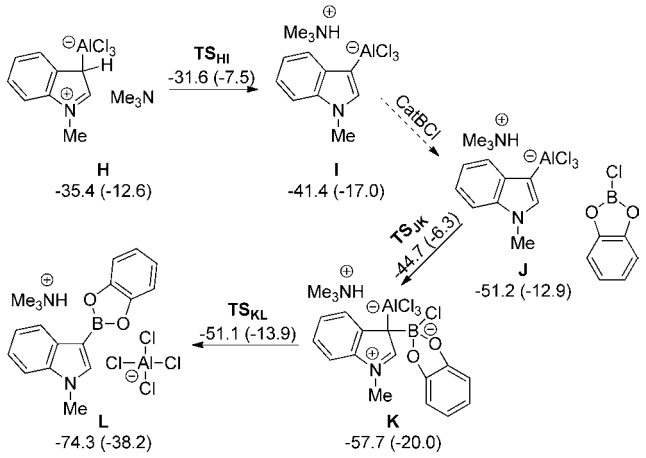

Figure 19. Relative E (G_{298}) in CH_2Cl_2 (kcal/mol) for the transmetalation pathway.

energy than those found in the borenium pathway, thus also rendering this mechanistic hypothesis less favored. The optimized geometries of the lowest-energy transition states for the three pathways considered are represented in Figure 20.

Alternative mechanisms must be operating at 20 °C when the hindered TBP bases are used as borylation cannot proceed via synthetically inaccessible $[Y_2B(TBP)]^+$ cations. With the dTBP base, we theoretically scrutinized the transmetalation and direct borylation (with CatBCl($AlCl_3$)) pathways for the borylation of *N*-Me-indole. The overall Gibbs energy barrier for the transmetalation pathway was calculated to be 29.6 kcal/mol.[37] This is inconsistent with the experimentally observed rapid (<10 min at 20 °C) borylation of *N*-Me-indole with CatBCl/$AlCl_3$/dTBP. Specifically, we found the direct proton transfer step to dTBP to be very energetically demanding due to steric crowding around the nitrogen atom. Addition of a second equivalent of *N*-Me-indole to act as the Brønsted base did not significantly lower the overall barrier, with a calculated Gibbs energy value (25.8 kcal mol^{-1}) still not consistent with a fast process taking place at 20 °C. The direct attack pathway has a barrier of only 19.1 kcal/mol (Figure 21), which is compatible

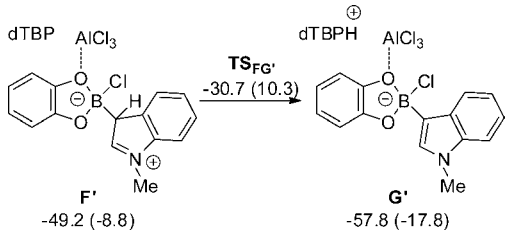

Figure 21. Relative E (G_{298}) in CH_2Cl_2 (kcal/mol) for the direct attack pathway with dTBP as Brønsted base.

with rapid borylation at 20 °C. Thus, the direct borylation pathway is feasible with dTBP-provided transfer of $AlCl_3$ from compound **9** to CatBCl is sufficiently rapid at 20 °C, as experimentally *N*-Me-indole is more nucleophilic toward $AlCl_3$ than CatBX.

SUMMARY

Amine-mediated electrophilic direct borylation has been demonstrated for a range of activated arenes and heteroarenes. The subsequent installation of the MIDA protecting group provides an alternative synthetic route to these increasingly popular Suzuki-Miyaura cross-coupling precursors. Electrophilic borylation is particularly well suited for preparing precursors for Suzuki-Miyaura polymerization and iterative cross coupling[39] due to its compatibility with halo functional groups and the ability to di- and triborylate activated arenes. Regioselectivity at 20 °C is high, operating under synergic steric and electronic control. Good yields are obtainable provided the correct borane/$AlCl_3$/amine ratios are used to prevent

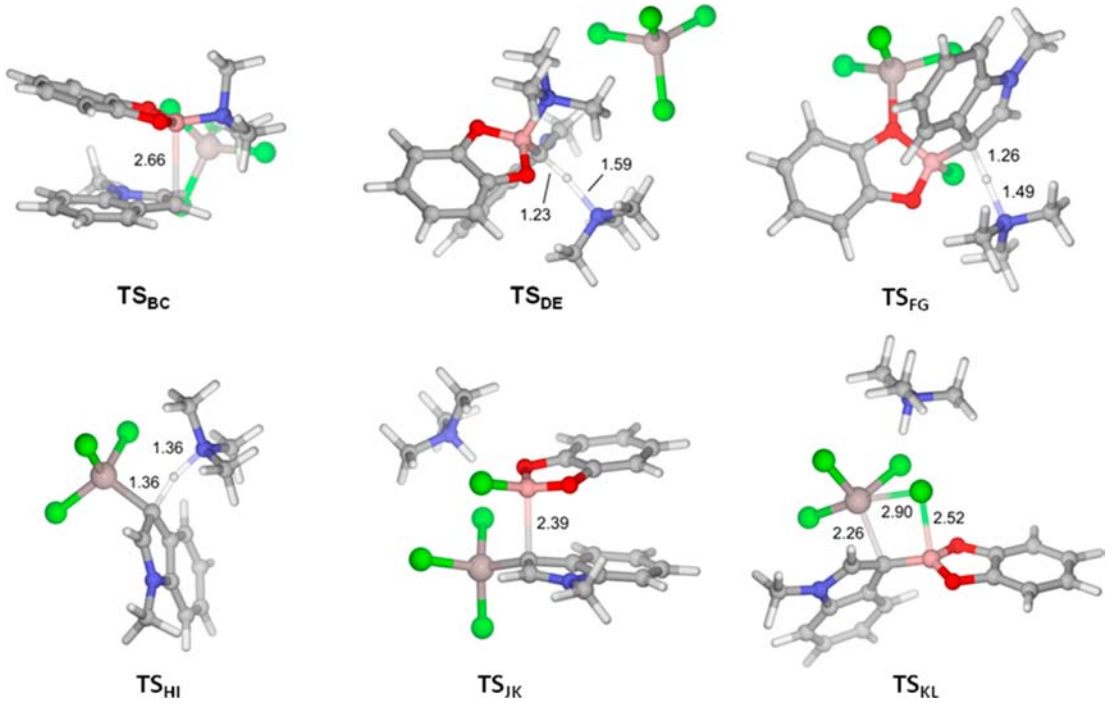

Figure 20. Optimized geometries of the transition states (distances in Å).

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deboronation and acid induced heterocycle decomposition. At raised temperatures, less activated arenes are also amenable to borylation. Regioselectivity under these more forcing conditions is dependent on the rate of positional isomerization in the borylated arenium cation (σ complex) relative to the rate of deprotonation. By using "noncoordinating" TBP bases, kinetic products can be selectively formed due to more rapid deprotonation of the σ complex.

Mechanistically, a range of amine and temperature dependent borylation pathways are viable (Figure 22). Using

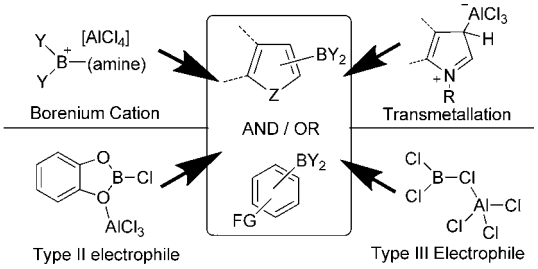

Figure 22. Viable direct borylation pathways.

inexpensive coordinating amines, the dominant mechanism at 20 °C involves a borenium cation as the key electrophile. Computational and experimental studies indicate that borylation proceeds by a S_EAr pathway. The deprotonation step was found to be highly amine dependent. With $[CatB(NEt_3)]^+$, an additional Brønsted base is required; thus, borylation is only rapid when FLP containing $[CatB(NEt_3)]^+$ and PPh_3 are used. The use of a FLP also enabled borylation of highly sensitive substrates (e.g., furans). Borylation with $[Y_2B(Me_2NTol)]^+$ and $[Cl_2B(2,6\text{-lutidine})]^+$ borenium cations was rapid relative to $[CatB(NEt_3)]^+$. This is due to the higher electrophilicity of these cations and the ability of the more weakly nucleophilic amines to dissociate more rapidly from the borylated arenium cations. Surprisingly, despite its high electrophilicity $[Cl_2B(Me_2NTol)]^+$ is not an active electrophile for the borylation of less activated arenes (e.g., toluene). Instead, this requires the formation of more activated species, presumably $Cl_2B(\mu\text{-}Cl)AlCl_3$ (solvated or nonsolvated by the arene). In the presence of a noncoordinating amine base borylation by borenium cations is also not energetically viable. In this case, at least two different mechanisms are feasible: (i) coordination of $AlCl_3$ to Y_2BCl to generate a highly reactive electrophile; (ii) transmetalation, involving initial attack of aluminum Lewis acids on the activated arene nucleophile. The latter mechanism would proceed via unusual (heteroarene)$AlCl_3$ adducts, an example of which has been structurally characterized. Irrespective of the significant mechanistic complexity, this new direct method to produce MIDA boronate esters complements the established route of organometallic deprotonation.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental, crystallographic, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(71) The contrasting experimental: computational relative Gibbs (298 K) energies of A1:A2 appears to be an artifact of the calculations at the M06−2X/6-311+G(2d,2p)//M06−2X/6-31G(d,p)/PCM$_{(CH2Cl2)}$ level. The discrepancy between computational and experimental observations cannot be ascribed to a change in sterics at amine from using NMe_3. Me_2NBu is signficiantly less bulky than Et_3N but this amine cleanly produced the borenium salt, $[CatB(Me_2NBu)][AlCl_4]$, with no analogue of A2 observed spectroscopically. Furthermore, calculations on the Et_3N analogues of A1, A2, and A3 produced the same order of relative energies (ΔE and ΔG). This discrepancy does not alter any mechanistic conclusions as the stationary points for borenium cation based borylation will remain significantly lower in energy (or be even lower in energy) than those found for alternative, nonborenium, borylation pathways.