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Letter

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Structure and Reactivity of Boron-Ate Complexes Derived from Primary and Secondary Boronic Esters

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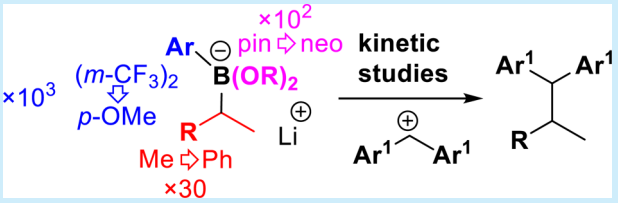
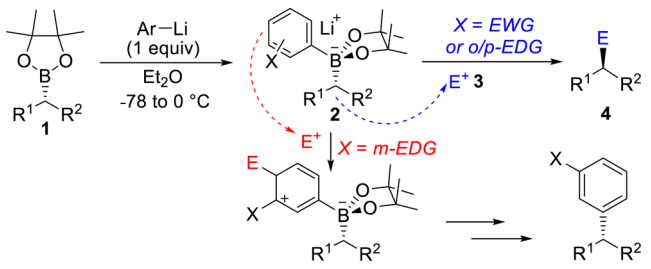
Supporting Information

ABSTRACT: Boron-ate complexes derived from primary and secondary boronic esters and aryllithiums have been isolated, and the kinetics of their reactions with carbenium ions studied. The second-order rate constants have been used to derive nucleophilicity parameters for the boron-ate complexes, revealing that nucleophilicity increased with (i) electron-donating aromatics on boron, (ii) neopentyl glycol over pinacol boronic esters, and (iii) 12-crown-4 ether.



Chiral organoboron compounds are widely employed in asymmetric synthesis since they can be transformed into a variety of functional groups, often with complete stereospecificity. The transformations are usually initiated by addition of a nucleophile to the electrophilic boron atom followed by a stereospecific 1,2-migration.[1] We recently reported an alternative mode of reactivity that further increases the synthetic utility of these valuable intermediates. We found that normally electrophilic boronic esters **1** could be rendered nucleophilic through addition of an aryllithium leading to the formation of boron-ate complexes (BACs **2**) and that such intermediates reacted with a range of electrophiles **3** to give different products depending on the substitution of the aromatic ring (Scheme 1).[2] With *para*-electron-donating or electron-withdrawing substituents on the aryl lithium, adducts **4** were obtained with inversion of configuration,[2] while use of *meta*-electron-donating substituents led to reactions on the aromatic ring ultimately leading to aryl coupled products.[3] To establish further the use of these reagents in synthesis we wanted to gain a deeper understanding of their reactivity and so applied the well-established benzhydrylium method to quantify their nucleophilic reactivity.[4] Herein, we describe how the nucleophilicity of alkyl and benzyl BACs is influenced by the nature of the aryllithium, the diol ester, and the structure of the organic component, in comparison with aryl and heteroaryl BACs.[5−7]

Scheme 1. Formation of Lithium Boron-Ate Complexes (BACs) 2 by Treatment of Boronic Esters 1 with Aryllithiums and Subsequent Reactions with an Electrophile E^+[2,3]



A range of boron-ate complexes (BACs) **2a−l** bearing different aryl groups, diol esters, and carbon substituents were prepared by addition of an aryllithium [PhLi, *p*-$CF_3C_6H_4Li$, or $(m\text{-}CF_3)_2C_6H_3Li$] to a solution of boronic ester **1** in Et_2O (Scheme 1). Crystallization at rt gave a range of analytically pure primary and secondary BACs **2a−l** in moderate to good yields, as white air-sensitive solids (Figure 1), all of which exhibited a singlet at $\delta \approx +5$ ppm in the ^{11}B NMR spectrum.

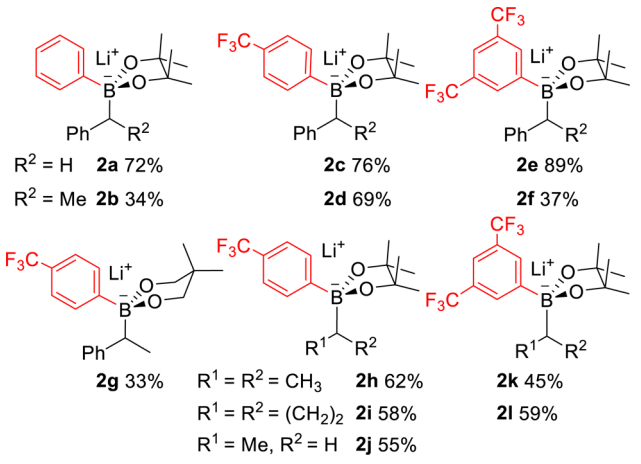


Figure 1. Lithium BACs **2a−l** derived from the corresponding pinacol and neopentyl glycol boronic esters **1**. Yields after recrystallization in Et_2O.

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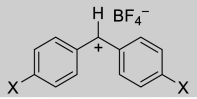
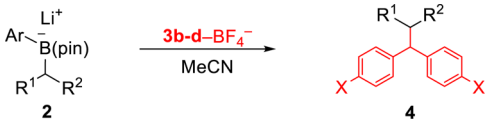
Table 1. Structures, Absorption Maxima λ_{max}, and Electrophilicity Parameters E for Benzhydrylium Ions 3a–d Used as Reference Electrophiles[4]



		λ_{max} / nm (in CH_3CN)	E
X = OMe	**3a**	500	0.00
X = $N(Me)CH_2CF_3$	**3b**	586	–3.85
X = $N(CH_2CH_2)_2O$	**3c**	611	–5.53
X = NMe_2	**3d**	605	–7.02

To elucidate the relationship between structures and reactivities of **2a–l**, we studied the kinetics of their reactions with benzhydrylium ions **3a–d** (Table 1). These have been used as reference electrophiles for the construction of comprehensive reactivity scales covering a reactivity range of more than 30 orders of magnitude[4] and have recently also been used for quantifying the nucleophilicities of various organoboron derivatives.[5−7] Carbenium ions **3a–d** were reacted with representative BACs, and the products were fully characterized (Scheme 2).[8]

Scheme 2. Products 4 from the Reaction of BACs 2 with Benzhydrylium Tetrafluoroborates 3b–d (For Details and Yields, see Supporting Information)



For kinetic analysis, these reactions were performed under pseudo-first-order conditions with at least a 10-fold excess of BACs **2a–l** and were monitored at λ_{max} of benzhydrylium ions **3b–d** (Table 1) by using a conventional or a stopped-flow spectrophotometer. Fitting of a monoexponential function to the observed decays of the absorbance values of **3b–d** gave the k_{obs} values, which were plotted against the boron-ate concentrations, giving straight lines with slopes equal to the second-order rate constant, k_2 (see Figure 2 and Tables 2 and 3). This behavior was observed for all systems reported in this letter, indicating the stabilities of the boron-ate complexes under these conditions.

We initially investigated the effect of the nature of the counterion, Li^+, on the rate by using 12-crown-4 as an additive. As illustrated in Table 2, a 2.5- and 3-fold increase of reactivity of BACs **2a** and **2e**, respectively, was observed when using 1 equiv of 12-crown4 ether, showing that Li^+ has a small effect on the nucleophilic reactivities of the boron-ate complexes. It is believed the 12-crown-4 sequesters the lithium cation of the BAC **2**,[9] preventing the Li^+ from binding to the diol oxygen atoms and thus slightly enhancing the reactivity of the C–B bond. This finding is consistent with our recent observations showing that the counterions of heteroaryl BACs have a negligible effect on their reactivity.[5]

We then investigated the effect of the aryl group on the nucleophilicities of the BACs. As shown in Table 3, rate constants k_2 for the reaction of BACs with benzhydrylium cations **3b–d** were used to obtain nucleophilicity parameters N and susceptibility parameters s_N, according to eq 1. Increasing the electron-withdrawing character of the aryl unit attached to

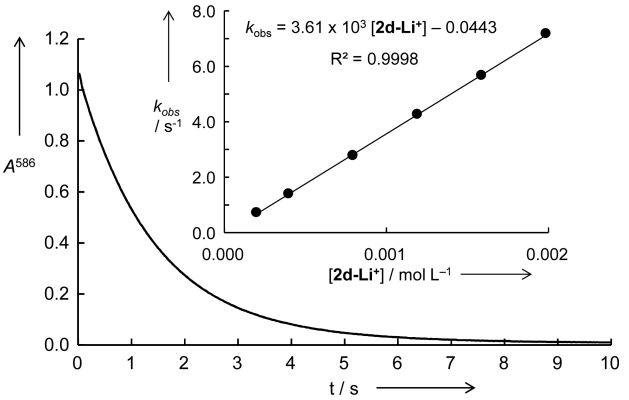


Figure 2. Exponential decay of the absorbance of benzhydrylium **3b** (7.8×10^{-6} M) in the presence of 25 equiv of the BAC **2d**–Li^+ (1.98×10^{-4} M) in CH_3CN ($k_{obs} = 7.11 \times 10^{-1}$ s^{-1}). Inset: Determination of the second-order rate constant, k_2, from the dependence of k_{obs} on the concentration of **2d**–Li^+ ($k_2 = 3.61 \times 10^3$ M^{-1} s^{-1}).

Table 2. Study of the Influence of 12-Crown-4 Ether on the Reaction Rates of BACs 2a and 2e with Benzhydrylium Ion 3b in CH_3CN at 20 °C

BACs		12-crown-4	k_2 (M^{-1} s^{-1}) / **3b**	k_{rel}
Ar, B(pin), Li+	**2a** (Ar = Ph)	-	3.52×10^3	1.0
		1 equiv	8.69×10^3	2.5
Ph, B(pin), Li+	**2e** (Ar = 3,5-$(CF_3)_2$-C_6H_3)	-	8.42×10^1	1.0
		1 equiv	$2.55 \times 10^{2\,a}$	$3.0^{\,a}$

[a]Only approximate value ±50%.

boron was found to greatly reduce the reactivity of the BACs. Thus, in reaction with the benzhydrylium ion **3b**, **2f** [Ar = (*m*-$CF_3)_2$-C_6H_3] was found to be 7 times less reactive than **2d** [Ar = *p*-CF_3–C_6H_4] and 61 times less reactive than **2b** [Ar = Ph] (from comparison of k_2 values). The same trend was apparent with the primary boron-ates **2a**, **2c**, and **2e**. BACs with electron-donating aryl substituents were too labile to be isolated; however, the *p*-OMe-Ar (attached to B) substituted analogue of **2b** was synthesized in solution and found to have a rate constant of 3×10^3 M^{-1} s^{-1}, approximately 1000-times more reactive toward the benzhydrylium ion **3d** than the bis(*m*-CF_3)-substituted BAC **2f** ($k_2 = 2.16$ M^{-1} s^{-1}). Thus, the substituents on the aryl moieties were found to have a much more pronounced effect on nucleophilicity in the benzyl series than for the recently reported thienyl BACs, where the difference in reactivity between the *p*-OMe and bis(*m*-CF_3) BACs was found to be 30-fold.[5]

The effect of the diol ligand attached to boron on reactivity was also explored. The neopentyl derivative **2g** was found to react with benzhydryliums **3b–d** on average 100 times faster than the pinacol analogue, **2d** (Table 3). This effect is weaker than that found for heteroaryl BACs, where the neopentyl derivatives were on average 10^4 times more reactive than the pinacol derivatives.[5] The activating effect of the neopentyl glycol ester ligand compared to the pinacol ester, although less pronounced in the benzyl series, is a general effect and may have important practical implications, as it should enable coupling with a broader set of electrophiles.[5,10] The higher reactivity of neopentyl glycol esters over pinacol boronic esters is thought to be due to their reduced steric hindrance.[5]

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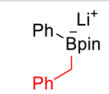
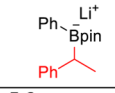
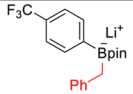
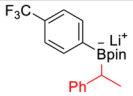
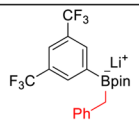
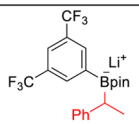
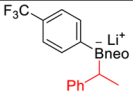
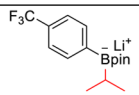
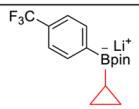
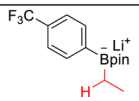
Table 3. Second-Order Rate Constants k_2 for the Reactions of Lithium BACs 2 with $Ar_2CH^+BF_4^-$ 3b–d in CH_3CN at 20 °C and Resulting Nucleophile-Specific Parameters N and s_N of BACs 2a–j

	BACs 2	Ar_2CH^+	k_2 / M^{-1} s^{-1}	N, s_N [a]
2a		**3b**	3.52×10^3	8.92, 0.70
		3c	$\approx 2 \times 10^2$ [b]	
		3d	2.14×10^1	
2b		**3b**	3.27×10^4	10.97, 0.63
		3c	2.81×10^3	
		3d	— [c]	
2c		**3b**	3.05×10^2 [d]	7.15, 0.77
		3c	2.35×10^1	
		3d	1.08	
2d		**3b**	3.61×10^3	8.56, 0.76
		3c	2.60×10^2	
		3d	1.34×10^1	
2e		**3b**	8.42×10^1	6.30, 0.78
		3c	4.05	
		3d	— [c]	
2f		**3b**	5.36×10^2	7.46, 0.76
		3c	$\approx 2 \times 10^1$ [b]	
		3d	2.16	
2g		**3b**	4.74×10^5	11.29, 0.76
		3c	2.15×10^4	
		3d	1.86×10^3	
2h		**3b**	1.22×10^2	(6.63, 0.75) [e]
2i		**3b**	7.95×10^2	(7.72, 0.75) [e]
2j		**3b**	9.75×10^2	7.68, 0.78
		3c	5.06×10^1	
		3d	3.19	

[a]Nucleophilicity parameter N and susceptibility parameter s_N, as defined in eq 1. [b]The decays were not strictly monoexponential, and the k_2 values were not used for determining N and s_N. [c]As observed by ^{1}H NMR spectroscopy, decomposition of the BAC in CH_3CN at 20 °C was faster than its reaction with **3d**, preventing the measurement of the k_2 value. [d]Second part of a biexponential decay. [e]s_N was estimated.

The effect of the substitution pattern of the sp^3 carbon attached to boron was then analyzed by comparing the second-order rate constants, k_2, of the reactions of the *p*-CF_3 BACs with **3b** (Figure 3). This comparison revealed a remarkable trend in reactivity due to substitution at the *ipso* position: in the benzylic series, phenylmethyl boron-ate **2d** was found to be 12 times more reactive than the benzylic analogue **2c**, despite its increase in steric hindrance. Thus, electronic activation, presumably through hyperconjugation from the methyl C–H bonds, outweighs the steric effects.

In contrast, isopropyl boron-ate complex **2h** was found to be 8 times less reactive than the primary BAC **2j** demonstrating the opposite effect of the addition of a methyl group at the *ipso* carbon atom on the nucleophilic reactivity of the BAC in the alkyl series. The surprisingly high reactivity of ethyl BAC **2j** is

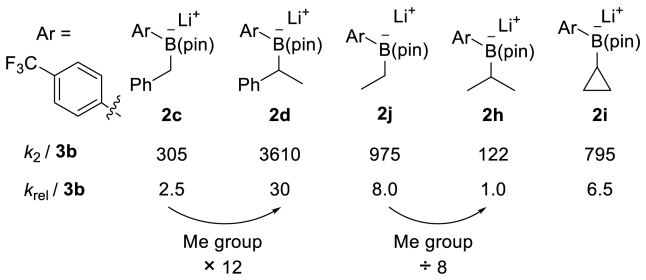


Figure 3. Effect of carbon substitution on the rate constant, k_2, in reaction of BACs **2** with carbenium ion **3b** (20 °C in CH_3CN).

thought to be due to its small size. These rate constants are in line with our previous work, where secondary benzylic boron-ate complexes were found to be more reactive than their secondary alkyl analogues.[2a] Cyclopropyl boron-ate **2i** was found to be more nucleophilic than the isopropyl boron-ate **2h** (k_{rel} = 6.5), demonstrating the combined effects of the electronic effects of the cyclopropyl ring and reduced steric hindrance.

Plots of log k_2 for these reactions vs the electrophilicity parameters E of **3b–d** (Table 1) were linear (Figure 4),

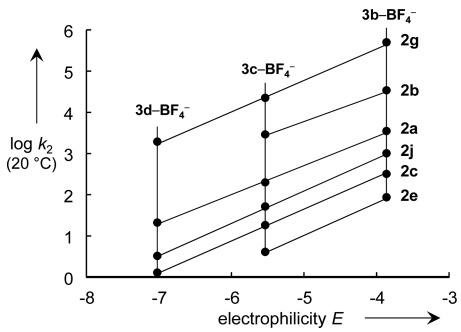


Figure 4. Correlation of the second-order rate constants k_2 (Table 3) for the reactions of lithium BACs **2** with benzhydrylium tetrafluoroborates **3** in CH_3CN toward the electrophilicity parameters E of **3** from Table 1.

indicating the applicability of eq 1 for determining the nucleophilicity parameters N and the susceptibility parameters s_N of the boron-ates **2a–j** (Table 3). The s_N values, which correspond to the slopes of these correlations, are in the narrow range $0.6 < s_N < 0.8$ (Figure 4 shows almost parallel lines), indicating that the relative reactivities of the BACs **2** depend little on the reactivity of the reference electrophile. As the s_N values are similar to those of borylated π-systems, the N values can be used for a direct comparison of the nucleophilic reactivities of these different classes of compounds (Figure 5).

$$\log k_2(20\ ^\circ\mathrm{C}) = s_N(N + E) \quad (1)$$

Figure 5 illustrates the nucleophilicity parameters N (susceptibility parameters s_N in parentheses) of these novel BACs, benchmarked against a range of other C-centered nucleophiles. The retarding effect of trifluoromethyl groups on the nucleophilic reactivities of phenethyl- and benzyl-substituted boron-ate complexes **2a–f** is shown. The greater nucleophilicity of phenethyl BACs in comparison to their benzyl analogues is also apparent, as well as the superior nucleophilicity of neopentyl BAC **2g** (N = 11.29) compared to its pinacol analogue **2d** (N = 8.56). It can be seen that these

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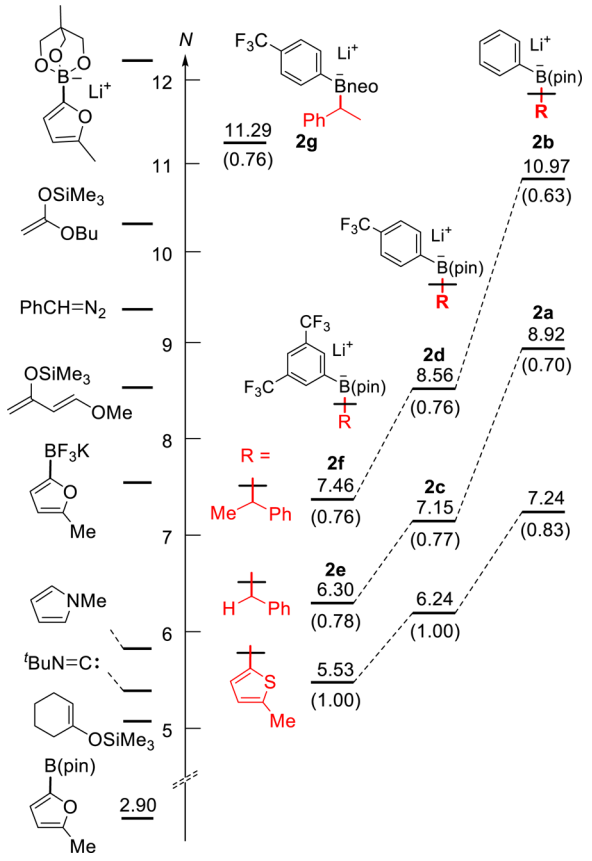

Figure 5. Comparison of nucleophilicity parameters N (susceptibility parameters s_N in parentheses) of BACs **2a**–**g** with N of other C-centered nucleophiles.

C_{sp^3} nucleophiles are slightly more nucleophilic than the corresponding 5-methylthienyl BACs, where the electrophilic attack occurs at a C_{sp^2} center.

In conclusion, the benzhydrylium method has allowed us to determine nucleophilicity parameters for a series of primary and secondary benzyl and alkyl boron-ate complexes. This is the first time N parameters have been measured for sp^3-centered C nucleophiles. A preliminary study showed that the lithium cation has a small retarding effect on the reactivity of the boron-ate complex. Nucleophilicity was observed to be dependent upon the electronic properties of the aryl ring, the diol attached to the boron atom, and the substitution of the sp^3 carbon. The diol used has a major effect with neopentyl glycol being 100-fold more reactive than pinacol. The nature of the aryl group has a potent effect; Ar = Ph is 100 times more reactive than the electron-deficient Ar = $(m\text{-}CF_3)_2C_6H_3$. The reactivity of the boron-ate complex was also affected by the nature of the sp^3 substituent, with the nucleophilicity parameters following the trend secondary benzylic > primary alkyl > primary benzylic > secondary alkyl. The reactivities of these BACs were found to be comparable to those of the structurally analogous thienyl and furyl BACs; this is the first direct comparison between the reactivities of C_{sp^3} and C_{sp^2} nucleophiles.[5] The fine balance of reactivity also accounts for why electron-rich aromatic boron-ate complexes sometimes react at the sp^3 carbon atom and sometimes at the aromatic ring depending on the substitution pattern of the aromatic ring.[3] Thus, the boron-ate complexes studied in this report have been shown to be powerful nucleophiles, and the relationship found between the structure and reactivity of these boron-ates has allowed us to optimize the nucleophilicity of the complexes. Work is ongoing to harness this nucleophilicity with other families of electrophiles such as imines and aldehydes.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, and spectroscopic data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00918.

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Notes

The authors declare no competing financial interest.

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