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Fine-Tuning the Nucleophilic Reactivities of Boron Ate Complexes Derived from Aryl and Heteroaryl Boronic Esters**

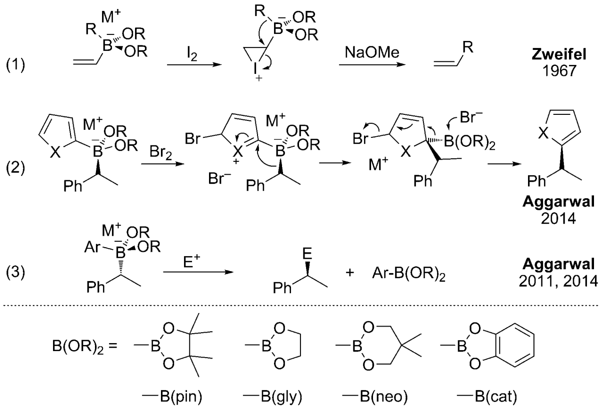
*Guillaume Berionni, Artem I. Leonov, Peter Mayer, Armin R. Ofial, and Herbert Mayr**

Dedicated to Dr. Klaus Römer on the occasion of his 75th birthday

Abstract: *Boron ate complexes derived from thienyl and furyl boronic esters and aryllithium compounds have been isolated and characterized by X-ray crystallography. Products and mechanisms of their reactions with carbenium and iminium ions have been analyzed. Kinetics of these reactions were monitored by UV/Vis spectroscopy, and the influence of the aryl substituents, the diol ligands (pinacol, ethylene glycol, neopentyl glycol, catechol), and the counterions on the nucleophilic reactivity of the boron ate complexes were examined. A Hammett correlation confirmed the polar nature of their reactions with benzhydrylium ions, and the correlation* $\lg k(20\,°C) = s_N(E + N)$ *was employed to determine the nucleophilicities of the boron ate complexes and to compare them with those of other borates and boronates. The neopentyl and ethylene glycol derivatives were found to be* 10^4 *times more reactive than the pinacol and catechol derivatives.*

Boron ate complexes (BACs), which are readily available by treatment of boronic esters R-B(OR)$_2$ with organolithium compounds, are air-stable, functional-group-tolerant nucleophiles,[1] which undergo various noncatalyzed reactions with electrophiles.[2–5] Their treatment with trifluoroacetic anhydride yields intermediate borinic esters which undergo stereoselective allylation reactions with aldehydes, ketones, and imines, when allylboronates are used as precursors.[2] Following the principle of the Zweifel olefination[3] (Scheme 1, reaction 1), Aggarwal et al. recently reported that treatment of BACs with suitable electrophiles led to the stereospecific coupling of arenes with secondary alkyl groups (Scheme 1, reaction 2).[4]

In contrast, BACs with less-electron-rich arenes (Scheme 1, reaction 3) were attacked by electrophiles at the boron-substituted sp^3-hybridized carbon, and the coupling products R-E were formed with a high degree of inversion.[5] Chiral BACs, derived from secondary boronic esters, reacted in this way with a broad range of carbon-, oxygen- and nitrogen-centered electrophiles, including carbenium and iminium ions.[5]



Scheme 1. Reactions of boron ate complexes (BACs) with electrophiles.

Borate salts M$^+$ arylBX$_3^-$ with electron-rich arene rings, on the other hand, are known to react with electrophiles at the *ipso* position of the aryl ring.[6] We have recently demonstrated that the nucleophilicities of thiophenes, furans, and indoles bearing boron substituents, such as -B(OR)$_3^-$, -BF$_3^-$, -B(pin), and -B(MIDA) (MIDA = *N*-methyliminodiacetate), span a reactivity range of ten orders of magnitude.[7] We now report that BACs with two aryl rings behave similarly and describe their isolation and X-ray structures as well as the determination of their nucleophilicities by the benzhydrylium methodology.[8]

Following a procedure by Brown,[1a,b] we added the thienyl boronic esters **1a–d** to ethereal solutions of the trifluoromethylated aryllithium compounds **2** and **2′** and then removed the solvent by evaporation to produce the lithium BACs (**3–4**)-**Li**$^+$ as colorless crystalline solids (Scheme 2). The ^{11}B NMR spectra of all BACs show a sharp resonance at δ $+2$ to $+10$ ppm that is characteristic of an anionic tetracoordinated boron atom derived from boronic esters.[1] No decomposition of these BACs in CD$_3$CN solutions was observed by ^{1}H NMR spectroscopy over several days at 20 °C.[9]

As shown in Scheme 3, addition of thienyl- and furyllithium derivatives **5** and **5′** to the pinacol boronates **6** and **7** produced the respective BACs (**8–14**)-**Li**$^+$ in good yields. The tetraethylammonium salt **8**-**Et$_4$N**$^+$ was obtained by cation metathesis from **8**-**Li**$^+$ with Et$_4$N$^+$Cl$^-$.

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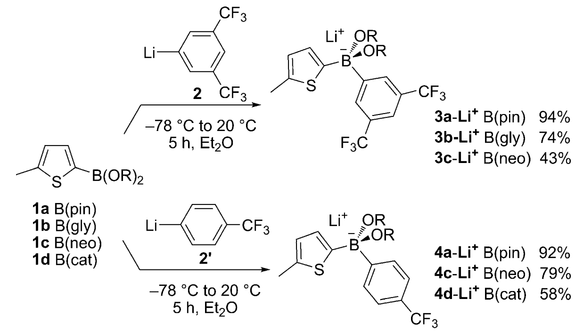
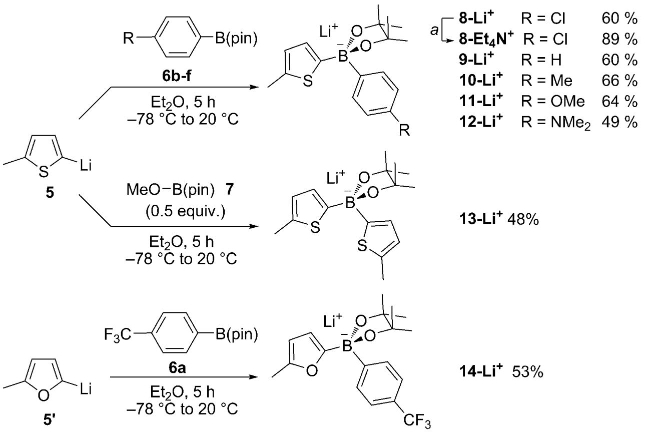


Scheme 2. Synthesis and yields of the isolated lithium BACs (**3**–**4**)-**Li**$^+$.



Scheme 3. Synthesis of the BACs **8**–**14** and yields after crystallization from THF/Et_2O or CH_3CN/Et_2O mixtures (see the Supporting Information for details). a) Reaction conditions: $Et_4N^+Cl^-$ (1 equiv), THF, 20 °C.

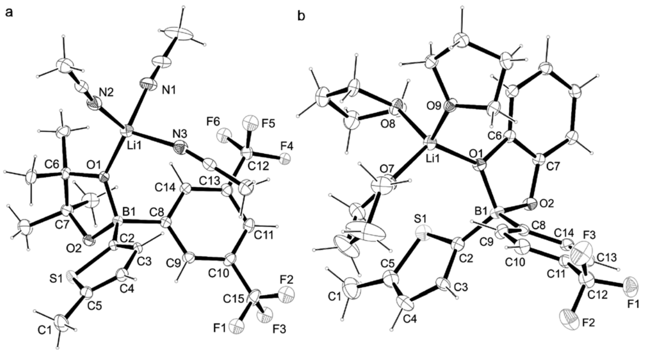


Figure 1. a) ORTEP view of the BACs **3a-Li**$^+$·$(MeCN)_3$ and b) of **4d-Li**$^+$·$(THF)_3$ (thermal ellipsoids at the 30% probability level).[10] For bond lengths and angles see the Supporting Information.

Crystals of **3a-Li**$^+$·$(MeCN)_3$ suitable for X-ray analysis were grown by storing a concentrated MeCN solution of **3a-Li**$^+$ at 0 °C for one week. Its solid-state structure (Figure 1a) shows that the lithium cation is coordinated to one oxygen of the pinacol moiety (Li–O1 = 1.924 Å) as well as to three MeCN molecules (Li–N = 2.070 Å average).[10] Single crystals of the catechol borate **4d-Li**$^+$·$(THF)_3$ were obtained by vapor diffusion of *n*-pentane into its solution in THF. Figure 1b shows that Li^+ is coordinated to a catechol oxygen and to three THF molecules.[10] The quaternary boron atoms in both BACs have perfect tetrahedral environments (tetrahedral character > 99.9 %).[11,12]

The kinetics of the reactions of the BACs **3**–**4** and **8**–**14** with the benzhydrylium ions **15a**–**d** were monitored by time-resolved UV/Vis spectroscopy in CH_3CN at the λ_{max} of **15** (Table 1). In the presence of more than ten equivalents of the BACs, monoexponential decays of the benzhydrylium ions' absorbances were observed, indicating pseudo-first-order kinetics. The second-order rate constants k_2 reported in Table 2 were derived from the slopes of the plots of k_{obs} (s^{-1}) versus the concentration of the BACs (see the Supporting Information).

Table 1: Absorption maxima λ_{max} (in MeCN) and electrophilicities E[8] of the benzhydrylium tetrafluoroborates $Ar_2CH^+BF_4^-$ **15a**–**d** used as reference electrophiles in this work.

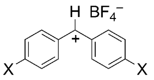
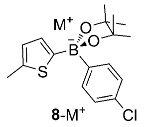
	λ_{max} [nm]	E
15a, X = OMe	500	0
15b, X = $N(Me)CH_2CF_3$	586	−3.85
15c, X = $N(CH_2CH_2)_2O$	611	−5.53
15d, X = NMe_2	605	−7.02

Table 2: Second-order rate constants k_2 for the reactions of lithium BACs with the benzhydrylium tetrafluoroborates **15b**–**d** in MeCN at 20 °C and the resulting nucleophilicity parameters N and s_N of **3**–**4** and **8**–**14**.

Lithium BACs	Nucleophilicities N, s_N[a]	k_2 [$M^{-1}s^{-1}$] **15b**	**15c**	**15d**
3a	(5.53, 1.00)[b]	4.84×10^1	< 1[c]	–
3b	11.23, 0.77	5.22×10^5	2.24×10^4	1.88×10^3
3c	10.13, 0.91	5.36×10^5	1.57×10^4	–
4a	6.24, 1.00	2.40×10^2	5.06	–
4c	11.85, 0.72	$>10^6$	3.73×10^4	3.12×10^3
4d	6.50, 0.77	1.10×10^2	5.57	–
8	6.77, 0.88	3.68×10^2	1.23×10^1	–
9	7.24, 0.83	6.82×10^2	2.70×10^1	–
10	6.98, 0.93	8.12×10^2	2.22×10^1	–
11	7.51, 0.87	1.49×10^3[d]	5.20×10^1[d]	–
12	8.02, 0.89	5.14×10^3	1.65×10^2	–
13	7.67, 0.87	2.08×10^3	7.19×10^1	–
14	8.13, 0.85	4.38×10^3	1.63×10^2	–

[a] Obtained with Equation (1), see text. [b] Derived from a single k_2 value, assuming $s_N = 1$ in analogy to **4a**. [c] Not accessible because of the high reversibility of the reaction and the nonlinearity of the plot of k_{obs} vs. [**3a**]. [d] Partial attack (< 5 %) of **15b**–**c** at the anisole ring of **11**.

Kinetic experiments revealed that **8-Li**$^+$ was three times less reactive than its sodium analogue **8-Na**$^+$ (Scheme 4),[13] in line with the coordination of the Li^+ cation to an oxygen atom of the pinacol ligand, which decreases the electron density of the thiophene–boron bond. The reactivity of **8-Et$_4$N**$^+$ is in between that of **8-Na**$^+$ and **8-Li**$^+$, indicating that Et_4N^+ slightly reduces the nucleophilicity of **8**, probably by the formation of a C−H···O hydrogen bond with the oxygen



8-M+	8-Li+	8-Na+	8-Et$_4$N+
k_2 with **15b** [M^{-1} s^{-1}]	3.68 × 10^2	1.26 × 10^3	6.77 × 10^2
k_{rel}	1	3.4	1.8

Scheme 4. Influence of the counterions on the reactivity of **8** toward the benzhydrylium ion **15b** in MeCN at 20 °C.

atoms of the pinacol ligand.[14] Nevertheless, the kinetic data show that counterions have only a small effect on the nucleophilicities of BACs in CH_3CN.

The small values of the Hammett reaction constants ($\rho \approx -1$), derived from the correlations in Figure 2, indicate a transition state resembling a σ-adduct (Scheme 5), in which the cleavage of the C−B bond is not far advanced.

As shown in Scheme 6, the reaction of the NMe_2 derivative **12-Li**$^+$ with electrophiles is not regioselective, and the attack at the thiophene ring of **12-Li**$^+$ is only slightly faster than the attack at the dimethylaniline ring. As electrophilic attack at the aryl group is least likely when these are carrying electron-withdrawing groups, the aryl lithium compounds **2** and **2′** are often used for the activation of boronic esters in synthetic applications.[4,5]

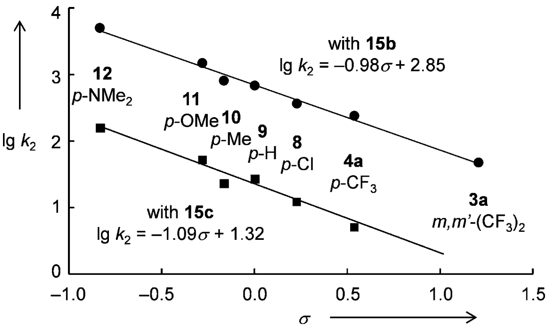
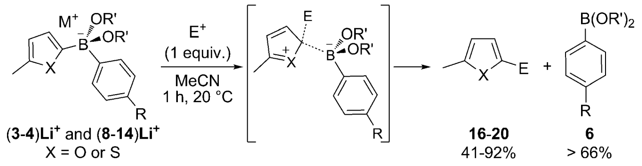
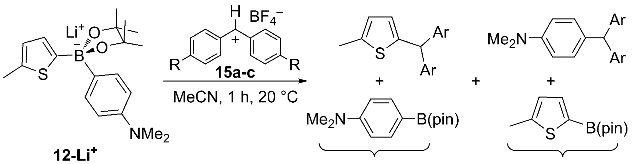


Figure 2. Correlation of the second-order rate constants lgk_2 for the reactions of the lithium thienyl pinacol BACs **3a**, **4a**, and **8–12** with the benzhydrylium ions **15b** (●) and **15c** (■) with Hammett's σ parameters.



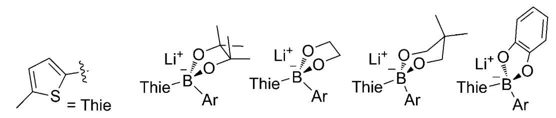
Scheme 5. Reactions of the BACs (**3–14**)-**Li**$^+$ with various electrophiles at 20 °C in MeCN. Yields and structures of **16–20** are given in the Supporting Information.



	attack at thiophene	attack at aryl
15a, R = OMe	66	34
15b, R = NMe(CH$_2$CF$_3$)	60	40
15c, R = N(CH$_2$CH$_2$)$_2$O	59	41

Scheme 6. Unselective reactions of **12-Li**$^+$ with $Ar_2CH^+BF_4^-$ **15a–c**. Product ratios determined by ^{1}H NMR spectroscopy and GC-MS of the crude reaction mixtures.

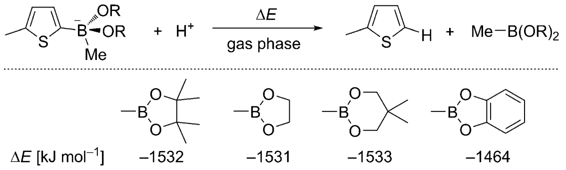
Scheme 7 shows that the ethylene glycol and neopentyl glycol derived BACs **3b**, **3c**, and **4c** are roughly 10^4 times more reactive than the pinacol and catechol BACs **3a**, **4a**, and **4d**, in line with previous qualitative observations.[15] The origin of these differences is revealed by quantum chemical calculations. It has already been reported that catechol boronates are significantly stronger Lewis acids than ethylene glycol and neopentyl glycol derived boronates because a phenolate oxgen exerts a weaker +M effect than an alkoxide oxygen.[16]



Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$	**3a-Li**$^+$	**3b-Li**$^+$	**3c-Li**$^+$	-
k_{rel} / **15b**	1	1.1 × 10^4	1.1 × 10^4	-
Ar = 4-CF$_3$-C$_6$H$_4$	**4a-Li**$^+$	-	**4c-Li**$^+$	**4d-Li**$^+$
k_{rel} / **15c**	1	-	7.4 × 10^3	1.1

Scheme 7. Relative reactivities of the thienyl BACs **3–4** derived from B(pin), B(gly), B(neo), and B(cat) toward carbenium ions **15b,c** in MeCN at 20 °C.

In line with these findings we calculated that the proto-deborylation of a catechol-derived BAC is significantly less exothermic than than the analogous reaction of the other BACs (Scheme 8). The fact that the nucleophilicity of the catechol-derived BAC **4d** is 10^4 times lower than that of **4c** (Scheme 7) shows that a fraction of this difference in reaction energies is already observed in the transition states of the reactions with benzydrylium ions.



Scheme 8. Proto-deborylation energies in the gas phase (B3LYP/6-31G(d)).

On the other hand, similar exothermicities are calculated for the proto-deborylations of the B(pin), B(gly), and B(neo) derivatives (Scheme 8). For that reason, we can conclude that the difference in nucleophilicities of the BACs **3a** and **3b** is exclusively due to steric effects. The identical nucleophilicities of **3b** and **3c**, in line with the comparable reaction energies of the corresponding proto-deborylations shown in Scheme 8, furthermore show that conceivable stereoelectronic effects (ideal overlap of the empty p orbital at boron with the oxygen lone pair) do not increase the reactivity of the neopentyl derivatives **3c** and **4c**.

Substitution of the second-order rate constants k_2 determined in this work into Equation (1),[7,8] which characterizes electrophiles by the electrophilicity parameter E and nucle-

$$\lg k_2\ (20\,^\circ\mathrm{C}) = s_\mathrm{N}(N + E) \qquad (1)$$

ophiles by the nucleophilicity parameter N and the sensitivity parameter s_N, allows us to determine N and s_N for the BACs **3**–**4** and **8**–**14** (Table 2) and to compare them with related nucleophiles (Figure 3).

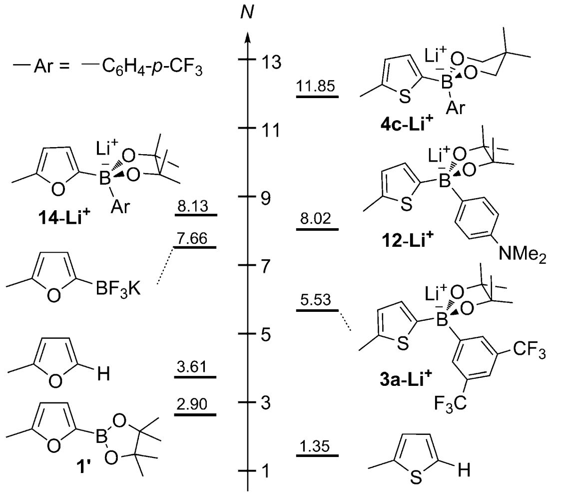


Figure 3. Comparison of the nucleophilicities of BACs with those of other borylated and electron-rich heteroarenes. N parameters from Table 2 and Refs. [7,8c].

In conclusion, we have found that the nucleophilic reactivity of the furylboronate **1′** ($N = 2.90$) is increased by a factor $> 10^5$ by the addition of 4-CF_3-phenyllithium (**2′**) to give **14** (Figure 3). A somewhat stronger activation can be achieved with aryllithium compounds carrying electron-donating substituents, but one has to take care that in these cases electrophiles are not directed to the aryl ring (Scheme 6).

While the nucleophilic reactivies of the BACs depend only slightly on their counterions, the nature of the diol ligand has a profound effect on its nucleophilicity. Thus, the -B(gly) and -B(neo) derivatives are 10^4 times more reactive than the -B(pin) and -B(cat) derivatives. With these data in hand, we now have a quantitative basis for fine-tuning the nucleophilic reactivities of boron ate complexes for synthetic applications.

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Keywords: arenes · boron compounds · kinetics · linear free energy relationships · nucleophilicity

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[1] a) H. C. Brown, M. Srebnik, T. E. Cole, *Organometallics* **1986**, *5*, 2300–2303; b) H. C. Brown, N. Vasumathi, N. N. Joshi, *Organometallics* **1993**, *12*, 1058–1067; c) T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono, M. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 10674–10676.

[2] a) J. L.-Y. Chen, H. K. Scott, M. J. Hesse, C. L. Willis, V. K. Aggarwal, *J. Am. Chem. Soc.* **2013**, *135*, 5316–5319; b) J. L.-Y. Chen, V. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 10992–10996; *Angew. Chem.* **2014**, *126*, 11172–11176.

[3] a) G. Zweifel, H. Arzoumanian, C. C. Whitney, *J. Am. Chem. Soc.* **1967**, *89*, 3652–3653; b) G. Zweifel, R. P. Fisher, J. T. Snow, C. C. Whitney, *J. Am. Chem. Soc.* **1972**, *94*, 6560–6561.

[4] a) A. Bonet, M. Odachowski, D. Leonori, S. Essafi, V. K. Aggarwal, *Nat. Chem.* **2014**, *6*, 584–589; b) D. Leonori, V. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/anie.201407701; *Angew. Chem.* **2014**, DOI: 10.1002/ange.201407701.

[5] a) M. Mohiti, C. Rampalakos, K. Feeney, D. Leonori, V. K. Aggarwal, *Chem. Sci.* **2014**, *5*, 602–607; b) R. Larouche-Gauthier, T. G. Elford, V. K. Aggarwal, *J. Am. Chem. Soc.* **2011**, *133*, 16794–16797.

[6] S. Roscales, A. G. Csákÿ, *Chem. Soc. Rev.* **2014**, *43*, 8215–8225.

[7] a) G. Berionni, V. Morozova, M. Heininger, P. Mayer, P. Knochel, H. Mayr, *J. Am. Chem. Soc.* **2013**, *135*, 6317–6324; b) G. Berionni, B. Maji, P. Knochel, H. Mayr, *Chem. Sci.* **2012**, *3*, 878–882.

[8] a) H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512; b) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; c) for reactivity parameters N, s_N, and E and links to the original literature, see: http://www.cup.lmu.de/oc/mayr/DBintro.html.

[9] The trifluoromethylated BACs **3** and **4** can be kept for a few minutes in aqueous acetonitrile but then they decompose quantitatively into 2-methylthiophene and the corresponding aryl boronic esters.

[10] CCDC 1014813 (BAC **3a-Li**$^+$) and 1014814 (**4d-Li**$^+$) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] The tetrahedral character has been calculated by taking into account the six bond angles around the boron atom, see a) H. Höpfl, *J. Organomet. Chem.* **1999**, *581*, 129–149; b) S. Toyota, M. Oki, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1832–1840.

[12] So far, the X-ray structures of only four BACs are known and no pinacol derivative has been reported: a) R. Anulewicz-Ostrowska, T. Klis, J. Serwatowski, *Main Group Met. Chem.* **2002**, *25*, 501–504; b) N. Yu, V. V. Bardin, U. Flörke, H.-J. Frohn, *Z. Anorg. Allg. Chem.* **2005**, *631*, 2638–2646; c) J. Knizek, H. Nöth, M. Warchhold, *Z. Naturforsch. B* **2006**, *61*, 1079–1093; d) P. K. Elkin, V. V. Levin, A. D. Dilman, M. I. Struchkova, P. A. Belyakov, D. E. Arkhipov, A. A. Korlyukov, V. A. Tartakovsky, *Tetrahedron Lett.* **2011**, *52*, 5259–5263.

[13] For the synthesis of **8-Na**$^+$, see the Supporting Information.

[14] Analogous interactions between tetraalkylammonium ions and enolates or carbanions have been reported: M. T. Reetz, S. Hütte, R. Goddard, *J. Prakt. Chem.* **1999**, *341*, 297–301.

[15] For the advantage of using neopentyl boronic esters in transition-metal-catalyzed reactions, see: a) Y. Zhao, V. Snieckus, *Org. Lett.* **2014**, *16*, 3200–3203; b) M. Takeda, K. Takatsu, R. Shintani, T. Hayashi, *J. Org. Chem.* **2014**, *79*, 2354–2367; c) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706–2707.

[16] A. Adamczyk-Woźniak, M. Jakubczyk, P. Jankowski, A. Sporzyński, P. M. Urbański, *J. Phys. Org. Chem.* **2013**, *26*, 415–419.

Communications

Boron Compounds

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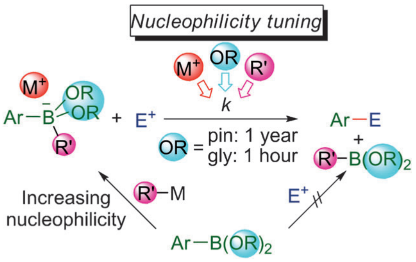
Fine-Tuning the Nucleophilic Reactivities of Boron Ate Complexes Derived from Aryl and Heteroaryl Boronic Esters



Tailor-made nucleophiles: Kinetic studies reveal that the nucleophilic reactivities of boron ate complexes depend mainly on the nature of the covalently bound ligands at boron. Thus ethylene glycol -B(gly) and neopentyl glycol -B(neo) derivatives are 10^4 times more reactive than analogous pinacol -B(pin) and catechol -B(cat) derivatives. These insights can be used to tailor the reactivities of boron ate complexes.